Recent Development in the Chemistry of Bicyclic 6-6 Systems Containing One Bridgehead Nitrogen Atom and One Extra Heteroatom and Their Benzologs (Update II).

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I. Introduction

This chapter covers the primary chemical literature of the title bi- and tricyclic ring systems cited in *Chemical Abstracts* Chemical Substance Indexes up to Volume 151 from Volume 144 between 2006 and 2009. Earlier literature data were systematically treated as primary subjects in *Comprehensive Heterocyclic Chemistry* series (96CHC-II(8)563, 08CHC-III(12)77).

The members of these ring systems occupy valuable parts of the chemical space for drug research, as most of their derivatives have drug-like properties and their outstanding representatives play an indispensable role in medicinal chemistry. The compounds, which were introduced into the human and veterinary therapies are depicted on Figure 1. Antofloxacin is the newest member of this class, which has been applied to combat antibacterial infections since 2009 in China. Some prominent members were isolated from different natural sources, and their structures are on Figure 2.

II. Pyrido[2,1-*b*][1,3]oxazines, -[1,4]thiazines and Their Benzologs

Perhydropyrido[2,1-*b*][1,3]oxazin-6-ones **8** and **10** were obtained when they **7** and **9** precursors were split from resins (07JCC1060).
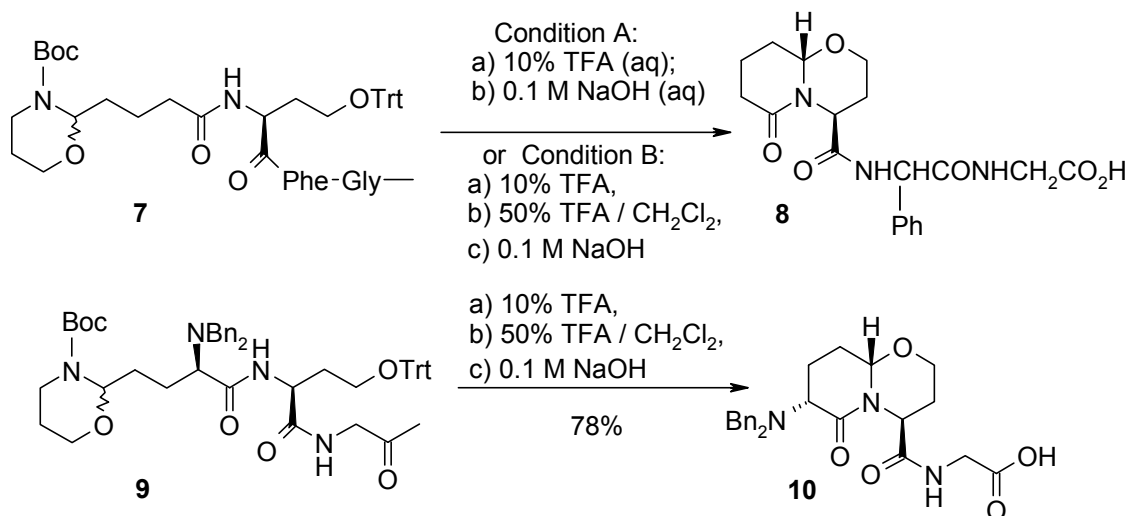
III. Pyrido[1,2-a] pyrimidines

A. Structure

1. Thermodynamic Aspects

Solubility for risperidon was calculated at pH 2 and with 13 with the ACD/Solubility DB computer program to be 7.3×10^{-3} and 9.6 mg/ml, respectively. The predicted distribution coefficient of risperidon is -1.02 and 1.82 between *n*-octanol and water at pH 2 and 13, respectively, calculated by the ACD/Log*D* DB computer program(05JSS1195).

A charge transfer comlex was formed by reacting risperidine with chloranil, and its spectral characteristic, stability constant and thermodynamic parameters were investigated (05OJC427).

Octanol-water partition coefficients of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one and its 2,3-dimethyl derivative was determined by traditional shake-flask and reversed phase thin-layer chromatographic methods (08MI11).

The rate of brain penetration of risperidone was predicted by different assays (MDR1-MDCKII, PAMPA-BBB, *in situ* brain perfusion) (09JPS1980).

Theoretical and experimental solubility of risperidone were determined in polymeric micelles formed from di-block polyethylene glycol and random copolyesters of ε-caprolactone and trimethylene carbonate (07PHA499). The experimental partition coefficients in octanol-water system and pK_a values of risperidone and paliperidone are 3.04, 8.24 and 2.35, 8.24, respectively (07DMD649). Risperidone and paliperidone were also included into a set of compounds to predict alkane/water partition coefficients (08JMC3720).

Pemirolast was determined in human plasma by a LC-MS method (05MI1).

Risperidone was determined by different HPLC methods in formulated products (06MI4), in biological fluids [06JCH(B)1, 06JCH(B)100, 06MI3, 06MI8, 07JC(B)20, 07MI9, 08MI1, 09DMD787]. Reversed-phase liquid chromatographic columns were classified/characterized by using different drugs, among them risperidone (06JPB751). Risperidone was determined by a flow-injection chemiluminescence method (06CPA288).

A reverse-phase HPLC method was developed for determination of **32-43** potential impurities and **44** degradation product of risperidone (08JPB165). Hydroxylated derivative on the pyridine moiety of paliperidone, 2-(9-hydroxy-2-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)acetic acid, 9-hydroxy derivative of

compound **39**, and its hydroxylated derivative on the pyridine moiety, furthermore 9-oxo

derivative of risperidone were identified in human urine and feces by LC-MS/MS method

as the metabolites of paliperidone (08DMD769).

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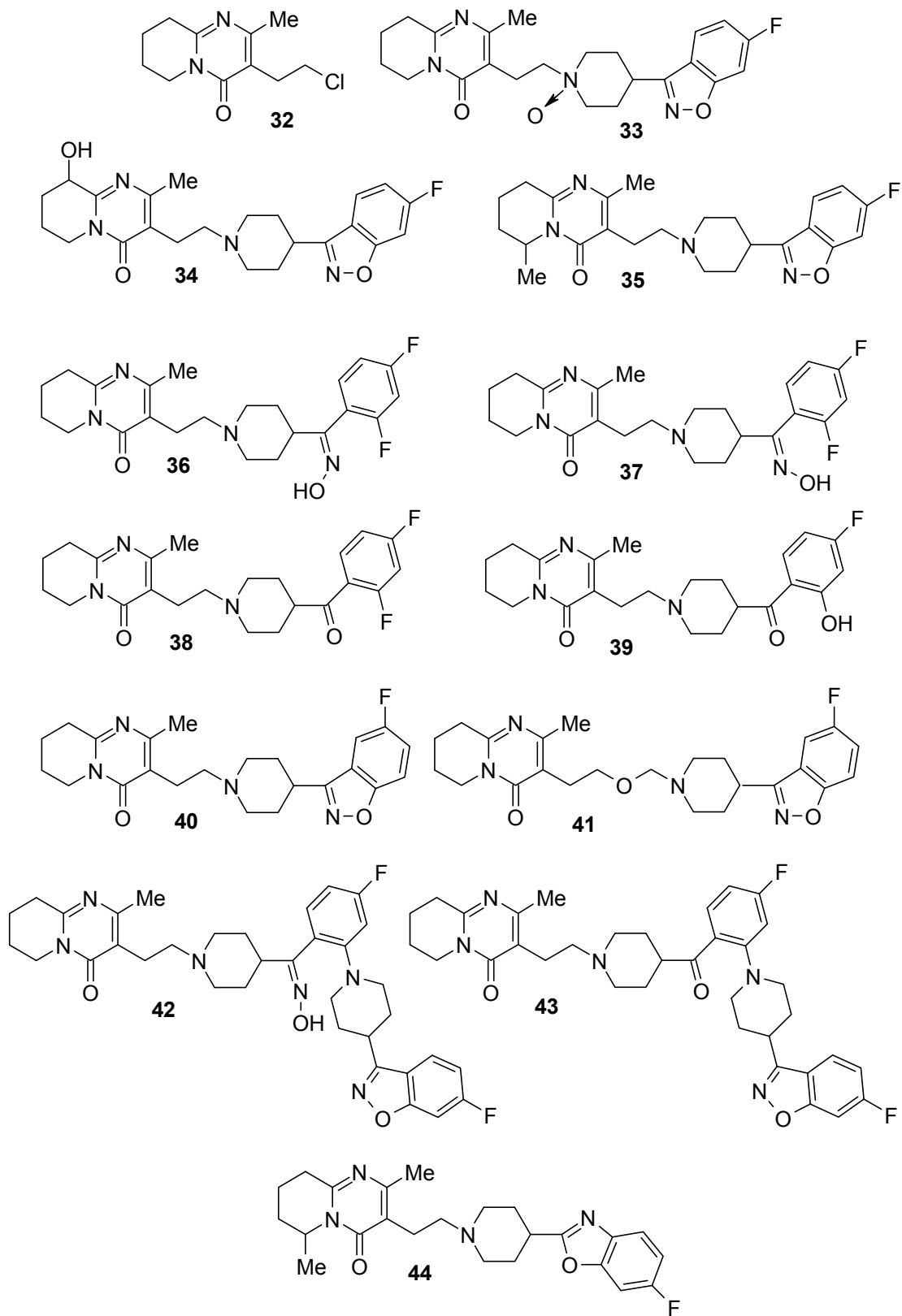
HPLC methods for the separation of enantiomers of paliperidone on an α1-acid glycoprotein (06MI9) and on Chiral-AGP (07MI8) columns were developed

Water solubility of risperidone base was increased by salt formation with saccharine (08CGD3483). Dissolution of risperidone tablets were determined by HPLC (06MI4). That of sustained release paliperidone was investigated in 0.001 M HCl (06ANA181).
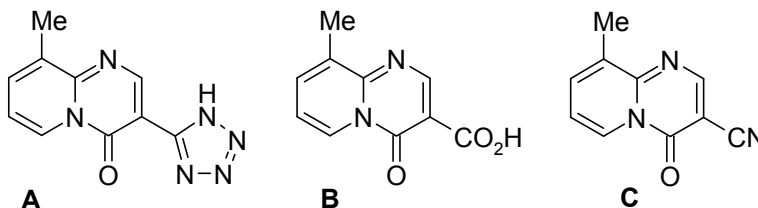
$$PDR = P_{B\ to\ A}/P_{A\ to\ B}$$

	$P_{A\ to\ B}$ 10^{-6} (cm/s)		$P_{B\ to\ A}$ 10^{-6} (cm/s)		PDR
A	4.7	0.2	26.4	0.5	5.7
B	19.0	3.5	18.6	2.1	1.0
C	19.2	0.5	20.1	1.4	1.0

While **A** tetrazole shows asymmetric permeability in Caco-2, this phenomenon was not observed with **B** carboxylic acid and **C** nitrile derivatives (06JPS717).

Compatibility and stability of risperidone with soft-drinks were investigated by isothermal titration microcalorimetry (06JTA681).

The lipophilicity of risperidone was determined by RP-TLC using RP-18-HPTLC plates (08MI5). The retention behavior of risperidone in different normal-phase TLC (06MI1), high pressure TLC (0808JLC1913) and in supercritical fluid chromatography (08JCH(A)186) was investigated. Risperidone was determined by a TLC method in formulated products (09CHR393). A sensitive and rapid liquid chromatographic-tandem mass spectrometry methods were developed for simultaneous quantification of

risperidone and its active metabolite 9-hydroxyrisperidone in rat plasma (07RCM920) and rat brain homogenate (07JC(B)276).

An isocratic reversed-phase HPLC method was developed for the separation of risperidone and its main metabolite, the 9-hydroxy derivative, from other psychotropic drugs (06JPB333). Risperidone and its active metabolite, 9-hydroxyrisperidone, were simultaneously determined in biological fluids by rapid and sensitive LC/tandem mass spectrometry methods (06RCM2104, 07TAL360, 08MI7, 09DMD787, 09JCH(B)2589), and by HPLC methods (07ANB235, 08CHR321, 08JCH(B)8, 09BCH929). 2,7-Dimethyl 3-{2-[4-[6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidyl]ethyl-4H-pyrido[1,2-a]pyrimidin-one was used as internal standard at the determination of risperidone and paliperidone in biological samples (09BCH929). Risperidone was determined by a differential pulse polarographic method (06CCA541) in pharmaceutical formulations. Risperidone and enantiomers of 9-hydroxyriperidone were determined in human plasma by a LC-MS/MS methods (06MI5, 07JC(B)497). An optimized sample preparation and chromatography was developed to minimize matrix effects in bioanalytical LC/MS/MS assays for determination of risperidone and 9-hydroxyriperidone (07JC(B)22). The bioequivalence of risperidone tablets was studied by HPLC/MS method (06MI6). Enantiomers of 9-hydroxyriperidone was separated by both a HPLC and a capillary electrophoresis method (07JC(A)228).

Extractive colorimetric methods (08CPB1092) and spectrophotometric methods (08MI8) were developed for the determination of risperidone in pure and in its formulated product (tablet).

Retention behavior of risperidone was investigatedon different plates with mixtures of phosphate buffer and six modifiers (acetone, MeCN, dioxane, EtOH, MeOH, THF) as mobile phases (07MI1).

Diverse marketed central nervous system-active drugs, among them risperidone and paliperidone, were tested in three P-glycoprotein in vitro assays and their permeability were measured in two in vitro models to predict the in vivo interactions of P-glycoprotein with drugs in the central nervous system (08DMD268).

Behavior of risperidone was characterized by liquid chromatography-electrospray ionization-mass spectrometry, ion trap mass spectrometry, gas chromatography-flame ionization detection and polarographic methods (07TAL755). An analytical method was developed for the simultaneous separation of risperidone and the enantiomers of 9-hydroxirisperidone using cyclodextrin-electrokinetic chromatography in the dual cyclodextrins mode using anionic and neutral cyclodextrins at acidic pH 2.5 (07ELP2683).

Risperidone and paliperidone were also measured, among other CNS-active drugs, on different in vitro P-glycoprotein assays to predict the in vivo interactions of P-glycoprotein with drugs in the central nervous system (08DMD268).

2. Theoretical Calculations

Quantitative structure-property relationship models that can predict the pK_a values of neutral and basic drugs, including risperidon, were developed. The predicted pK_a value of risperidon is 7.757 and 7.534 with a heuristic model and radial basis function neural networks, respectively (05PR1454). Its experimental pK_a value is 8.30.

Risperidon is a substrate of P-glycoprotein, but it was predicted to be an inhibitor by a GRIND-based descriptor model (05MP33). Different QSAR studies were carried out to predict hERG potassium channel affinity of compounds, among them risperidone (06BMC3153, 06JCI392, 06JCI1371, 08BMC6252, 08CHJ2125, 08QSC1305, 09EJM1926, 09JCI247) and paliperidone (08QSC1305, 09JCI247), too. A structure-based virtual screening model was developed to estimate the IC_{50} value of a wide range of ligands (including risperidon too) for the hERG potassium channel (07BBR889). Predictive quantitative structure-toxicity and toxicophore models were developed for a diverse series of hERG K^+ channel blockers, including risperidone, too (08JGM966).

Risperidon was also included into a group of compounds to analyze the scaffold diversity of commercially available screening collection (06JCI512). An in silico P450 profiler based on pharmacophore models was developed and validated by using a set of drugs, including risperidone, too (06CDDT1). Paliperidone was also used, among other drugs to predict cytochromes P450 2D6 and 1A2 inhibition (06JMC6231).

Blood-to-plasma concentration ratio of drugs, including risperidone, was predicted well by artificial neural networks model (09EJP544).

A data set of 130 diverse compounds, including risperidone, was used to generate a renal clearance model using a classical Volsurf approach (06JCI1312). A topological substructural molecular design approach was developed to classify P-glycoprotein substrate/nonsubstrate compounds. Risperidon was also applied in this development (06JPS589).
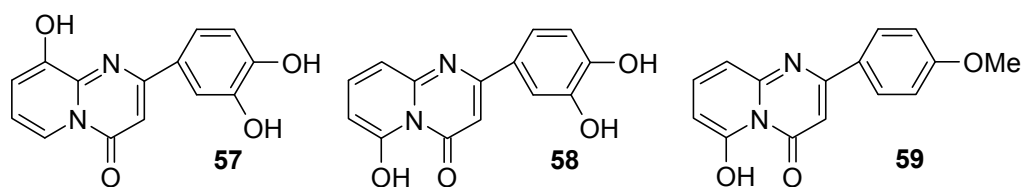
The theoretical binding mode of compounds **57**-**59** obtained by docking simulations into the active site of human aldose reductase crystal structure was fully consistent with the structure – activity relationship (07JMC4917).

Different new approaches, boosted regression trees and two-step boosted regression trees (07MI7), a method based on ab initio calculated quantum chemical descriptors (08JMG1223) and biopartitioning micellar chromatograpy system (09JCH(A)5190) were evaluated for modeling and predicting the blood-brain barrier passage of drugs including risperidone, too. Blood-brain partitioning of risperidone and paliperidone was predicted by a chemometric method called genetic algorithm variable selection (08QSC704). A combinatorial quantitative structure-activity relationship analysis was carried out for a set of 159 compounds, including also risperidone and paliperidone, with known blood-brain permeability data (08PR1902).

Compound **156** was identified as a potential novel glycogen synthase kinase-e inhibitor hit by a sequential virtual screen (08BMC636).
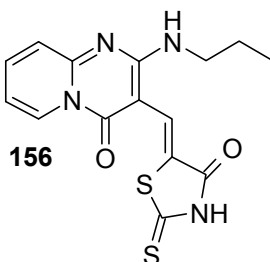
Risperidone was included into a test set of compounds at the development a hologram QSAR model for the prediction of human oral bioavailability (07BMC7738).

A physiologically based modeling approach was developed for predicting metabolism, tissue distribution, and bioavailability in rat for a structurally diverse set of compounds, including risperidone and paliperidone, too (07DMD649). Risperidon was also included into a set of drugs to predict their human pharmacokinetics by physiologically based pharmacokinetics models (07DMD1766).

Multiple pharmacophore models predict that risperidone a P-glycoprotein substrete (07JCI2429).

2-Methylthio-3-phenylsulfonyl-4-imino-4*H*-pyrido[1,2-*a*]pyrimidine was selected by a virtual screening based on a ligand-based pharmacophore model as a potent serotonin 5-HT_6 receptor antagonist (08JCI197).

Experimental blood-brain partition coefficients for a diverse set of drug, including risperidone and paliperidone, are correlated with computed structural descriptors using CODESSA-PRO and ISIDA programs to give statistically significant QSAR models (06BMC4888). Risperidone was also included in a set of drugs to develop a QSAR model for the prediction of blood - brain barrier permeability (07JCC1252) and to develop a high-throughput screening of drug-brain tissue binding and in silico prediction for assessment of central nervous system drug delivery (07JMC4606, 09JMC1693). A supervised artificial neural network model has been developed for the accurate prediction of blood-brain barrier partition of a structural diverse set of compounds, included risperidone, too (08QSC586). Risperidone was also included intro a set of structurally diverse molecule to predict human plasma protein binding by hologram QSAR (07DLD502).

A quantitative structure-activity relations approach was used to explore relationship of drug-induced neutrophil immaturity and haemotological toxicity to physicochemical characteristics of 10 antipsychotic drugs, including risperidone, too (09. Pharmacophore representation concept was used to elucidate molecular similarity of dopamine antagonists, including risperidone, too (07JCAM239).

Magnetic criteria, magnetic susceptibility isotropic and nucleus-independent chemical shifts calculated with B3LYP levels at the 6-31G** basis set were used to evaluate aromaticity of a set of 29 planar bicyclic π-electron systems: naphthalene and its mono- and di-aza- (among them 9*aH*-pyrido[1,2-*a*]pyrimidine), -phospha-derivatives (07IJQ1846).

The complexation of risperidone and paliperidone with seven cyclodextrines was studied by affinity capillary electrophoresis and NMR for acidic pH 2.5 and physiological pH 7.4 (08JCH(A)185). Melting point of risperidon was predicted using principal component-genetic algorithm–artificial neural network (08BKC833).

3. UV Spectroscopy

Risperidone formed a charge transfer complex with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (06OJC139) and tetracyanoethylene (06OJC95). Their stability constants and ultraviolet spectra were determined.

4. IR and Raman Spectroscopy

Structures of 2-oxo-1,2,3,4-tetrahydropyrido[,2-*a*]pyrimidinium chloride (08JST244) and 1-methyl-2-oxo-1,2,3,4-tetrahydropyrido[,2-*a*]pyrimidinium bromide (07JST107) have been confirmed by Raman and Fourier transformed infrared and NMR spectra, and DFT (B3LYP) calculations.

A FT-Raman spectroscopic method was developed for non-destructive quantitative analysis of risperidone in commercially available film-coated tablets (08JPB631)

5. NMR Spectroscopy

2-Oxo-1,2,3,4-tetrahydropyrido[,2-*a*]pyrimidinium chloride (**32**) shows a ring-chain tautomerism in wet DMSO-d_6 (08JST244).
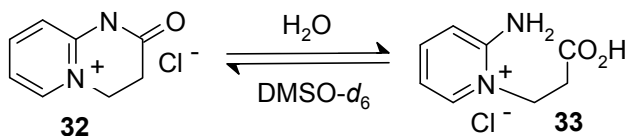

Structures of two impurities **20** and **21**, isolated from risperidone, were characterized by mass and ^{1}H and ^{13}C NMR spectroscopy (06JPB598).
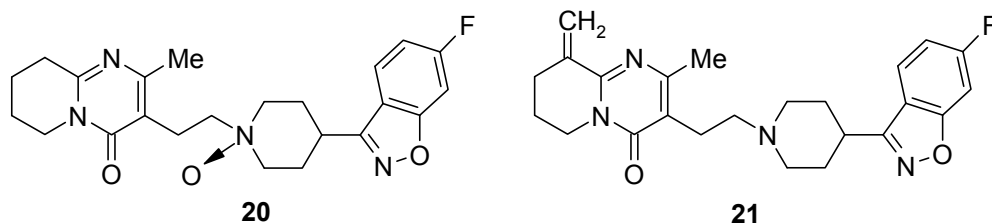

^{1}H NMR investigations were applied to study the mechanism of racemization of enantiomers of paliperidone (09TA1125). All results confirm that racemization occurs via an imine-enamine tautomerism.

A ^{1}H NMR NOESY experiments on **23** *cis*-5*aH*,9*H*-hexahydropyrido[2,1-*b*]quinazoline-9-carboxylate showed a strong spatial relationship between 5*a*-H and 9-H protons. This was not observed with **22** *trans*-5*aH*,9*H* derivatives (06OL239).
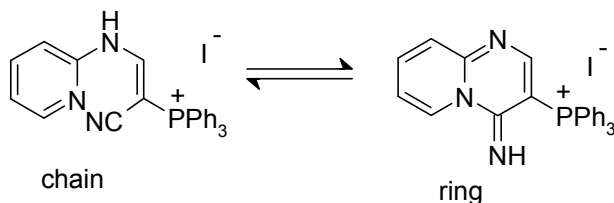

In DMSO-d_6 only the signals of the ring tautomer could be identified (05RJC527). The possible ring – chain tautomerism was not investigated in CDCl$_3$, which usually favoured for the ring tautomers (96JOC).

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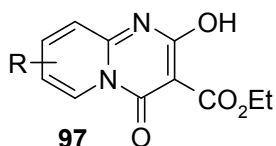
The ^{1}H, experimental and calculated ^{13}C NMR spectra of compounds **97** have indicated that these compounds exist mainly in 2-hydroxy tautomer form in DMSO-d_6 solutions (07CHE729).

^{1}H and ^{13}C NMR spectra of **51** 2-oxo-1,2,3,4-tetrahydropyrido[1,2-*a*]pyridinium chlorid revealed an ring – chain tautomerism in DMSO-d_6, and the ring form was the main component in the equilibrium mixture (07ARK55).
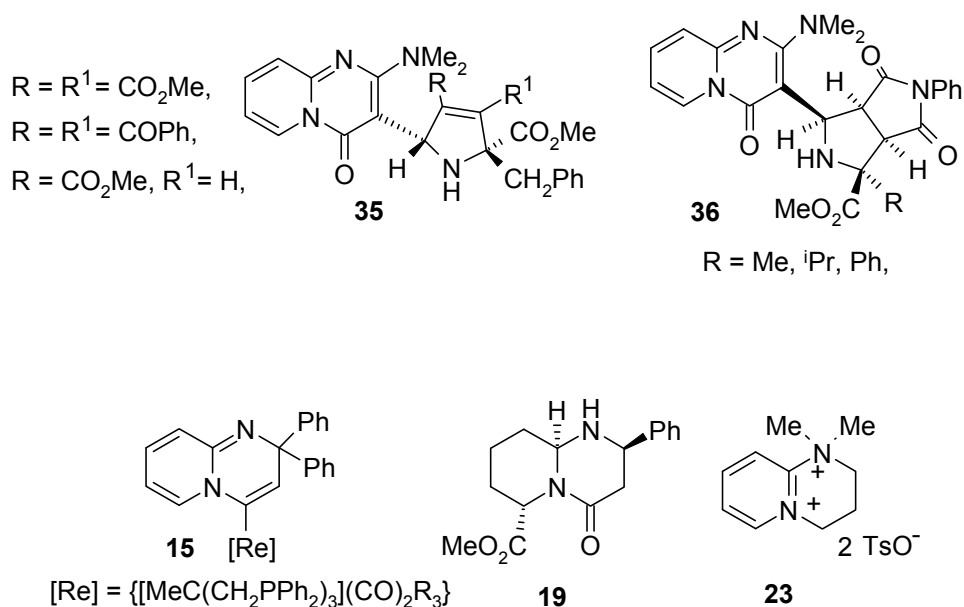

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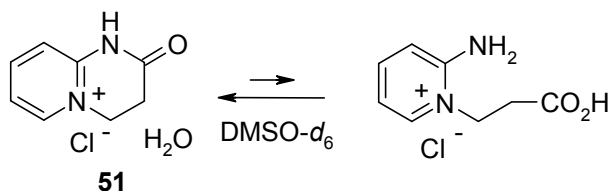
6. Mass Spectrometry

A tandem mass spectrometric investigation of the collosion-induced dissociation of risperidone and its 9-hydroxy metabolite was carried out. (07RCM2031). A selective and sensitive time-of-flight mass spectrometers method was validated to determine risperisdone and paliperidone in rat plasma using midazolam as an internal standard (08JLC2737). Structures of **97** 2-hydroxy-4*H*-pyrido[1,2-*a*]pyridine-3carboxylates were characterized by mass spectrometric analysis, too (07CHE729).

7. X-Ray Investigations

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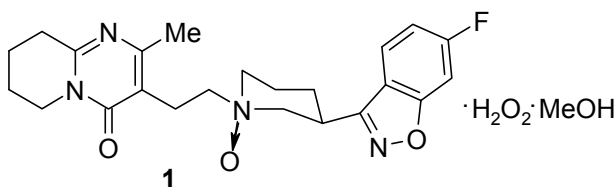
X-Ray investigation of **1** risperidone *N*-oxide hydrogen peroxide methanol solvate revailed, that the piperidine ring adopts a chair conformation, while the tetrahydropyridine ring has a sofa conformation (05AXE2515). Crystal structure of risperidone hydrochloride 2.5-hydrate [06AX(E)768] and crystalline form B of risperidone [06AX(E)3527] were determined by single crystal X-ray diffraction investigation. The tetrahydropyridine moiety of the bicycle adopts a sofa conformation.

Structures of **35** and **36** 3-substituted 2-dimethylamino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones were confirmed by single-crystal X-ray analysis (07TL941, 07T1630).

R = R^1= CO$_2$Me,
R = R^1= COPh,
R = CO$_2$Me, R^1= H,

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R = Me, ^{i}Pr, Ph,

15   [Re]

[Re] = {[MeC(CH$_2$PPh$_2$)$_3$](CO)$_2$R$_3$}

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23

2 TsO$^-$

The structures of **23** disalt (09JA9174), **15** 2*H*-pyrido[1,2-*a*]pyrimidine (06OM416), 9-benzoyl-7-nitro-6-phenyl-1,2,3,47,8-hexahydro-6*H*-pyrido[1,2-*a*]pyrimidine (08SL1357), 2-morpholino-9-trifluoromethylsulfonyloxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (07OBC2670), 3-bromo-7-chloro-2-(2-methylprop-1-enyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (08SL2836), 3-bromo-7-chloro-2-[2,2-bis(ethoxycarbonyl)ethyl]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (08SL2836), ethyl 2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-carboxylate (07CHE729), methyl 3-pivaloyloxy-7-bromo-4-oxo-4*H*-pyrido[1,2-

a]pyrimidin-2-carboxylate (08TL6556), *N*-(2-diethylaminoethyl)-8-methyl-2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-carboxamide (08CHE50), *N*-[(2-methoxyphenyl)methyl]-8-methyl-2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-carboxamide (08CHE565), 9-(4-methoxybenzoyl)-1,2,3,4-tetrahydro-6*H*-pyrido[1,2-*a*]pyrimidin-6-one (07AX(E)3186), 6-imino-8-methylthio-9-benzoyl-1,2,3,4-tetrahydro-6*H*-pyrido[1,2-*a*]pyrimidine-7-carbonitrile (07SL761), and dimethyl 2-[*N*-cyclohexyl-*N*-(ethoxycarbonylcarbonyl)amino]-4*H*-pyrido[1,2-*a*]pyrimidine-3,4-dicarboxylate (07TL4195, 07T11135) were characterized by X-ray crystallography. The stereostructure of **19** (2*R*,6*S*,9*aR*)-4-oxoperhydropyrido[1,2-*a*]pyrimidine-6-carboxylate was also determined by X-ray crystallography (06OL239). Two conformers are present in the single crystal of 1-methyl-2-oxo-1,2,3,4-tetrahydropyrido[,2-*a*]pyrimidinium bromide (07JST107)

Structures of two impurities of risperidone, **20** and **21** were unambiguously confirmed by single crystal X-ray diffraction investigations (06JPA598). Structures of 2-methyl-3-(2-chloroethyl)-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (06AX(E)3730), 3-ethyl-2-(4-methylthiazol-2-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (06T12064), 9-(4-methoxybenzoyl)-1,2,3,4,7,8-hexahydro-6*H*-pyrido[1,2-*a*]pyrimidin-6-one (06AX(E)3040) have been assigned by X-ray measurements.

X-ray powder diffraction study proved that polymorph A of risperidone was stable during the manufacturing process and after a storage period of 2 years (07TAL1382).

Distribution of risperidone on and in thin polymer coatings was investigated by a TOF-S-SIMS method (06ASS6628).
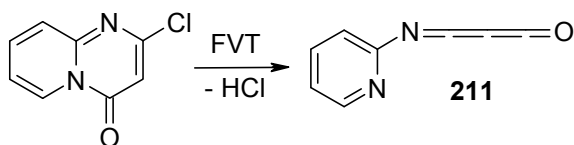
B. Reactivity

1. Ring Opening

Heating **37** 4-aryl-2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidines in EtOH gave **38** ring opened products (05RCB2841)
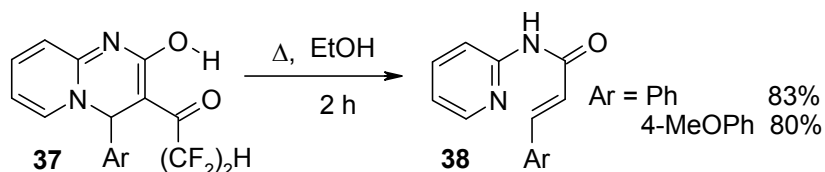
2-Chloro-4*H*-pyrido[1,2-*a*]pyridine-4-one was used as precursor to synthesize 211 iminopropadienone by flash vacuum thermolysis (FVT) (2008JPC(A)9742).


2. Oxidation, Dehydrogenation

Reaction of methyl 3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate with 2,3-dichloro-4,5-dicyano-1,4-benzoquinone in dioxane at 60 °C for 1h, then treatment of the reaction mixture with 5 equiv. NEt$_3$ for 4h gave 6,7-dihydro derivative (07WOP2007/039218). 3-Hydroxy-4-oxo-6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate and was dehydrogenated over 10% Pd/C catalysts by heating in *o*-xylene for 48 h to 3-hydroxy-4-oxo-6,7-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate. Dehydrogenation of *N*-(4-fluorobenzyl)-3-hydroxy-9-methylamino-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxamide trifluoroacetate over 10% Pd/C catalyst in the presence of Hüning's base in o-xylene at 156 °C for 7 h afforded *N*-(4-fluorobenzyl)-3-hydroxy-9-methylamino-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxamide.

2-Methyl-3-(2-chloroethyl)-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one and risperidone were enzymatically hydroxylated in the position 9 by using oxidoreductase enzymes (08WOP2008/144073).

Instead of the oxidation of 9-CH$_2$ group of methyl 3-benzoyloxy-6,7,8,9-tetrahydro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate to a carbonyl group with PDC, PCC, CrO$_3$, MnO$_2$ or KMnO$_4$ degradation occurred (07TL6552).
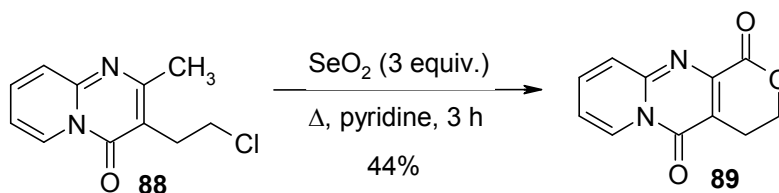
Oxidation of 2-methyl-3-(2-chloroethyl)-4*H*-pyrido[1,2-*a*]pyrimodin-4-one (**88**) with SeO2 in boiling pyridine yielded **89** tricyclic derivative (08TL1301).

Treatment of 2-methyl-3-vinyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one with 9-borabicyclo[3.3.1]nonane in THF at 60 $^{\circ}$C for 3 h, then at room temperature pyridinium chlorochromate in CH$_2$Cl$_2$ was added to the reaction mixture, which was heated at 90-98 $^{\circ}$C for 3 h gave 3-(2-oxoethyl) derivative in 53% yield (05APR1019).

Oxidation of risperidon with 30% H$_2$O$_2$ in MeOH gave **1** risperidone *N*-oxide hydrogen peroxide methanol solvate (05AXE2515).

6,7,8,9-Tetrahydro-2*H* derivative was obtained when 4-(4-fluorophenyl)-9-[3-methoxy-4-(4-methylimidazol-1-yl)benzylidene]-3,4,6,7,8,9-hexahydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one was reacted first with LDA followed by the addition of PhSeBr at -78 °C, then the reaction mixture was treated with H$_2$O$_2$ at ambient temperature (08WIO2008/153793).

3. Hydrogenation, Reduction

Catalytic reduction of **23** disalt yielded **24** ring opened disalts (09JA9174). Reduction with LiAlH$_4$ gave **25** 2*H*,6*H*-3,4-dihydropyrido[1,2-*a*]pyrimidinium salt.
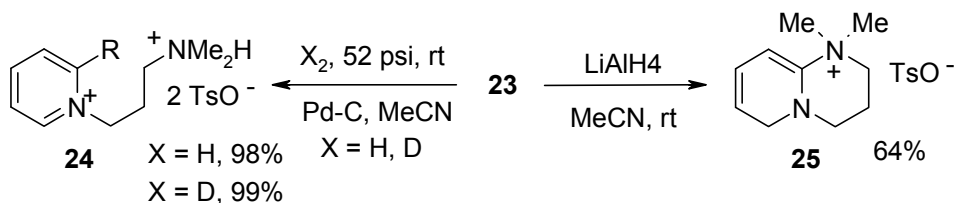
Reductive alkylation of a 9-amino-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate with aldehydes in the presence of NaBH$_3$CN yielded 9-alkylamino derivatives (09BML1930).

Catalytic reduction of methyl 3-benzyloxy-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate, furthermore that of 9-benzylamino derivatives of 3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate over Pd/C catalyst in MeOH gave 3-hydroxy and of 9-amino derivatives, respectively (07TL6552, 08JMC861). Reductive *N*-methylation of a diastereomeric mixture of 9-[(*S*)-α-methylbenzylamino]-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylates with H$_2$CO in the presence of NaBH$_3$CN in MeOH afforded 9-methylamino derivatives (07TL6552). A diastereomeric mixture of 9-[*N*-methyl-*N*-(*R*)-α-methylbenzylamino]-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylates was obtained by the reduction of a diastereomeric mixture of 9-formamido derivatives with BH$_3$-SMe$_2$ in THF at 0-45 °C.

Catalytical hydrogenation of methyl 2-vinyl-3-(1,3-dioxolan-2-yl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-8-carboxylate in MeOH over 10% Pd/C catalyst provided a 2-ethyl-3-(dimethoxymethyl) derivative in 98% yield (06BMC1993). That of 2-methyl-4*H*-

pyrido[1,2-*a*]pyrimidin-4-one in 6N HCl solution over Pd/C under a 125 psi pressure for 18 h provided 6,7,8,9-tetrahydro derivative in 73% yield (05APR1019).

9-Ethylamino derivative was obtained from *N*-(4-fluorobenzyl)-3-hydroxy-9-amino-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxamide by treatment with MeCHO and NaBH$_3$CN in a 1:1 mixture of CH$_2$Cl$_2$ and MeOH at room temperature (07WOP2007/039218).

Reduction of 2-butyl-3-(5-indolyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one with NaBh3Cn in glacial AcOH at ambient temperature gave 3-(5-indolinyl) derivative (08USP2008/0194616, 08WOP2008/097991). Treatment of (*R*)-2-butyl-3-{4-[3-pyrrolidinylamino]phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one with 37% H$_2$CO in THF in the presence of Et$_3$N, NaB(O$_2$CMe)$_3$H and catalytic amount of AcOH at room temperature for 16 h gave a 7 : 1 mixture of 3-{4-[(1-methyl-3-pyrrolidinyl)amino]phenyl and 3-{4-[methyl(1-methyl-3-pyrrolidinylamino]phenyl derivatives.

A side-chain aromatic nitro group of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones was reduced to amino group with Zn powder in AcOH (06WOP2006/109081).

Catalytic hydrogenation of 9-benzyloxy-2-methyl-3-(2-chloroethyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one in acidified aqueous MeOH over 5% Pd/C catalyst gave 9-hydroxy-6,7,8,9-tetrahydro derivative in 73% yield (08WOP2008/128436).

4. Reactivity of the Ring Carbon Atoms

Reaction of *anhydro*-(2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidinium)hydroxyde
and EtOAc in benzene in the presence of catalytic amount of piperidine and AcOH at
room temperature overnight afforded 3-acetyl-2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one in 80% yield (06MI10).

Condensation of **22** 2,4-dimethylpyrido[1,2-*a*]pyrimidinium salt with **23** methosulphates in Ac$_2$O in the presence of Et$_3$N at ambient temperature gave **24** dyes (07DP466).
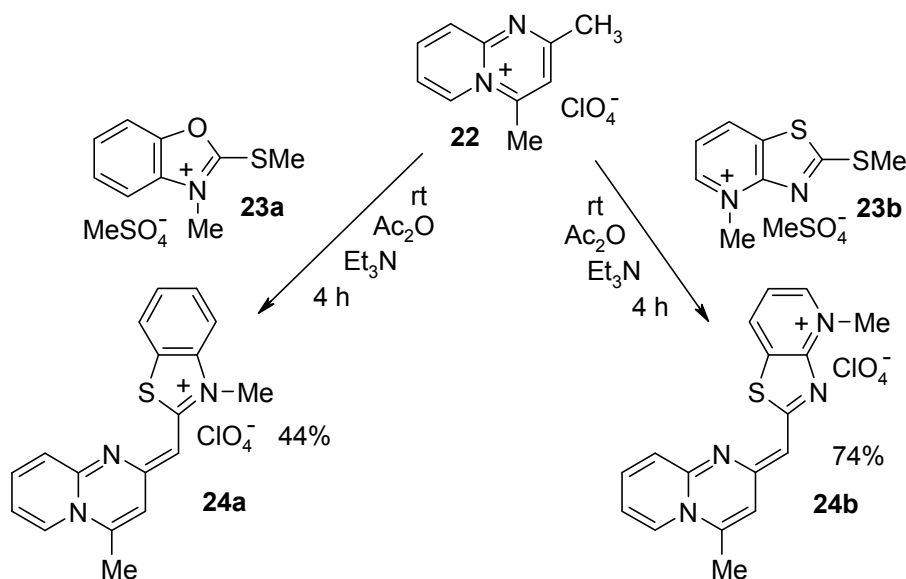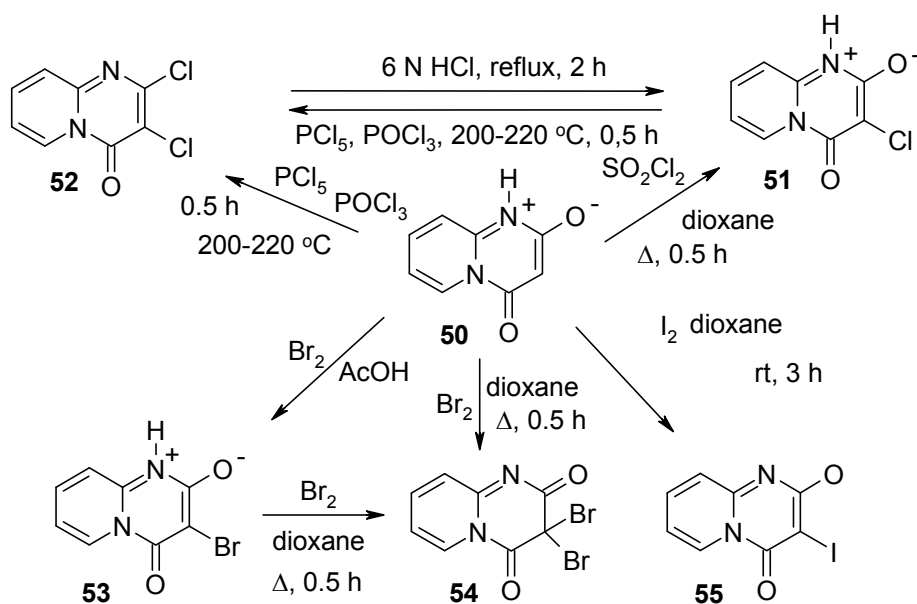

Reactions of 3-unsubstituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones with Br$_2$ (05APR1019, 08SL2836, 08USP2008/0194616, 08WOP2008/097991) and NBS yielded 3-bromo derivatives (07WOP2007/002701, 08BMCL688, 08USP2008/0194616, 08WOP2008/097991). 3-Bromo-2-propoxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was prepared from the 3-unsubstituted bicycle with NBS in CHCl$_3$ (08USP2008/0194616, 08WOP2008/097991).

Bromination of methyl 3-benzoyloxy-6,7,8,9-tetrahydro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate and methyl 9-methyl-3-benzoyloxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate with NBS under radical conditions in CCl$_4$ gave 9-bromo (07TL6552, 08JMC861) and 9-bromomethyl (09BML1930) derivatives, respectively. 9-Bromo derivative was reacted with secondary amines in DMF and (*S*)-(-)-1-phenylethylamine to yield 3-hydroxy-9-disubstituted amines (08JMC861) and 9*a*-diastereomers of methyl 9-[(*S*)-α-methylbenzylamino]-3-hydroxy-6,7,8,9-tetrahydro-4-

oxo-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate (07TL6552), respectively. Polar protic solvents (MeOH-H$_2$O, 7:3) and low temperature (-30 °) increased the diastereoselectivity. Reaction of methyl 9-bromomethyl-3-benzoyloxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate under Staudinger conditions with NaN$_3$ followed by treatment with PBu$_3$ afforded 9-aminomethyl derivative, which contained a small amount of 9-[(benzoylamino)methyl] impurity, formed during this reaction by migration of the benzoate from position 3 to the newly formed amino group (09BML1930). 9-Bromomethyl group was reacted with morpholine and 4-acetylpiperazine, too

Reactions of *anhydro*-(2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidinium)hydroxyde (**50**) with SO$_2$Cl$_2$, Br$_2$ in AcOH, and I$_2$ gave **51** 3-chloro, **53** 3-bromo and **55** 3-iodo derivatives (05MI2, 07HC19). Treatment of either **50** or **55** with Br$_2$ in boiling dioxane yielded **54** 3,3-dibromo derivative. Heating **50** and **51** in a mixture of PCl$_5$ and POCl$_3$ at 200-220 °C provided **52** 2,3-dichloro derivative, which could be converted back into **51** by heating in 6 N HCl.

Vielsmeier-Haack formylation of a 3-unsubstituted 2-hydroxy-4-oxo-4*H*-pyrido[1,.2-*a*]pyrimidine-8-carboxamide with a mixture of $(COCl)_2$ and DMF in CH_2Cl_2 at 0 °C gave 3-formyl derivative which was condensed with 2-[1-(4-methoxybenzyl)tetrazol-5-yl]acetic acid in the presence of piperidine in boiling pyridine to provide a 3-{2-[1-(4-methoxybenzyl)tetrazol-5-yl]vinyl derivative in 71% yield(07BMC7087).

Vielsmeier-Haack formylation of a 2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one with $POCl_3$ and DMF at 80 °C gave 2-chloro-3-formyl derivative (06BMC1993). Chloro atom was changed for secondary amino group with secondary amines in the presence of NEt_3 in MeOH at ambient temperature in good yields (07T1630). Reaction of the formyl group with (*tert*-butoxycarbonylmethylene)triphenylphosphorane yielded a 3-[(1*E*)-(3-tert-butoxy-3-oxoprop-1-en-1-yl)-2-chloro derivative (06BMC1993). The formyl group was converted into a 1,3-dioxolan-2-yl moiety by treatment with $HOCH_2CH_2OH$ in boiling toluene in the presence of Amberlyst® 15. 3-Formyl group was prepared from the 3-(1,3-dioxolan-2-yl) group by treatment with AcOH in aqueous acetone.

Dropwise treatment of a solution of 7-chloro- and 7-bromo-2-chloromethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones in conc H_2SO_4 with 65% HNO_3 at 0° C provided 3-nitro derivatives in good yields (08H(75)925).

Bromination of *N*-[(4-fluorophenyl)methyl]-3-pivaloyloxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxamide in a 3:1 mixture of MeCN and AcOH with NBS for 4 days provided 7-bromo derivative (07WOP2007/039218).
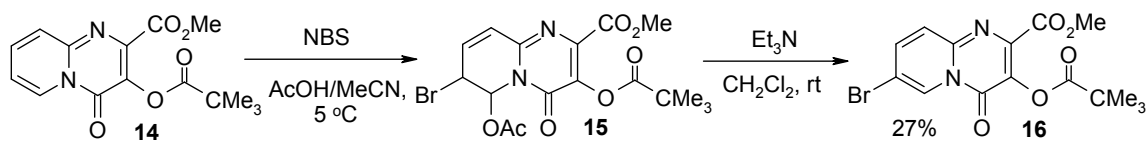
Bromination of **14** 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate did not occur with Br$_2$, but **15** addition product was obtained with NBS in a mixture of AcOH and MeCN. Treatment of **15** with Et$_3$N gave **16** 7-bromo derivative (08TL6556).

Heating compounds **36** in MeCN in the presence of PPTS or AcOH gave mixtures of **40** 2-amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones and **41** pyrrolo[3,4-*c*]pyrrole-1-carboxylates (07T1630). Similar reaction mixtures were obtained when one-pot three component reaction mixtures containing **39** 3-formyl derivative, α-amino acid methyl ester and *N*-phenylmaleimide were heated under similar reaction conditions.
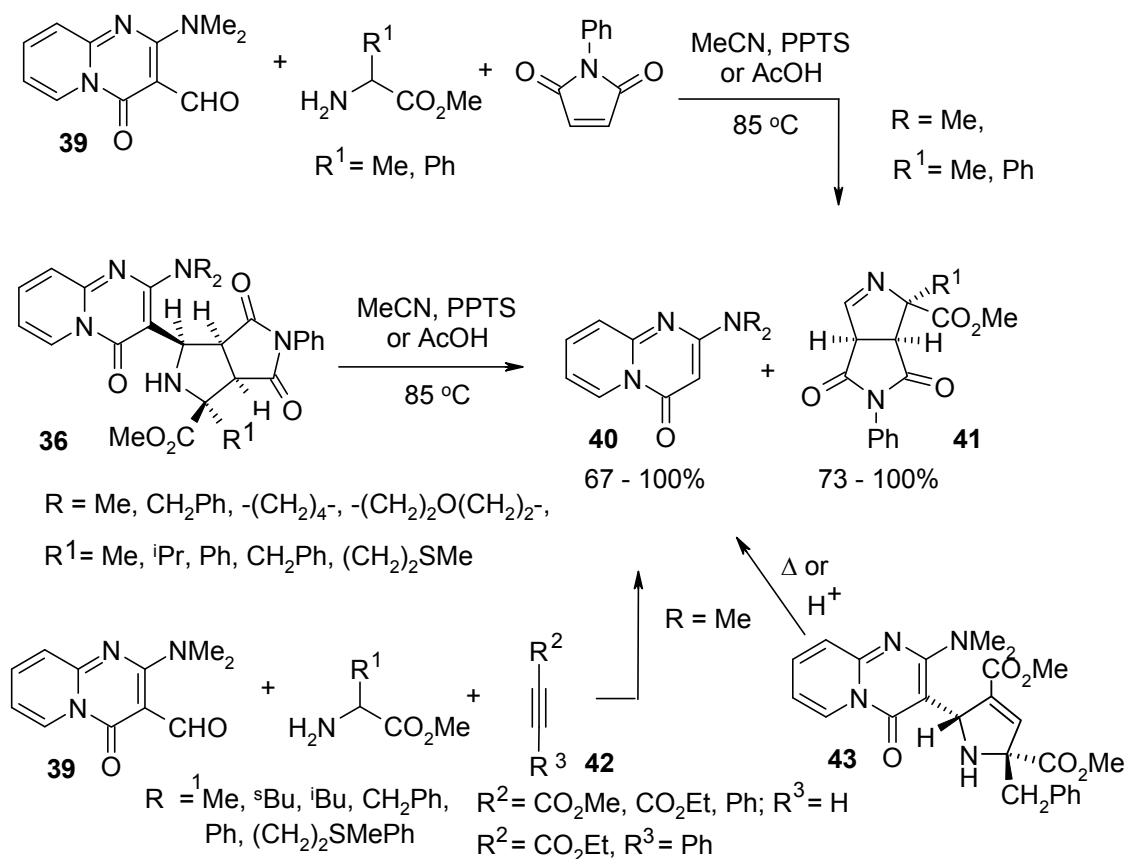
Beside 2*H*-pyrrolidine derivatives compound **40** was also obtained from **43** and one-pot three component reactions of **39** 3-formyl derivative, α-amino acid methyl ester and **42** acetylene derivatives (2007TL941).

Reaction of **34** 2-methylthio-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbonitriles with amines, $H_2NNH_2 \cdot H_2O$, NH_2OH and acetamidine·HCl yielded **35** 2-amino derivatives, and **36-38** tricyclic compounds, respectively (08MI10).
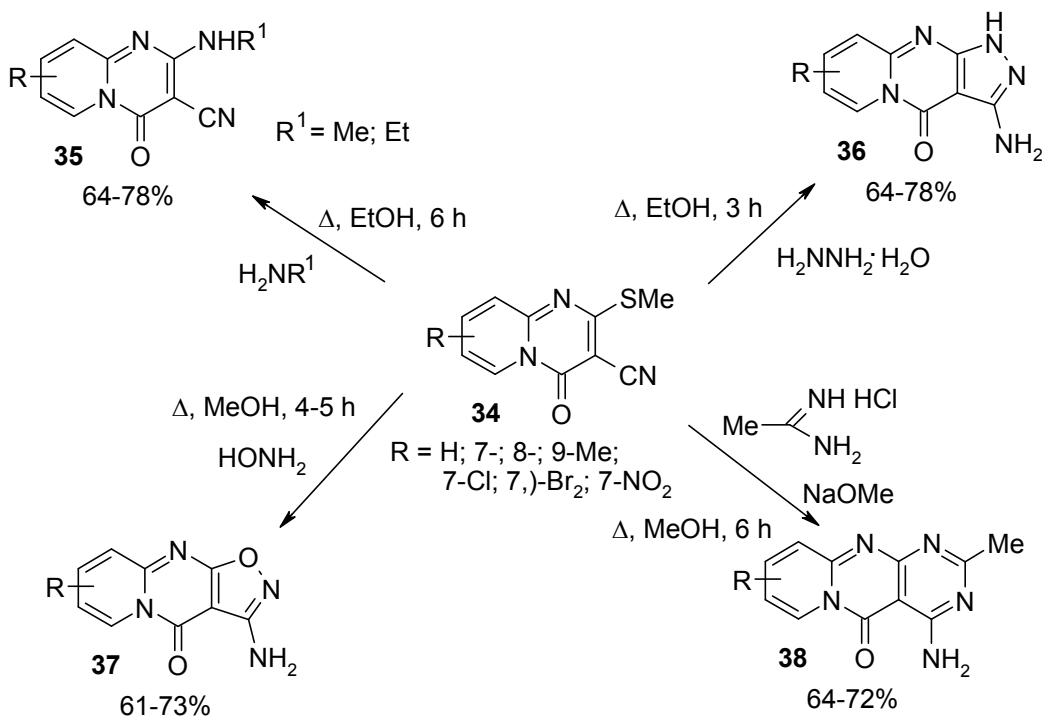
Oxidative Heck-type alkenylation of **39** 1,2,3,4-tetrahydro-6*H*-pyrido[1,2-*a*]pyrimidin-6-one leaded to exclusive formation of **40** 7-(2-substituted vinyl) derivatives (09OL2639). Similar reaction with 2-vinylpyridine failed. It is likely, that palladation is followed by formation a stable chelate **41**, involving the pyridine lone pair and the adjacent π-bond, which prevented the further reaction. ^{1}H NMR spectra indicated that in DMSO-d_6 cca. 16% of **42** formed from **40** in the presence of 20 mol % of $Pd(OAc)_2$.
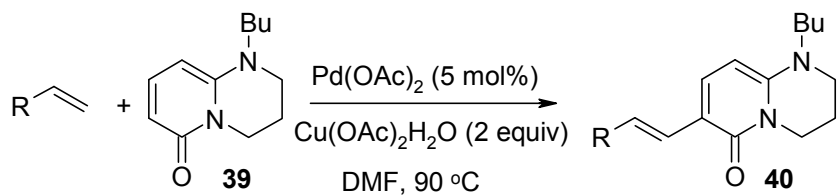
R = COMe 89%; R = CO$_2$Et 90%; R = CO$_2$tBu 93%;

R = Ph 83%; R = ciklocexil 85%, R = 4-pyridyl 86%
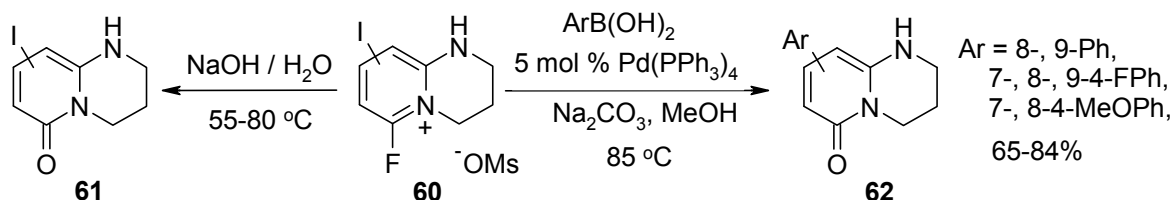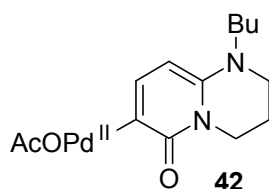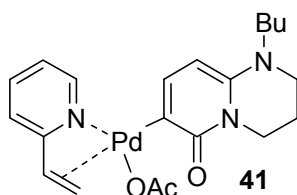
Hydrolysis of 8-iodo derivative of **60** tetrahydropyrido[1,2-*a*]pyrimidinium mesylate afforded **61** 8-iodo-1,2,3,4-tetrahydro-6*H*-pyrido[1,2-*a*]pyrimidin-6-one (07OL5175). Under similar reaction conditions 9-iodo derivative of **60** yielded a mixture of 9-iodo derivative of **61** and the deiodinated 1,2,3,4-tetrahydro-6*H*-pyrido[1,2-*a*]pyrimidin-6-one. 7-Iodo derivative **60** (7-I) gave only the deiodinated 1,2,3,4-tetrahydro-6*H*-pyrido[1,2-*a*]pyrimidin-6-one. Iodo atom of 7-, 8-, and 9-iodo derivatives **60** was easily changed for aryl groups in Suzuki-Miyaura coupling, and the quaternary salts were hydrolyzed to **62** aryl substituted 1,2,3,4-tetrahydro-6*H*-pyrido[1,2-*a*]pyrimidin-6-ones.

Reaction of 2-chloro-3-bromo-4*H*-pyrido[1,2-*a*]pyrimidin-4-one with NaOMe in boiling MeOH and with primary and secondary amines in boiling EtOH yielded 2-alkoxy and 2-amino derivatives, respectively (08USP2008/0194616, 08WOP2008/097991).

5. Reactivity of the Ring Nitrogen Atom

It was assumed, that the reaction of *anhydro*-(2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidinium)hydroxyde and ClCH$_2$CN under phase transfer conditions afforded mesoionic tricyclic compound (05MI2, 07HC19).
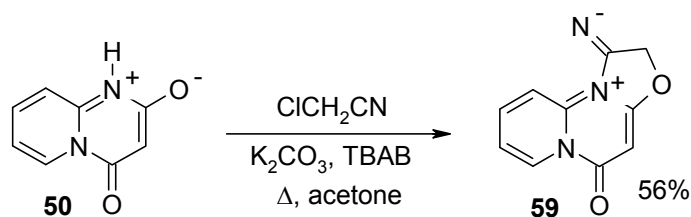

1-Allyl derivative was prepared in 58% yield when 1,2,3,4-tetrahydro-6*H*-pyrido[1,2-*a*]pyrimidin-6-one was treated with NaH, then with allyl bromide in boiling THF for 5 h (09OL2639).

6. Reactivity of Substituent Attached to a Ring Carbon Atom

Phase transfer alkylation of *anhydro*-(2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidinium)hydroxyde with MeI, EtI, PrBr, CH$_2$=CHCH$_2$Br, ClCH$_2$CO$_2$Me, BrCH$_2$CO$_2$Et, ClCO$_2$Et, epichlorohydrin, and 2-(2-bromoethyl)isoindole-1,3-(2*H*)-dione in the presence of K$_2$CO$_3$ and Bu$_4$NBr in boiling acetone for 4-8 h provided 2-*O*-alkylated products (05MI2, 07HC19). Reaction of *anhydro*-(2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidinium)hydroxyde with PrBr in the presence of Cs2CO3 in boiling acetone gave 2-propoxy derivative (08WOP/2008097991). When *anhydro*-(2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidinium)hydroxyde was heated with (COCl)$_2$ under reflux for 1 h 2-chloro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was obtained in 44% yield.

Reaction of 2,9-dihydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one and POCl$_3$ for 48 h at reflux gace 9-hydroxy-2-chloro derivatives in 60% yield (07OBC2670). The 2-chloro atom was changed for morpholino group when the chloro derivative was reacted with morpholine

in boiling EtOH for 18 h in 97% yield. 2-Morpholino-9-hydroxi-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was reacted with (CF$_3$SO$_2$)$_2$O in CH$_2$Cl$_2$ in the presence of NEt$_3$ at (-30)-(-20) °C to give 9-trifluorosuylfonyloxy derivative, which was involved in Suzuki reactions with (het)arylboronic acids in the presence of Pd(Ph$_3$)$_4$ in dioxane at 95 °C for 48 h provided 9-(het)aryl derivatives. Suzuki reaction of 2-substituted 3-bromo-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones with (het)arylboronic acids in the presence of Pd(Ph$_3$)$_4$ and 2M Na2CO3 in boiling 1,2-dimethoxyethane for 16 h provided 3-(het)aryl derivatives (08USP2008/0194616, 08WOP2008/097991).
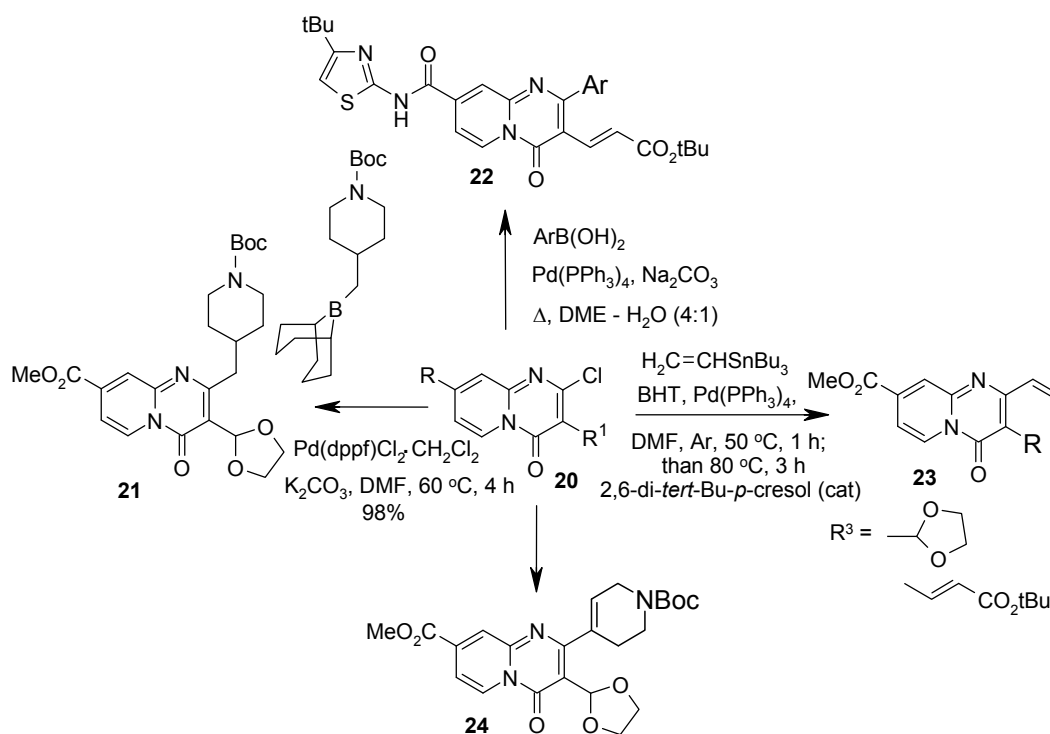
Scheme 1

Suzuki-Miyaura reactions of **20** 2-chloro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones afforded **21** 2-{[1-(*tert*-butoxycarbonyl)piperidin-4-yl]methyl}-, **22** 2-aryl derivatives (06BMC1993, 06BMC8506). Reaction of methyl 7-bromo-3-pivaloyloxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate and (2-morpholin-4-ylphenyl)boronic acid in the presence of

Pd(OAc)$_2$, dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine and K$_3$PO$_4$ in BuOH at 90 °C for 10 min gave 7-(2-morpholin-4-ylphenyl derivative) (07WOP2007/039218).

Stille reactions gave **23** 2-vinyl and **24** 2-[1-*tert*-butoxycarbonyl-1,2,5,6-tetrahydropiridin-4-yl] derivatives (Scheme 1) (06BMC1993). Stille reaction of 3-bromo-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one with tributyl(vinyl)stannane in the presence of P(PPh$_3$)$_4$ in toluene at 100-105 °C for 15 h afforded 3-vinyl derivative in 83% yield (05APR1019).

Bromination of 3-substituted 2-ethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones with NBS in α,α,α-trifluorotoulene at 90 °C for 3 days, and in boiling CCl$_4$ in the presence of benzoylperoxide gave 2-(1-bromoethyl) derivatives (07WOP2007/002701, 08BMCL688). 2-(1-Bromoethyl) derivatives were reacted with phthalimide in the presence of K$_2$CO$_3$ in DMF to give 2-(1-phthalimidoethyl) derivatives, which were converted into 2-(1-aminoethyl) derivatives by treatment with H$_2$NNH$_2$·H$_2$O in boiling EtOH overnight. Addition of ethylsulfonylethene to amino group of 2-(1-aminoethyl) derivatives afforded 2-(1-(2-(ethylsulfonyl)ethylamino]ethyl} derivatives, which were *N*-acylated with 2-[4-fluoro-3-(trifluoromethyl)phenyl]acetic acid in the presence of EDC, HOBt, and *N*-methylmorpholine in DMF. A 2-(1-aminoethyl) derivative was also obtained from a 2-{1-[*N*-(benzyloxycarbonyl)amino]ethyl} derivative by treatment with BBr$_3$ in CH$_2$Cl$_2$ (07WOP2007/002701).

Reaction of 3-amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**33**) with NaNO$_2$ in 6M HCl at 0 °C gave **34** diazonium chloride, which was converted into **35** 3-azido derivative by treatment with aqueous NaN$_3$ solution (08AJC107).
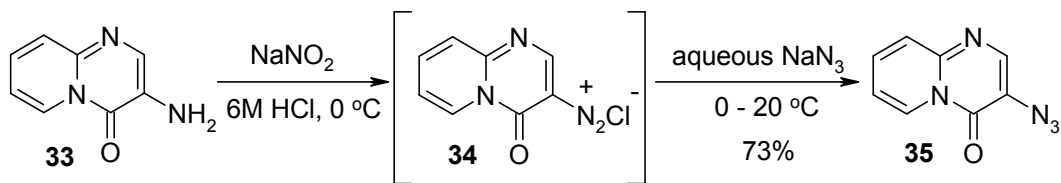
Hydroxy group of a 3-substituted 2-hydroxy-4-oxo-4*H*-pyrido[1,.2-*a*]pyrimidine-8-carboxamide was changed for different piperidine groups by treatment first with (PhO)$_2$P(O)Cl in the presence of Hüning's base at 0 °C in a solvent, then with different piperidine derivatives at 80 °C (07BMC7087). That of a methyl 3-hydroxy-6,7,8,9-tetrahydro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate was acylated with (PhCO)$_2$O in the presence of pyridine (07TL6552, 08JMC861) and Ac$_2$O in the presence of Et$_3$N and DMAP (07TL6552).

Reaction of 9-hydroxy-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones with 3,4-dihydro-2*H*-pyran in the presence of PhSO$_3$H in CHCl$_3$ at room temperature gave protected 9-(2-pyranyloxy) derivatives (09WOP2009/015828). The hydroxyl group was liberated from the 9-(2-pyranyloxy) group by treatment with conc. HCl in MeOH.

9-Amino group of a 9-[(R)-α-methylbenzylamino]-6,7,8,9-tetrahydro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate was formylated with a mixture of HCO$_2$H and Ac$_2$O in the presence of Et$_3$N (07TL6552). Acylation of the amino group of 9(*S*)-amino-6,7,8,9-tetrahydro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate was carried out with the enantiomers of α-methoxy-α-trifluoromethylphenylacetic acids in the presence of EDC, HOBt and DIPEA in DMF (07TL6552). The absolute configuration of tetrahydropyrido-pyrimidine in position 9 was determined by comparison of the chemical shifts of he resulting diastereomers, and by molecular mechanics and semiempirical (AM1) calculations.

Heating 3-benzyl-2-dimethoxymethyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one in 10% aqueous H_2SO_4 solution at 50 ^{o}C for 50 min gave 2-formyl derivative in 89% yield (06WOP2006/008523). The formyl derivative was reacted with EtMgBr at -78 ^{o}C for 1 h in THF to afforded 2-(1-hydroxypropyl) derivative, which was treated first with $(MeCO)_2O$ in the presence of 2,6-lutidine in CH_2Cl_2, then with 2-(dimethylamino)ethylamine under microwave conditions providing 2-{1-(2-dimethylamino)ethylamino]propyl} derivative in 4% yield. The secondary amino group was acylated with 4-chlorobenzoyl chloride in CH_2Cl_2 in the presence of aqueous solution of K_2CO_3.
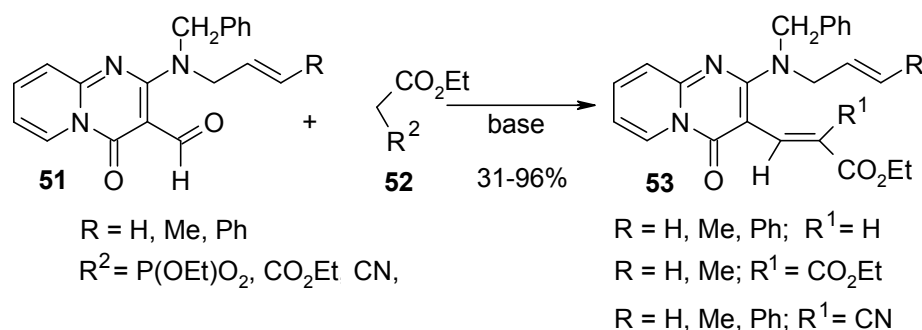
Reaction of **51** aldehyde with **52** CH active compounds in the presence of a base in a solvent afforded **53** condensation products, sometimes as mixtures of *E* and *Z* isomers (07T4548).

2-Amino derivative was obtained from a 2-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one derivative in the reaction with pTsCl in the presence of DMAP in CH_2Cl_2, followed by 3,4-dimethoxybenzylamine in dioxane at 50 °C for 3 h and finally the treatment of the obtained 2-[(3,4-dimethoxybenzyl)amino] derivative with CF_3CO_2H at 60 °C for 0.5 h (09WOP2009/034976).

Heating 2,9-dihydroxy-4H-pyrido[1,2-a]pyrimidin-4-one in $POCl_3$ under reflux for 48 h furnished 2-chloro-9-hydroxy derivative in 60% yield (06WOP2006/109081,

06WOP2006/109084). Chloro atom was changed for morpholino group by reacting with morpholine in boiling EtOH for 18 h in 97% yield. 9-Hydroxy group was reacted with $(CF_3CO)_2$ in CH_2Cl_2 in the presence of NEt_3 at -20 °C to give 9-triflate in 90% yield. Suzuki-Miyaura reaction of 9-triflate with 3-phenylphenylboronic acid (06WOP2006/109084) and with (06WOP2006/109081) in the presence of a palladium catalyst [Pd(PPh$_3$)$_4$ and PdCl$_2$dppf] and a base (K$_2$CO$_3$ and Cs$_2$CO$_3$] in dioxane or THF at 80-95 °C for 18-48 h yielded 9-aryl derivatives. Under microwave conditions reaction time was only 30 min. Suzuki-Miyaura reaction of 3-bromo-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones with 4-cyanophenyl boronic acid in the presence of Pd(dppf)$_2$Cl$_2$, Na$_2$CO$_3$ in THF under microwave conditions in THF at 150 °C for 10 min yielded 3-(4-cyanophenyl) derivatives (07WOP2007/002701, 08BMCL688). Reaction of 7-iodo-4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives with (2-fluoro-3-chlorobenzyl)zinc chloride in the presence (2-MePh)$_3$P and Pd(dba)$_2$ in THF at 70 °C, with isothiazolidine 1,1-dioxide and tetrahydro-2*H*-[1,2]thiazine 1,1-dioxide in the presence of Cu(I)I, MeNHCH$_2$CH$_2$NHMe and K$_2$CO$_3$ in DMF at 80 °C gave 7-(2-fluoro-3-chlorophenyl)methyl, 7-(1,1-dioxoisothiazolidin-2-yl) and 7-(1,1-dioxo-tetrahydro-2*H*-[1,2]thiazin-2-yl) derivatives, respectively (08WOP2008/077188). *N*-(4-Fluorobenzyl)-7-trifluoroacetamido-3-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxamide was obtained, when 7-bromo-3-benzyloxy derivative was reacted with trifluoroacetamide in the presence of Cu(I)I, MeNHCH$_2$CH$_2$NHMe and K$_2$CO$_3$ in DMF at 80 °C in 31% yield.
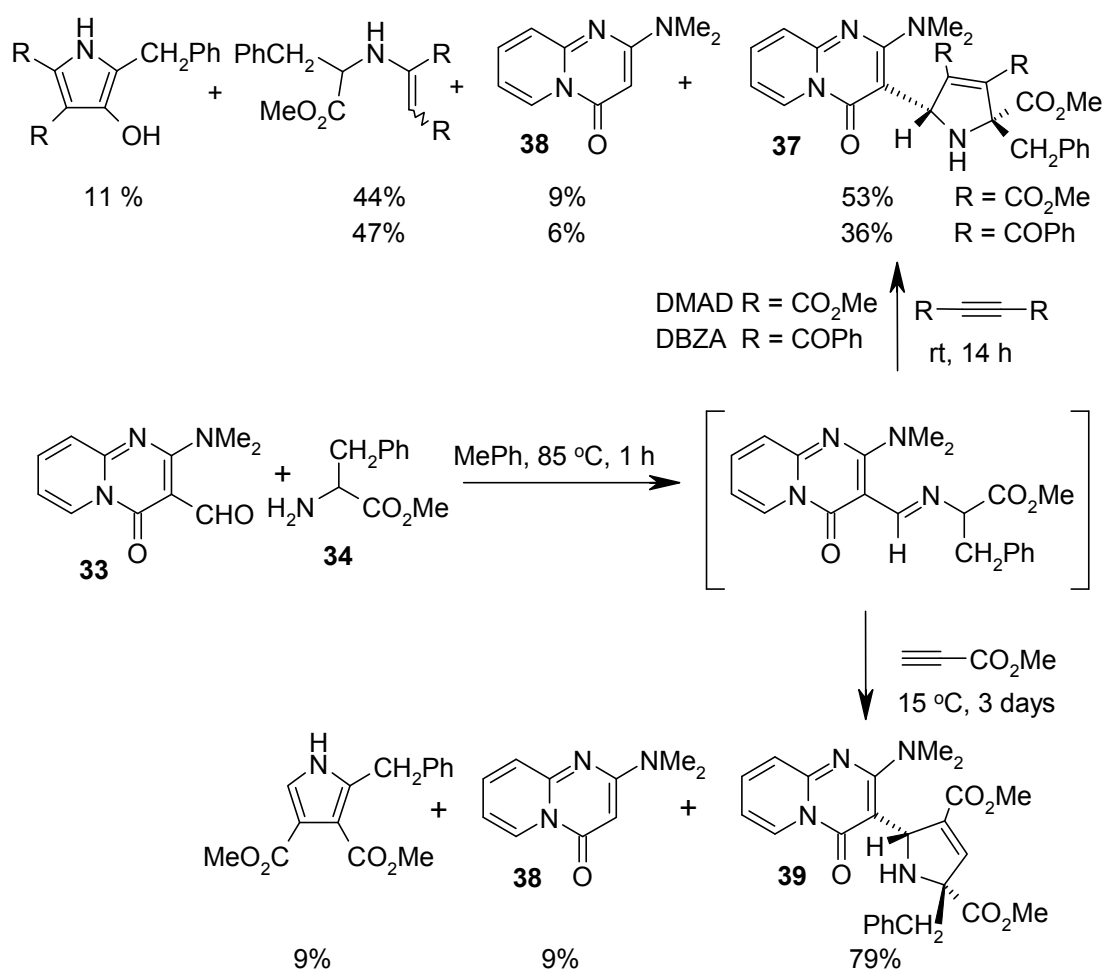
Scheme

Reaction of **33** aldehyde and **34** phenylalanine ester at 85 °C, then treatment of the reaction mixture with DMAD or DBZA at ambient temperature afforded a complex reaction mixture containing **37** cycloadducts and **38** 3-unsubstituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-one (07TL941). Treatment of the cold reaction mixture with methyl propiolate provided **39** cycloadduct together with **38** and 2-benzyl-1*H*-pyrroline-3,4-dicarboxylate. When the reaction mixtures of **33** aldehyde and different amino acid methyl esters were treated with ethyl or methyl propiolate at 85 °C for 20-66 h **38** was obtained in 57-98% yield together with diethyl and dimethyl 2-substituted 1*H*-pyrroline-

3,4-dicarboxylates, respectively. When PPTS additive was added to the reaction mixture somewhat shorter reaction period (2-45 h) could be applied.
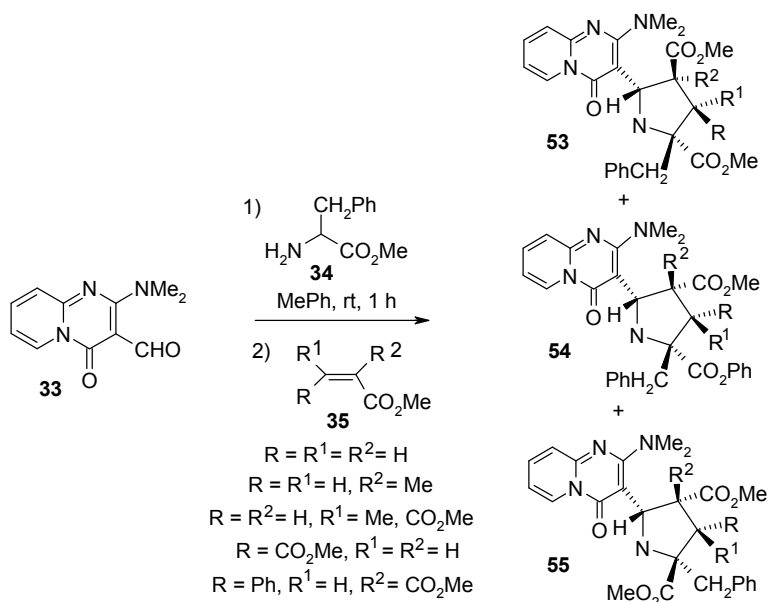
Reaction mixture of **33** aldehyde and **34** phenylalanine ester was reacted with **35** olefinic dipolarophiles at room temperature and 50 °C for 19-48 h gave diestereomeric mixtures of **53**, **54** and **55** 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (06H(70)647). When the obtained mixtures were treated with PPTS in toluene afforded 2-dimethylamino-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**38**) in 78-90% yields. When the reaction mixtures of 33, 34 and 35 were heated in the presence of 2 equiv. of PPTS 2-dimethylamino-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**38**) could be isolated from the reaction mixture 78-85% yields besides mixture of diastereomeric trimethyl 2-benzyl-2,3-dihydropyrrolidine-2,3,4-tricarboxylates.

R = Me, CH_2Ph, -$(CH_2)_4$-, -$(CH_2)_2O(CH_2)_2$-
R^1 = H, Me, iPr, CH_2Ph, $(CH_2)_2SMe$

E,E - dipole   *E,Z* - dipole

endo-approach   endo-approach   exo-approach

36   **37**   **38**

yield 74-100%   endo : exo = 100-97 : 0-3

Scheme
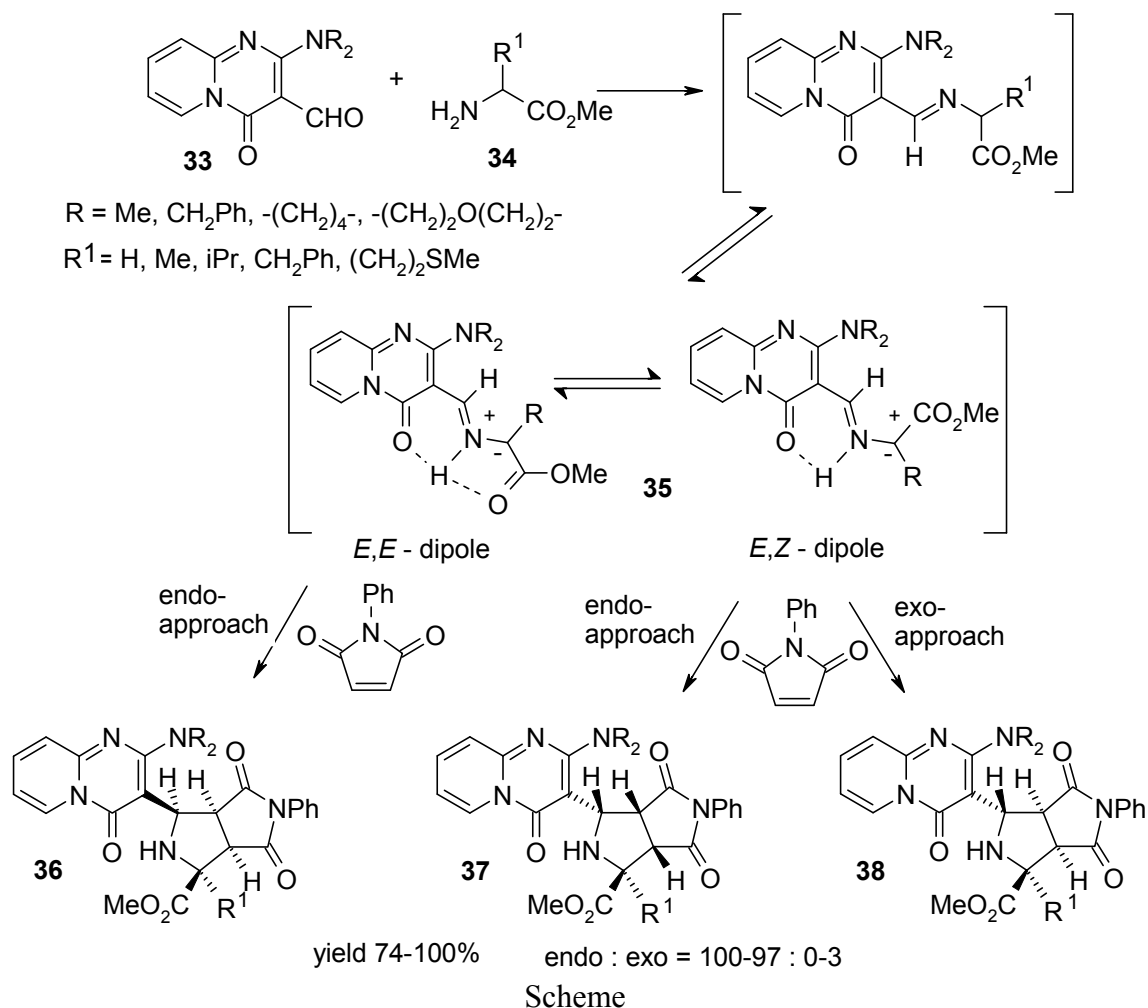
Cyclocondensation reactions of **35** imines, formed in situ from **33** aldehyde and **34** α-amino acid methyl esters, with *N*-phenylmaleimide resulted in the formation of mixtures of **36**-**38** diastereomeric adducts with the preference of **36** (2007T1630). In all cases the cycloadditions gave excellent yields and *endo*-selectivity. Reaction periods were usually 1, 27 and 32 h in MePh, MeCN and DME, respectively. In EtOH only **36** (R = Me, R^1 = Ph) was obtained after 45 h reaction period in 43% yield. Increasing the reaction temperature usually slightly increased the yield of **37**. When **34** (R = NMe_2, R^1 = ^{i}Pr) was applied the diastereomeric ratio of **36** and **37** (R = NMe_2, R^1 = ^{i}Pr) was 43-38 : 57-62. In this case, the ratio of **37** versus **36** increased when the reaction temperature was

increased. Applying glycine methyl ester (**34**, R^1 = H) the ratio of **36** *endo* and **38** (R = NMe$_2$, R^1 = H) *exo* products was 82 to 18.

Condensations of 3-acetyl-2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one with aromatic aldehydes in the presence of catalytic amounts of piperidine and AcOH in boiling benzene for 2 h provided 3-(3-aryl-1-oxo-allyl)-2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**40**) in 82-85% yields (06MI10). Cyclocondenzations of compounds **40** with H$_2$NNH$_2$·H$_2$O, HONH$_2$·HCl, CH$_2$(CN)$_2$ and heating in the presence of 40 % KOH yielded **41-43** 3-substituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones and **44** tricyclic derivatives, respectively.
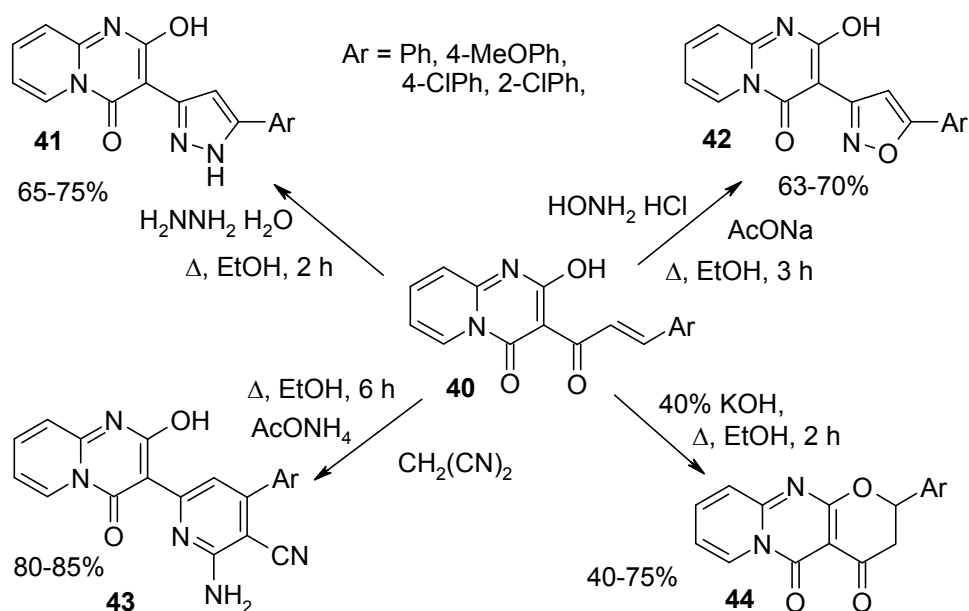
Cyclocondenzation of **134** 2-phenoxy-3-formyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one and **135** 5-aminopyrazole in refluxing DMF gave **136** tetracyclic derivatives (06MI6).
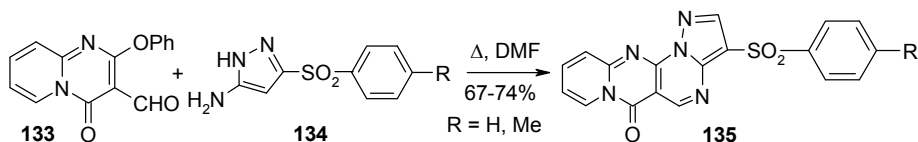
Reaction of 7-chloro- and 7-bromo-2-chloromethyl-3-nitro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones with diethyl oxomalonate in DMF at -20 °C for 30 min, than TDAE was added to the reaction mixtures and they were stirred at this temperature for an additional 2 h, followed by gradual heating to room temperature for 2 h to give diethyl 2-[(7-halo-3-nitro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)methylene]malonates in 19-24% yields (08H(75)925).

At room temperature amine salt was obtained from 2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate and EtNH₂ in EtOH (08CHE565). Reaction of 2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates and alkylamines, benzylamines and aniline in boiling EtOH and DMF afforded the corresponding amines in good yields (08CHE50, 08CHE565). Reaction of methyl 3-benzyloxy- and 3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylates with 4-fluorobenzylamine in MeOH at 60-65 °C gave *N*-(4-fluorobenzyl-3-hydroxy-2-carboxamides (08JMC861, 09BML1930). In a four component Ugi condensation between **43** 3-formyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, **44** amine, **45** carboxylic acid and **46** isonitrile the expected **47** product formed only in trace amount (07TL2563).
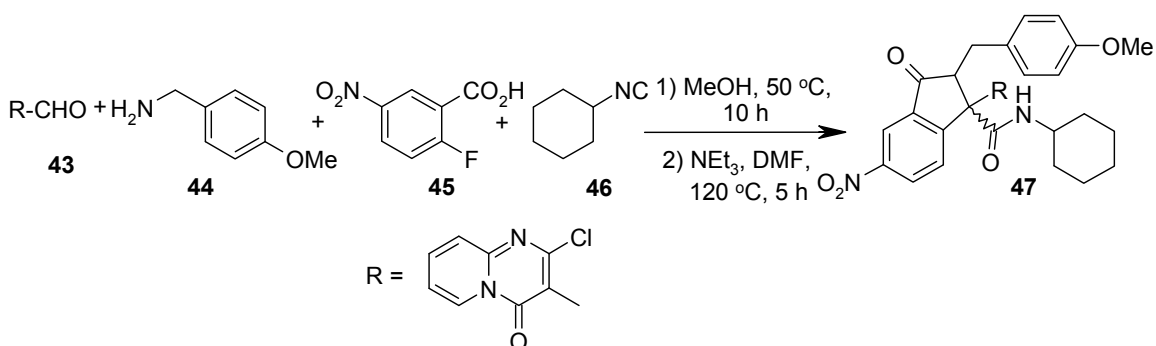
After drop-wise addition of TMSCl to a reaction mixture of 7-bromo-2-chloromethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one and 4-methoxycarbonylbenzaldehyde, the reaction mixture was heated in a pressure tube on a water bath to yield compound **123** (07S3163).
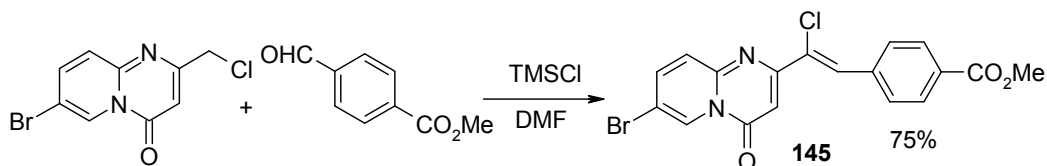
Under $S_{RN}1$ conditions (inert atmosphere, photostimulation), the reaction of **146** 2-chloromethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one with anions formed from 2-nitropropane and malonates gave **147** ethylenic derivative resulting from a consecutive C-alkylation and HNO_2 elimination and **148** alkylated malonates, respectively (08SL2836). Boths reactions were strongly inhibited by TEMPO, a free radical scavenger. Reactions of **146** and sodium salt of thiophenol and arylsulfinic acids yielded **149** *S*-alkylated derivatives in S_N2 reactions, as addition of TEMPO did not decreased the yields significantly.
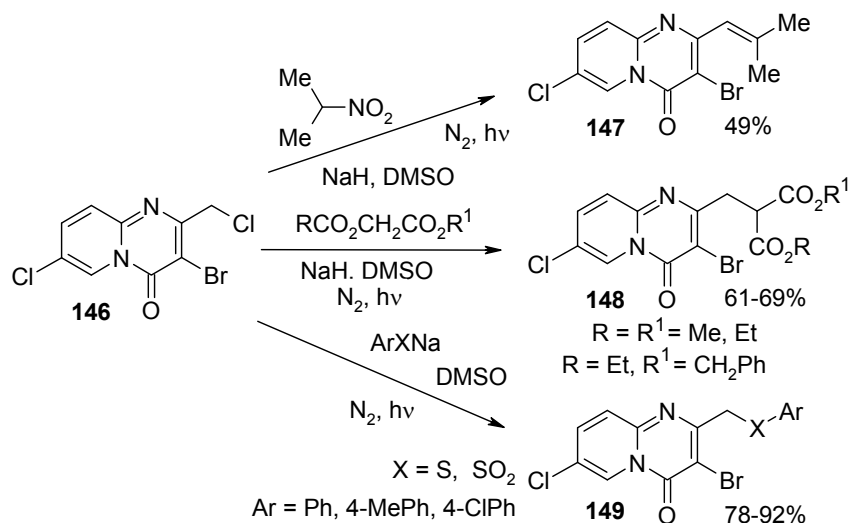
9-Amino-2-hetaryl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones were obtained from 9-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl) derivatives with $H_2NNH_2 \cdot H_2O$ in boiling EtOH (07WOP2007/057790, 08EPP1939187, 08WOP2008/078196). The amino

group was reacted with PhNCO, PhO$_2$CCl (07WOP2007/057790), and with different hetaroyl chlorides (08EPP1939187, 08WOP2008/078196) in the presence of NEt$_3$.

Treatment of 3-benzyloxyamino-4H-pyrido[1,2-a]pyrimidin-4-ones with HBr in AcOH at 50-60 °C for 2 h afforded 3-amino derivatives (08H(75)2477). Amino group was reacted with different sugars in refluxing MeOH in the presence of small amount of AcOH to give N-glycosides in 62-100% yields.

Different N-benzyl derivatives of 3-benzoyloxy- and 3-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamides were obtained by the treatment of methyl 3-benzoyloxy- (07WOP2007/039218, 08JMC861) and 3-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxylates with benzylamines in MeOH at 65 °C (07WOP2007/039218, 08JMC861, 08WOP2008/077188). N-[(4-Fluorophenyl)methyl] 2-carboxamide was also obtained when methyl 3-pivaloyloxy-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxylate was reacted first with [(4-fluorophenyl)methyl]amine, and the obtained 3-pivaloyloxy-2-amide was hydrolyzed with 0.1 M aqueous NaOH (07WOP2007/039218, 08JMC861). 9-Amino derivative was obtained from N-(4-fluorobenzyl)-3-hydroxy-9-(benzyloxycarbonylamino)-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamide by treatment with 30% HBr in AcOH at ambient temperature for 2 h (08JMC861, 09BML1930). 9-Alkylamino group of N-(4-fluorobenzyl)-3-hydroxy-9-alkylamino-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxamides was acylated with methylsulfonylacetyl chloride and N,N-(diethylamino)(oxo)acetyl chloride (08JMC861) furthermore with acyl chlorides and methyl oxalyl chloride (09BML1930). Hydroxy group of methyl 3-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidine-2-carboxylates was reacted with pivaloyl chloride, benzyl bromide, tBu,Me$_2$SiCl in the presence of a base to yield 3-pivaloyloxy,

3-benzyloxy and 3-*t*-butyldimethylsilyloxy derivatives, respectively. 3-Hydroxy derivatives were liberated from 3-methylsylfonyloxy-, 3-benzyloxy- and 3-*t*-butyldimethylsilyloxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones by treatment with NaOH in MeOH, with Me_3SiI in MeCN under N_2 at room temperature and under acidic and basic conditions, respectively.

Methyl group of methyl 7-methyl-3-(*t*-butyl,dimethylsilanyloxy)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate was brominated with NBS in boiling CCl_4 in the presence of *t*-butyl peroxide to afford 7-bromomethyl derivative. The 7-bromomethyl derivative was reacted with morpholine in an 1 : 1 mixture of CH_2Cl_2-MeOH at ambient temperature and with P(OEt)3 in boiling MePh to give 7-morpholinomethyl and 7-$(EtO)_2(O)PCH_2$ derivatives, respectively. The 7-$(EtO)_2(O)PCH_2$ group was hydrolyzed by treatment with Me3SiI in MeCN at 0 °C temperature to a phosphonic acid.
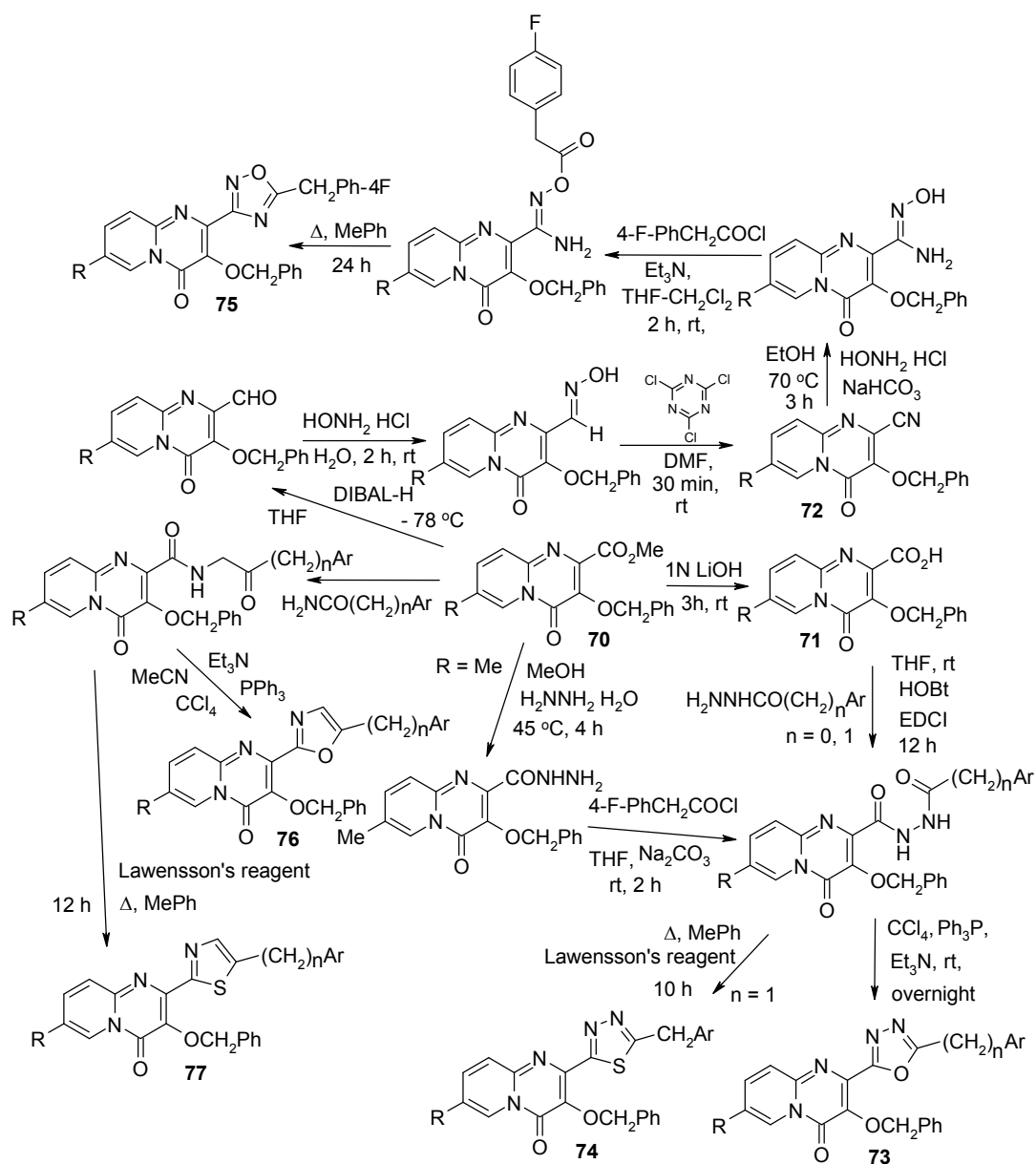
Scheme 4.

Ester group of **70** 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate was converted into different five-membered heterocyclic group to give **73-77**, as it is depicted on Scheme 4 (08WOP2008/077188). Esterification of **78** (R[1] = H) carboxylic acid with **79** amidoximes provided compounds **80**, which were cyclized by heating in toluene to yield **81** derivatives. Compounds **80** and **84** were prepared starting from **78** (R[1] = H) carboxylic

acid and **79** amidoximes, furthermore **78** (R^1 = Me, R^2 = H) and **82** amino alcohol, respectively, as it is depicted on Scheme 5.
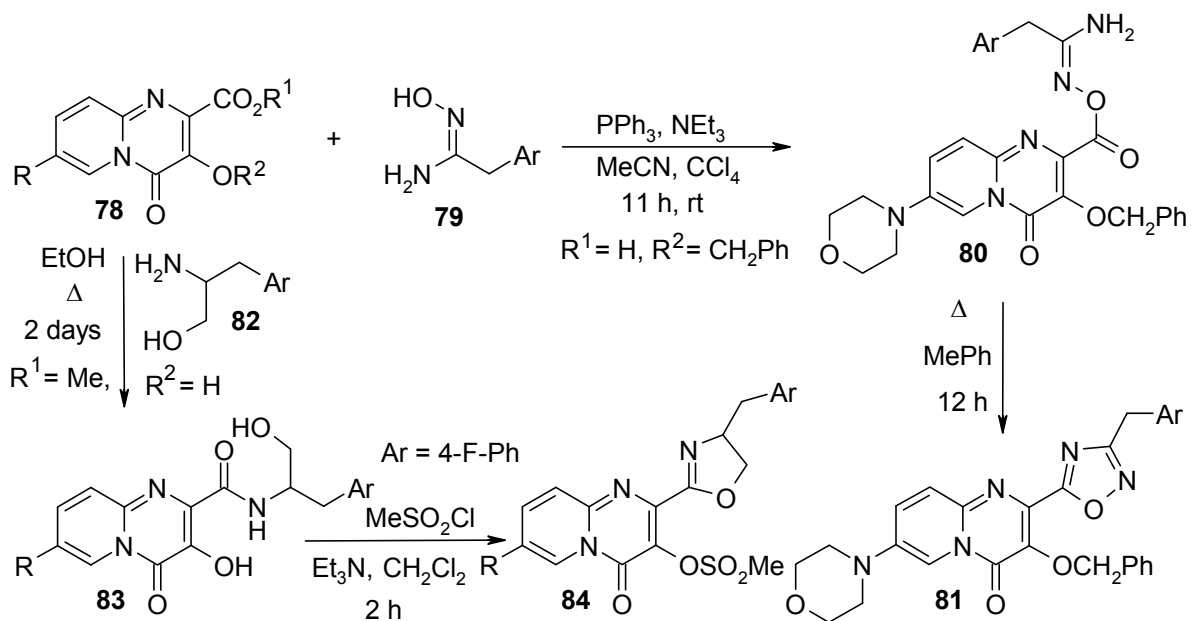
Scheme 5.

Hydrolysis of ethyl 7-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate with 1 N NaOH at room temperature for 16 h yielded 3-carboxylic acid, which was coupled with an aromatic acid in CH_2Cl_2 in the presence of HATU give a 3-carboxamide in 24% yield (06WOP2006/116713). A 8-carboxylic acid was obtained from a 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-8-carboxylate by hydrolysis with aqueous NaOH solution (06BMC1993). A 8-carboxamide was prepared by reacting the 8-carboxylic acid with 2-amino-4-*tert*-butylthiazol in the presence of Huning's base and *N,N*-bis-(2-oxo-3-oxazolidinyl)phosphinic acid chloride in CH_2Cl_2.

Heating a *tert*-butyl (2-vinyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)acrylate in dioxane in the presence of 4 N HCl for 15 h gave a 2-chloroethyl-3-acrylic acid in 62% yield

(06BMC1993). (4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)acrylic acids were obtained from *tert*-butyl esters by treatment with an acid (TFA, HCl) (06BMC1993, 06BMC8506).

Chloro atom of 2-chloromethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was substituted with 4-substituted phenols in DMF in the presence of Cs_2CO_3 at 60 ^{o}C for 18 h (06WOP2006/072828) and with 1-(2-fluorophenyl)piperazine in DMF in the presence of Et_3N at ambient temperature overnight (07WOP2006/110868).

Reaction of 2-methyl-3-(1,3-dioxobutyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones with $H_2NNH_2 \cdot H_2O$ in boiling EtOH, and with $HONH_2 \cdot HCl$ in refluxing MeOH gave 3-(5-methylimidazol-2-yl) and 3-(3-methyl-1,2-oxazol-5-yl) derivatives, respectively (05MI3). Same products were obtained with these reagents from 2-methyl-3-[3-(2-pyridylamino)-1-oxobut-2-enyl]- and 2-methyl-3-{3-(5-methyl-2-pyridyl)amino]-1-oxobut-2-enyl}-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones, too

Hydroxy group of paliperidone was acylated with different aromatic carboxylic chlorides and it was reacted with phenyl chloroformate, and alkyl chloroformates (08WOP2008/128436).

7. Reactivity of Substituent Presents in a Side Chain

Treatment of **14** diacetoxy derivative of 1,2,3,4-tetrahydro-6*H*-pyrido[1,2-*a*]pyrimidines with Na in MeOH yielded trihydroxy derivatives in 92% yield (07MIP2).
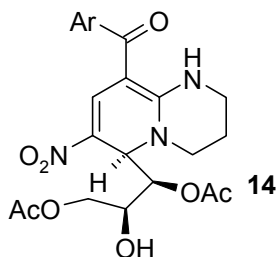
At the synthesis of a library of heterocyclic compounds a 1,2,3,4-tetrahydro-1,4-benzothiazine derivative was *N*(4)-alkylated with 2-chloromethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one in the presence of K_2CO_3 in MeCN (06IVU119).

2-Butyl-4-chloro-5-formyl-1*H*-imidazole was *N*(1)-alkylated with 3-(2-chloroethyl)-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one and its 6,7,8,9-tetrahydro derivative in DMF in the presence of powdered K_2CO_3 in 78% and 56% yields, respectively (07MD269).
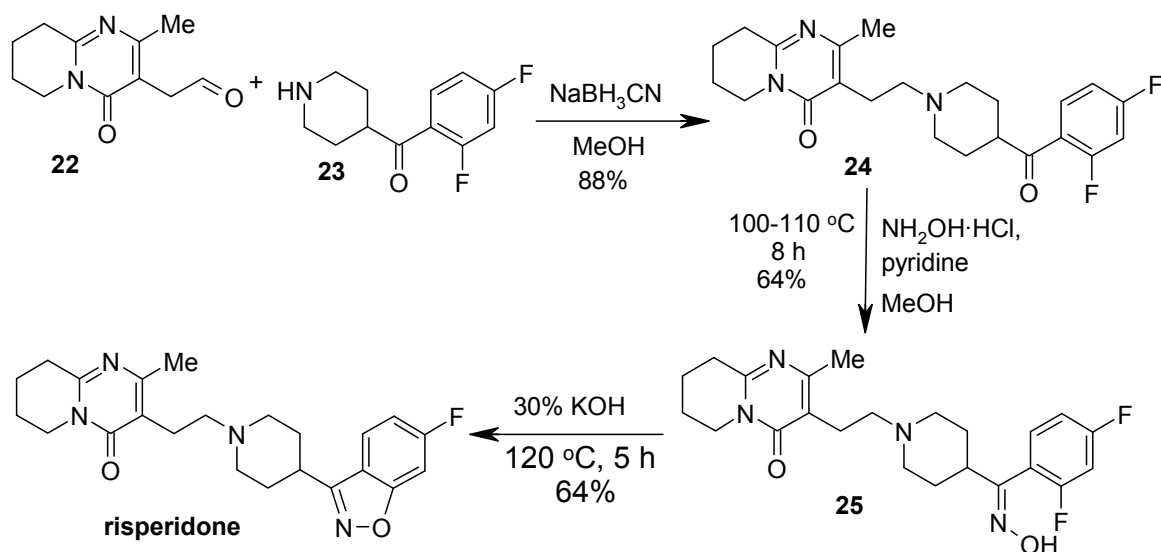
Scheme 2

Reductive amination of **22** aldehyde with **23** piperazine in the presence of $NaBH_3CN$ yielded **24** 3-{2-[4-(2,4-difluorobenzoyl)piperazin-1-yl]ethyl}tetrahydropyrido[1,2-*a*]pyrimidin-4-one (Scheme 2). The keto group of compound **24** was reacted with $NH_2OH \cdot HCl$, and the treatment of **25** oxime with KOH provided risperidone (05APR1019).
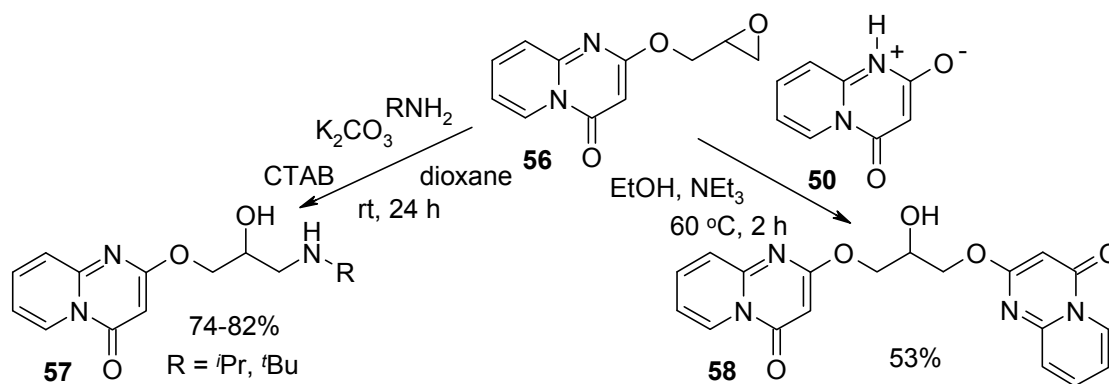
Reactions of **56** oxirane with primer amines and *anhydro*-(2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidinium)hydroxyde (**50**) gave the corresponding **57** and **58** 2-(3-substituted 2-hydroxypropyl) derivatives, respectively (05MI2, 07HC19).

6-Phenylpirazin-3(2*H*)-one was *N*(3)-alkylated with 2-chloromethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one in 46% yield (0606IVU24).

Chloro atom of 3-(4-chlorophenyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones was replaced with different primary amines in the presence of (2-biphenyl)di-*tert*-butylphosphine, Pd(OAc)$_2$ and NaOtBu in toluene at 100 °C yielded 3-[4-(substituted amino)phenyl] derivatives (08USP2008/0194616, 08WOP2008/097991). Similarly 3-[5-(1-*tert*-butoxycarbonyl-3-pyrrolidinyl)-3-pyridinyl]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was obtained from 3-(5-chloro-3-pyridinyl) derivative. Amino group of a 3-(4-aminophenyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was acylated with *N*-*tert*-butoxycarbonyl-L-proline in the presence of EDCI and HOBt in CH$_2$Cl$_2$ at 0 °C. Side chain *N*-(*tert*- butoxycarbonyl) groups were eliminated by stirring with 4 M hydrochloric acid in a solvent and by treatment with CF$_3$CO$_2$H in CH$_2$Cl$_2$ at room temperature. Treatment of 3-(4-methoxyphenyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones with 1.0 M BBr$_3$ in CH$_2$Cl$_2$ dropwise at -78 °C yielded 3-4-hydroxyphenyl derivatives. Hydroxy group was reacted with (CF$_3$SO$_2$)$_2$O in the presence of Et$_3$N CH$_2$Cl$_2$ at 0 °C and with (*S*)-(1-*tert*-

butoxycarbonyl)-3-hydroxypyrrolidine in the presence of Ph_3P and $EtO_2CN=NCO_2Et$ in at ambient temperature in THF to give 3-[(4-trifluorosulfonyloxy)phenyl] and 3-{4-[1-(*tert*-butoxycarbonyl)-3-pyrrolidinyloxy]phenyl} derivatives, respectively.

Chloro atom of 3-(2-chloroethyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (03MIP1, 03MIP4, 06USA2006/0122206, 06WOP2006/061373, 09USA2009/0270369) and their 6,7,8,9-tetrahydro derivatives (09USA2009/0270369, 09WOP2009/015828, 09WOP2009/016653) was replaced by secondary cyclic amines to give 3-{2-aminoethyl} derivatives. 3-(2-Bromoethyl)-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was reacted with 1-[bis(4-fluorophenyl)methyl]piperazine in DMF in the presence of powered K_2CO_3 to yield 3-(2-substituted ethyl) derivative (06BML3932). A hydroxymethyl group attached to phenyl group in position 2 of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one was converted into a bromomethyl group by treatment with CBr_4 and PPh_3 (06BMC8506). Bromo atom was replaced by different secondary amines. A side chain piperazino group was *N*(4)-alkylated with $Br(CH_2)_2OH$ and $BrCH_2CO_2{}^tBu$. Treatment of a side chain 4-allylpiperazino group with *N,N*-dimethylbarbituric acid, and $Pd(PPh_3)_3$ in CH_2Cl_2 gave piperazino group.

Demethylation of **55** methoxy derivatives by treatment with BBr_3 in CH_2Cl_2 at -10 °C gave the appropriate hydroxy derivatives (07JMC4917)

R = H, R^1 = H, OH
R = OH, R^1 = H
R^2 = OMe, R^3 = H, MeO

55
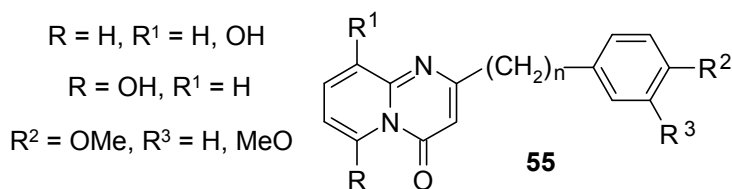
Reaction of $^{11}CH_2O$ with **45** 4*H*-pyrido[1,2-*a*]pyrimidin-4-one in aqueous formic acid at gave radiolabeled compound **46** with 99% chemical and radiochemical (06BMC4526).
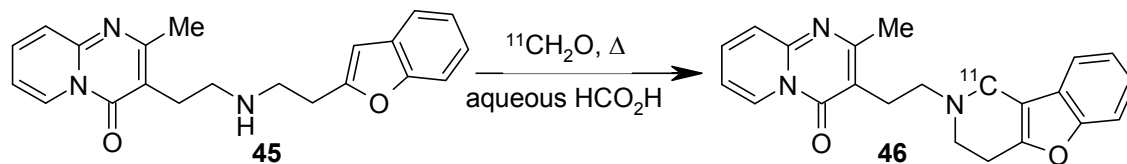
A side-chain aromatic amino group was diazotated by treatment with t-butylnitrite in the presence of HBF$_4$ in EtOH, then the filtered diazonium salt was treated with Cu(NO$_2$)$_2$ and cuprous oxide in water at ambient temperature for 1 h to give deaminated by product and hydroxy derivative in 17% and 19% yields, respectively (06WOP109081). A side-chain aromatic amino group were acylated with ClCH$_2$COCl and Br(CH$_2$)$_2$COCl, and the products were reacted with different amines.

Thermal cyclization of **40** 3-formyl-2-amino derivatives furnished **41** tricyclic compounds (06H(70)181). That of compound **40** (R = H) gave a 4:3 mixture of compounds **41** (R = H) and **42**. Similar reaction of **43** cyclic amino ester failed probably due to steric reason. The ester group in **40** seems to be essential for cyclization, as 3-formyl-2-(dibenzylamino) and -2-pyrrolino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones did not happened even at more harsh reaction conditions.

R = Me, Pr, ^{i}Pr, ^{s}Bu, ^{i}Bu, (CH$_2$)$_2$SMe, CH$_2$Ph, Ph
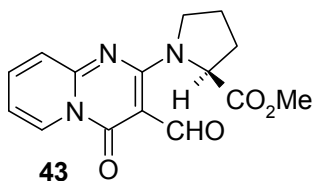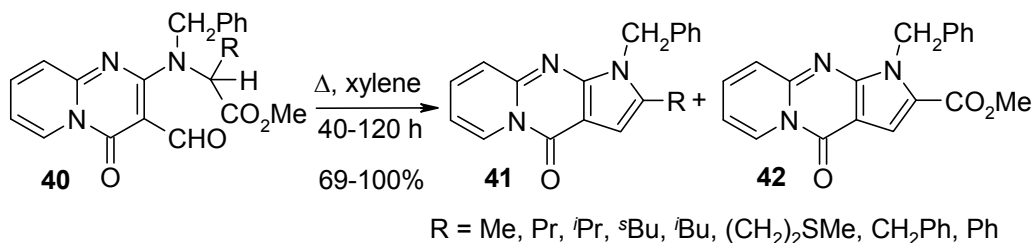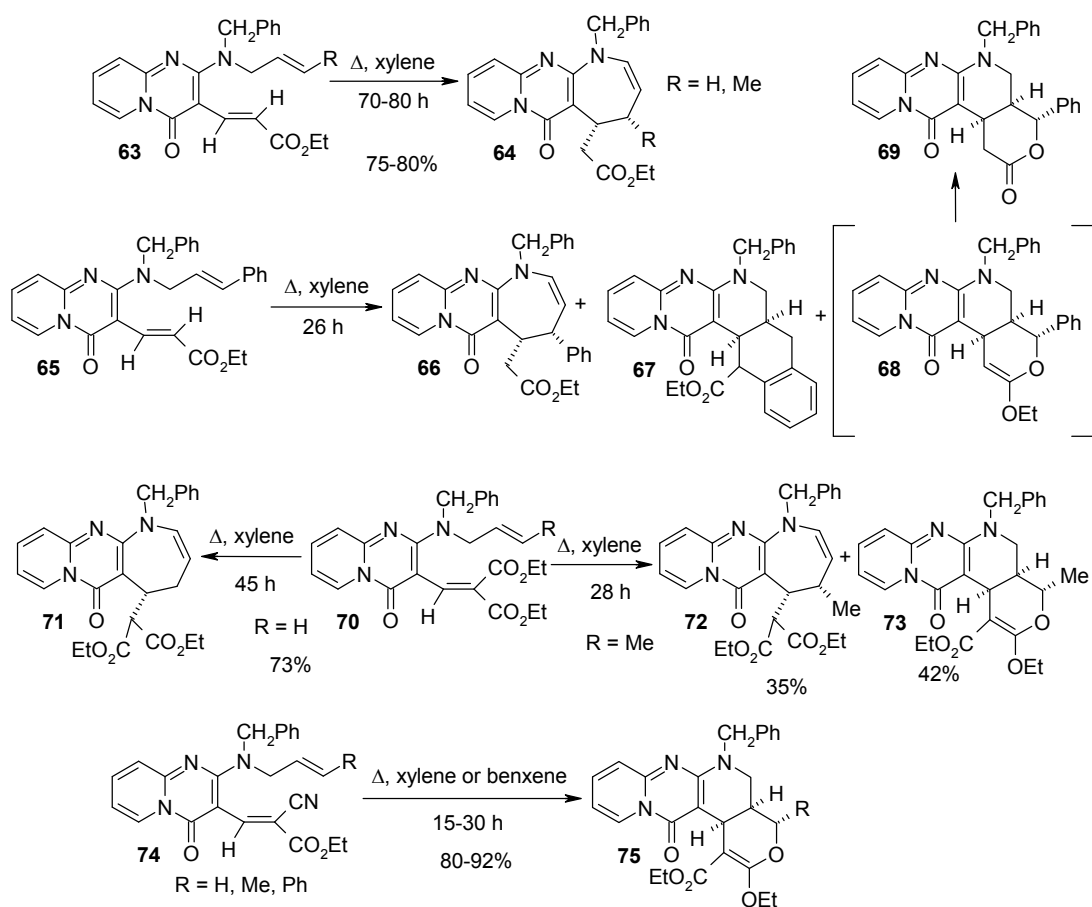
Scheme

Competitive thermal ene reaction and Diels-Alder reactions of **63** acrylates and **70** (R = H) in boiling xylene afforded **64** and **71** tricyclic compounds, respectively (07T4548). Similarly **74** 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones gave **75** tetracyclic compounds, and **65** acrylate provided a mixture of **66** tricyclic, **69** tetracyclic and **67** pentacyclic derivatives. Heating **70** (R = Me) diester yielded a mixture of **72** tricyclic and **73** tetracyclic compounds.

4-Methoxybenzyl group of 3-{2-[1-(4-methoxybenzyl)tetrazol-5-yl]vinyl-4-oxo-4*H*-pyrido[1,.2-*a*]pyrimidine-8-carboxamides was removed by with TFA in anisole at 60-80 °C to yield 3-[2-(tetrazol-5-yl)vinyl derivatives (07BMC7087). A side chain hydroxyl group was converted into an aminocarbonyloxy group by treatment first with

CCl$_3$CONCO at 0 °C in EtOAc, followed by the treatment with HCO$_2$Na in aqueous MeOH at ambient temperature. Side chain hydroxyl groups were reacted with ω-dimethylaminoalkylamines in the presence of CDI in CH$_2$Cl$_2$ to yield *N*-(ω-dimethylaminoalkyl)aminocarbonyloxy groups. The dimethylamino group was quaternized by MeI, 2-iodoacetamide and *tert*-butyl bromoacetate. A side chain methoxycarbonyl and *tert*-butoxycarbonyl group was converted into a carboxyl group by treatment with aqueous NaOH solution and 4 N HCl in dioxane, respectively. *N*-(2-dimethylaminoethyl)aminocarbonyl group was obtained from a side chain carboxyl group by treatment with 2-dimethylaminoethylamine in the presence of EDC and HOBt in a mixture of DMF and CH$_2$Cl$_2$.

8. Rearrangement, Ring Transformation

Heating 6-methyl-2-phenyl- and 2,6-dimethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones in Ph$_2$O under reflux for 5 h (06WOP2006/086381, 07WOP2007/052120, 08USA2008/0107623, 08USA2008/0107624, 08USA2008/0107625) and 300 °C for 1 h (08TL3380), respectively, gave 7-methyl-2-phenyl- and 2,7-dimethyl-1,4-dihydro-1,8-naphthyridin-4-ones in 92% yield.

Heating 3-azido-4*H*-pyrido[1,2-*a*]pyrimidin-4-one in boiling Ac$_2$O for 3 h afforded 3-(diacetylamino)imidazo[1,2-a]pyridine in 815 yield (08AJC107).

9. Miscellaneous

3,4-Dihydro-2*H*-pyido[1,2-*a*]pyrimidine was investigated as catalyst for acyl transfer reaction, together with other similar bi- and tricyclic compounds containing amidine moiety (06TL4347).

212
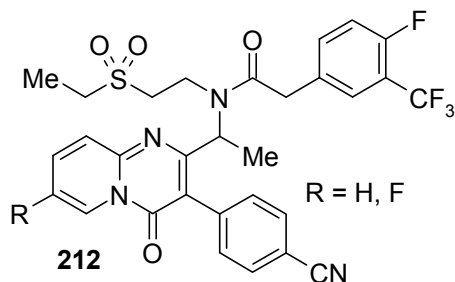
Enantiomers of **212** 2-(1-aminoethyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones were separated on a Chiralpak AD-H column (07WOP2007/002701, 08BMCL688). Those of 9-hetaroyl-2-(pyrimidin-4-yl)-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones and a 9-methyl-9-(2-methoxynicotinoyl) derivative were separated on a Chiralcel OD-I column by chiral preparative HPLC (07WOP2007/057790, 08EPP1939187, 08WOP2008/078196).

Diastereomeric mixtures of methyl 9-[(*S*)- and 9-[(*R*)-(α-methylbenzylamino]-3-hydroxy-6,7,8,9-tetrahydro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylates and 9-*N*-methyl-9-[(*S*)-α-methylbenzylamino] derivative were separated by preparative RP-HPLC (07TL6552).

Purification of paliperidone by crystallization was patented (228WOP2008/021346). Polimorphs of paliperidone were patented (228WOP2008/021342).

Copper(II) complexes **39** and **40** were obtained from **37** and **38** 4*H*-pyrido[1,2-*a*]pyrimidines with Cu(QAc)$_2$ dihydrate in aqueous acetone in 85-93% yields (05RCB2841).
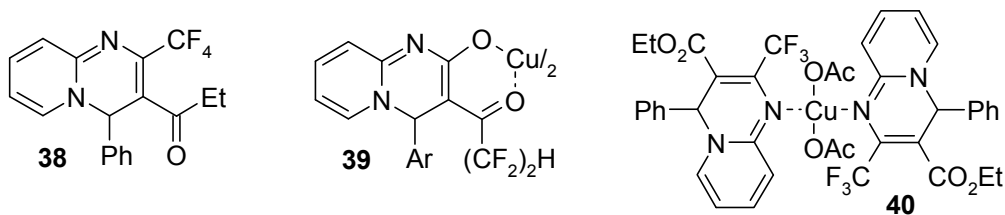
C.   Synthesis

1. By Formation of One Bond α to the Bridgehead Nitrogen Atom [6+0(α)]

When 2-(3-hydroxypropyl)amino]pyridine was reacted with $SOBr_2$ at 0 °C for 0.5 h in CH_2Cl_2, then the evaporated residue was treated with 3 M NaOH 3,4-dihydro-2H-pyrido[1,2-a]pyromidine was obtained (08JOC6899).
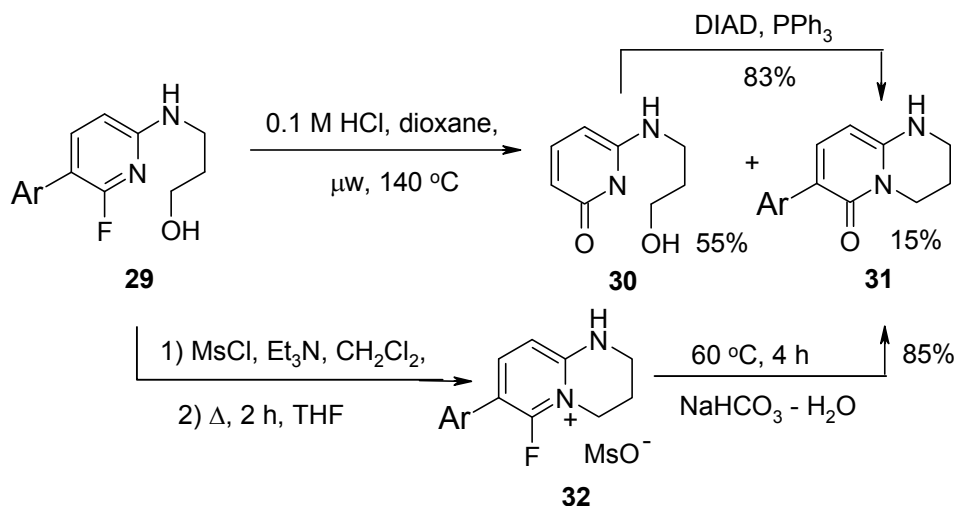
Reaction of **29** (Ar = H) 6-fluoro-2-(3-hydroxypropylamino)pyridine, prepared from 2,6-difluoropyridine and 3-hydroxypropylamine, in acidified dioxane at 140 °C under microwave irradiation afforded **30** pyridone which was accompanied by **31** (Ar = H) bicyclic compound (07OL5175). 1,2,3,4-Tetrahydro-6*H*-pyrido[1,2-*a*]pyrimidin-6-one was obtained from **30** pyridone under Mitsunobu cyclodehydration conditions in 83% yield. When **29** (Ar = H) pyridine was reacted first with MsCl, then the mesylated product was heated in THF **32** (Ar = H) mesylate formed, which was hydrolyzed into **31** (Ar = H) 1,2,3,4-tetrahydro-6*H*-pyrido[1,2-*a*]pyrimidin-6-one in 85% yield. In similar reaction sequence 2-[*N*-benzyl,*N*-(3-hydroxypropyl)amino] derivative of **29** (Ar = H) and 5-aryl derivatives **29** (Ar = 4-MeOPh, 4-NO$_2$Ph) gave 1-benzyl derivative of **31** and 7-aryl derivatives of **31** (Ar = 4-MeOPh, 4-NO$_2$Ph) in 86% and 73-86% yields, respectively. 7-, 8- and 9-Iodo-1,2,3,4-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidinium

mesylates were prepared similarly from 3-, 4- and 5-iodo derivatives of 6-fluoro-2-(3-hydroxypropylamino)pyridine.

Heating **44** 3-[(2-pyridylamino)methylidene]-4,5-dihydrofuran-ones in boiling POCl$_3$ gave **45** 3-(2-chloroalkyl)-4H-pyrido[1,2-a]pyrimidin-4-ones (07T8157).

R = R^1= H, R^2= H, Me;
R = R^2= H, R^1= Me
R = Me, R^1= H, R^2= H, Me;
R = R^1= Me, R^2= H;
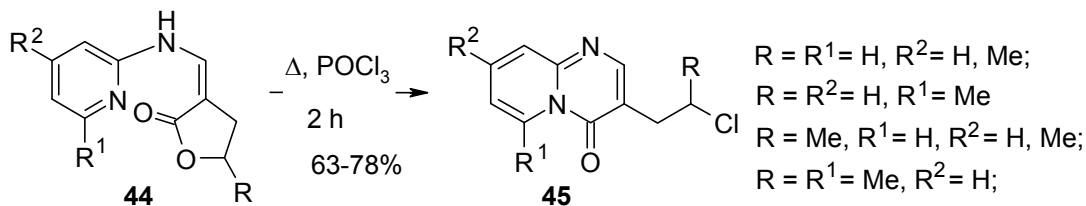
Cyclization of **9** enamine by heating in 1 mol KOH solution afforded **10** pemirolast potassium (03MI1).
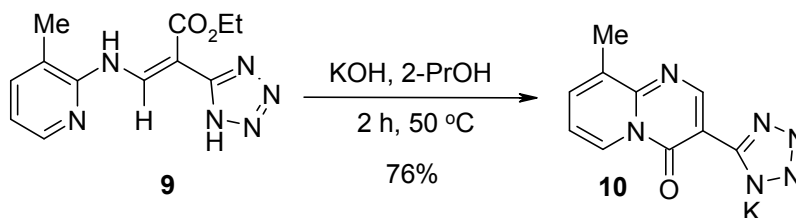
Heating 2-[(3-hydroxypropyl)amino]-3,4,5,tetrahydropyryridine hydrochloride in SOCl$_2$ at 65 °C for 1 h gave 3,4,6,7,8,9-hexahydro-2H-pyrido[1,2-a]pyrimidine in 44% yield

Condenzation of N-(2-pyridyl)-2-cyanoacetamide (**39**) and 3-methylbutanal in the presence of pypiridine yielded **40** 2-amino-3 substituted 4H-pyrido[1,2-a]pyrimidin-4-one (07RJO83)
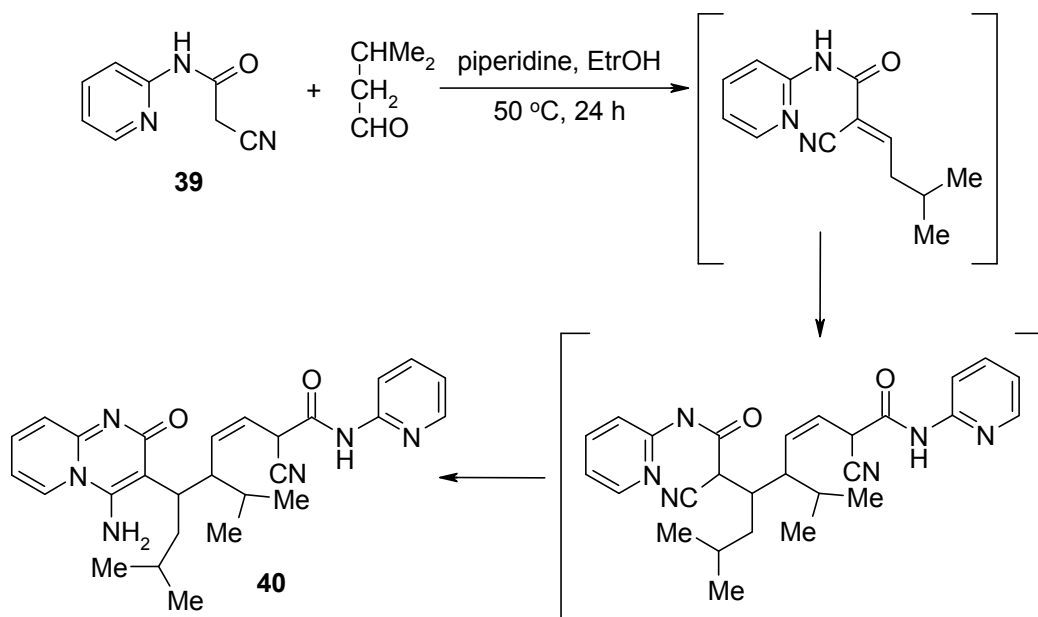
Heating **48** ethyl malonamate in tetraline provided **49** *anhydro*-(1-substituted 2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidinium)hydroxyde (09WOP2009/099929).
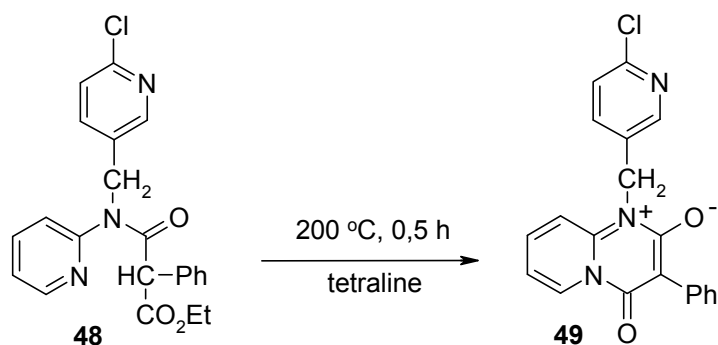
2. By Formation of One Bond β to the Bridgehead Nitrogen Atom [6+0(β)]

3. By Formation of One Bond γ to the Bridgehead Nitrogen Atom [6+0(γ)]

4. By Formation of Two Bond from [3+3] Atom Fragments

Reaction of 2-dimethylaminopyridine and 1,3-bis(trifluoromethanesulfonyloxy)propane provided **23** disalt in 98% yield (09JA9174). Reactions of 2-aminopyridines and **15** enone

Mannich bases in acidified EtOH yielded **16** 3-aroyl-3,3-dihydro-2*H*-pyrido[1,2-*a*]pyrimidinium salts (09EJM2877).
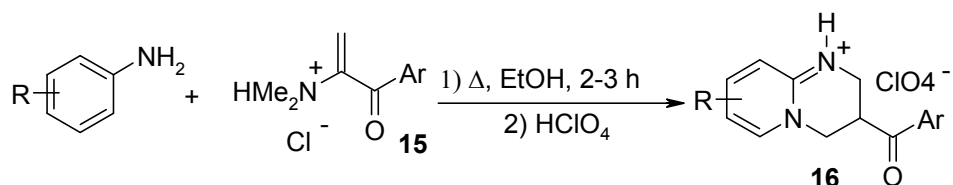
Cyclocondenzation of **7** (R = Ph) Baylis-Hillman acetate and **8** (Ar = Ph) ketene aminal in different solvents (THF, DMF, MeCN) gave a mixture of isomeric **9** (Ar = R = Ph) 6-phenyl and **10** (Ar = R = Ph) 8-phenyl derivatives of 9-benzoyl-7-nitro-1,2,3,4,7,8-hexahydro-6*H*-tetrahydropyrido[1,2-*a*]pyrimidine (08SL1357). At lower reaction temperature (0 °C) the ratio of 6-phenyl isomer was higher than at room temperature. In CH$_2$Cl$_2$ at 0 °C regioselectively only **9** (Ar = R = Ph) 6-phenyl isomer formed, while at ambient temperature a 6 : 1 mixture of **9** (Ar = R = Ph) 6-phenyl and **10** (Ar = R = Ph) 8-phenyl derivatives was obtained. Reactions of **7** (R =2-furanyl) and **8** in CH$_2$Cl$_2$ at 0 °C afforded only **9** (R = 2-furanyl) compounds in 75-90% yields.

R = Ph, 2-furanyl; Ar = Ph, 4-FPH, 4-ClPh, 4MePh
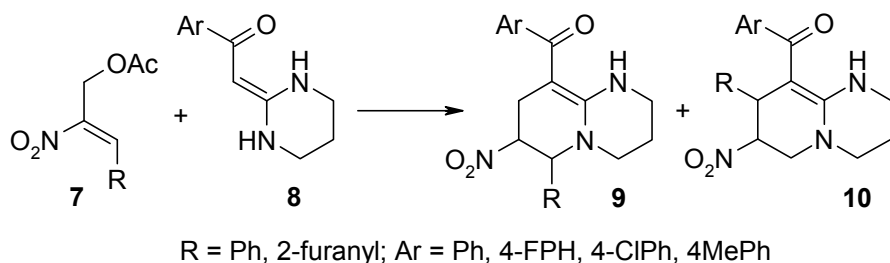
Reaction of **12** 2*H*-3,4-dihydropyrane and **13** 2-aroylmethyleneperhydropyrimidine in CH$_2$Cl$_2$ in the presence of Et$_3$N at ambient temperature afforded **14** 9-aroyl-7-nitro-1,2,3,4-tetrahydro-6*H*-pyrido[1,2-*a*]pyrimidines (07MIP2).

Ar = Ph, 4-MePH, 4-ClPh, 4-MeOPh
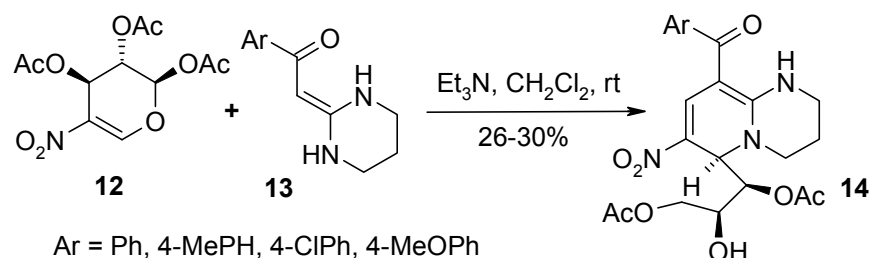
Cyclocondenzation of 2-methylaminopyridine and 3-bromopropionic acid in MeCN at ambient temperature for 2 days gave 1-methyl-2-oxo-1,2,3,4-tetrahydropyrido[1,2-a]pyrimidinium bromide in 84% yield (07JST107). That of 2-aminopyridine and 3-chloropropionic acid yielded 2-oxo-1,2,3,4-tetrahydropyrido[,2-a]pyrimidinium chloride (08JST244).

Cyclocondenzations of 2-aminopyridine and its 5-methyl derivative and N-aryl-3-oxobutanethioamides at 100-105 °C for 1-2 h gave 4H-pyrido[1,2-a]pyrimidine-4-thione and its 7-methyl derivative in 47% and 43% yields, respectively (07RJO1548).

Reaction of 2-aminopyridine and 15 allene in boiling MeOH gave 17 2H-pyrido[1,2-a]pyrimidin-2-one (07T10511). In the initial step the pyridine nitrogen attacked on the allenic moiety, followed by the cyclization of the formed 16 to yield 17.
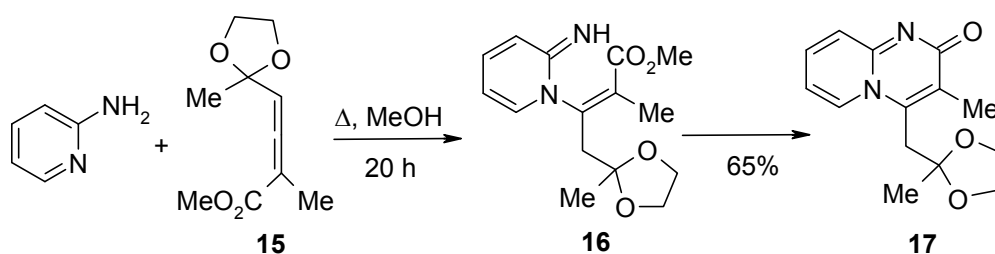
Reactions of 21 2-aminotetrahydropyridine with 22 and 23 3-ethoxyacrylonitriles provided 24 and 25 2-amino-7,8-dihydro- and 2-imino-1,2,7,8-tetrahydro-6H-pyrido[1,2-a]pyrimidine-6-thiones, respectively (08MI9).
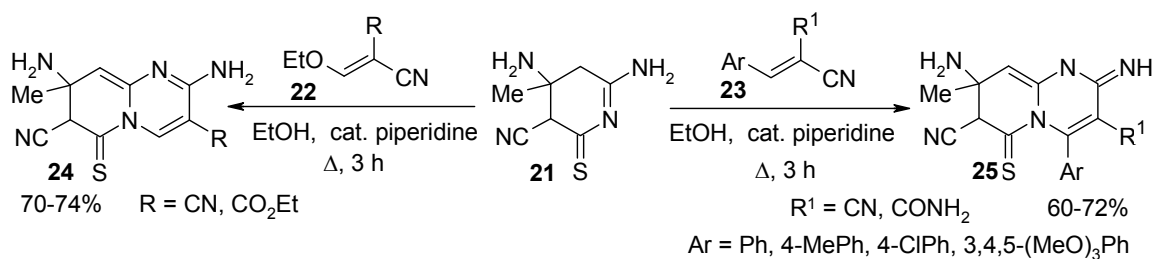
Thermal reaction of 2-aminopyridine and diethyl malonate at 100-110 °C for about 6 h gave a mixture of *anhydro*-(2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidinium)hydroxyde and 4-hydroxy-1,8-naphthyridin-2(1*H*)-one (05MI2, 07HC19). The yield of naphthyridinone was higher when the reaction was carried out at higher reaction temperature (180-200 °C). 2,9-Dihydroxy-4*H*-pyrido[1,.2-*a*]pyrimidin-4-one was obtained in the reaction of 3-hydroxy-2-aminopyridine with diethyl malonate at 170 °C for 18 h and with bis(2,4,6-trichlorophenyl) malonate in boiling bromobenzene for 3 h in 82% and 98% yield, respectively (07OBC2670). When 2-aminopyridine and bis(2,4,6-trichlorophenyl) malonate was reacted in boiling POCl$_3$ for 48 h 2-chloro-9-hydroxy-4*H*-pyrido[1,.2-*a*]pyrimidin-4-one was the product in 32% yield. Cyclocondenzation of a 2-aminopyridines and bis(2,4,6-trichlorophenyl) malonate in high boiling solvent (toluene, xylene) afforded 2-hydroxy-4-oxo-4*H*-pyrido[1,.2-*a*]pyrimidin-4-one derivatives (07BMC7087, 09WOP2009/034976). Heating an 1 : 2 ratio of 2-aminopyridine and bis(2,4,6-trichlorophenyl) 2-phenylmalonate at 250 °C for 15 min under solvent-free microwave reactor afforded 2-hydroxy-3-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one in 82% yield (07TL8250).

R = H, 3(9)-Me, 4(8)-Me, 5(7)-Me, 6(6)-Me, 5(7)-Cl

97 70-84%

98 11-26%

99
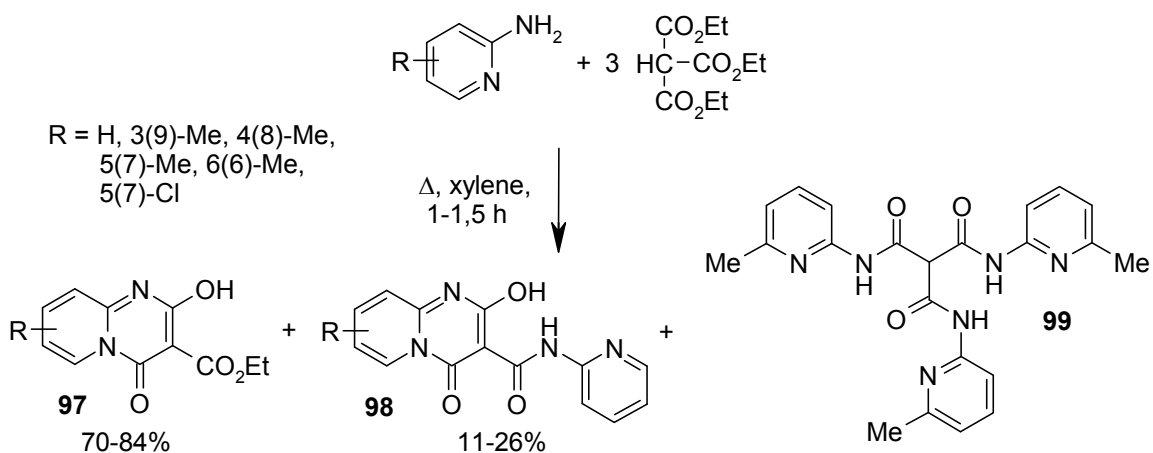
Thermal reaction of 2-aminopyridines and triethyl methanetricarboxylate was studied in different high boiling solvents (07CHE729). The amount of **98** side products, formed from **97** ester by amidation with the respective 2-aminopyridine, were minimized using a two fold excess of methanetricarboxylate in boiling xylene to give the best yields of **97** esters. From 6-methyl-2-aminopyridine only a mixture of **98** (R = 6-Me) amide and **99** non-cyclized product was obtained.

R = Ph, CH$_2$CF$_3$

R^2 =

R = CH$_2$CF$_3$
CH$_2$CH=CH$_2$
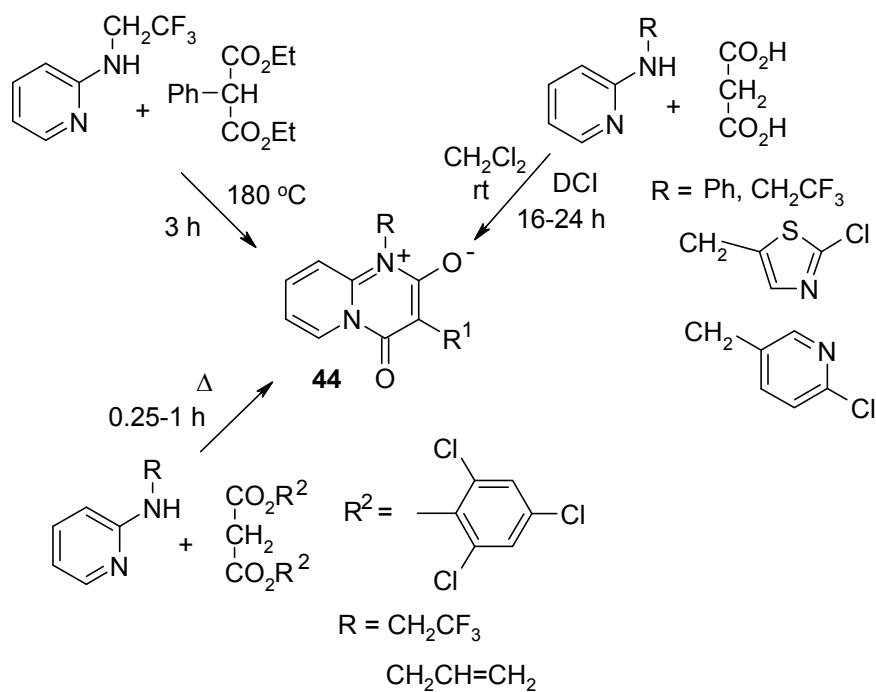
1-Substituted *anhydro*-(2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidinium)hydroxyde **44** (R^1 = H, Ph) were prepared in the reaction of 2-(substituted amino)pyridines with diethyl 2-phenylmalonate, bis(2,4,6-trichlorophenyl) malonate and malonic acid (09WOP2009/099929).

45 + **46** → **47**
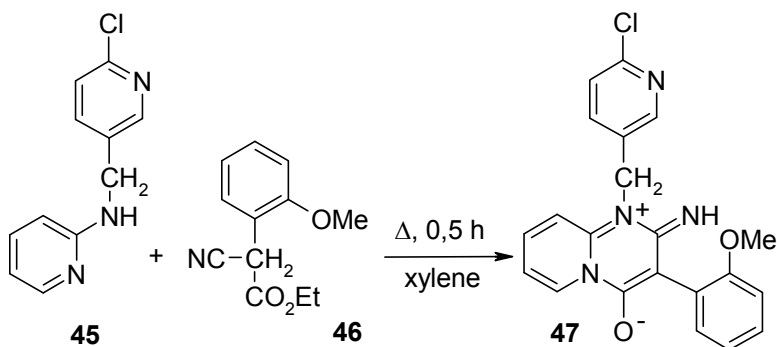
Cyclocondensation of **45** 2-(substituted amino)pyridine and **46** cyanoacetate in boiling xylene yielded **47** Zwitter ionic bicycle (09WOP2009/099929).

R = 5(7)-Me, 5(5)-Cl, 5(7)-Br, 5-iodo, 5(7)-piperidino, 3(9)-morpholino,
4(8)-morpholino, 5(7)-morpholino, 3(9)-5(7)-morpholino,
5(7)-iodo-3(9)-ethoxycarbonylamino,
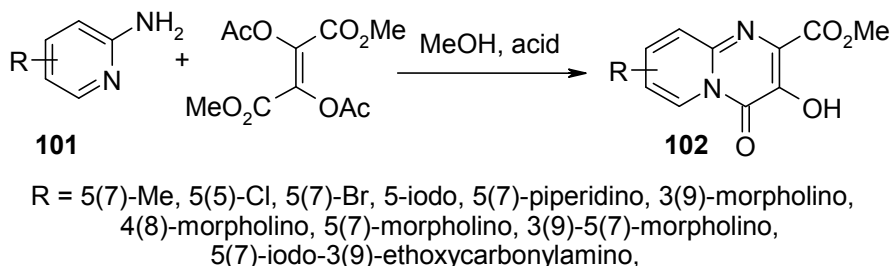
Reaction of **101** 2-aminopyridines and dimethyl diacetoxyfumarate in the presence of an acid (AcOH, *p*TSA) in MeOH afforded **102** methyl 3-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylates in poor yields (08WOP2008/077188).

Cyclocondenzation of 2-aminopyridines and β-oxo esters under acidic conditions [in boiling toluene in the presence of *p*-TsOH under a water separator (05APR1019), in PPA at 110 °C (06WOP2006/086381, 07WOP2007/052120, 07WOP2007/002701, 08BMCL688, 08H(75)925, 08SL2836, 08TL3380, 08USA2008/0107623,

08USA2008/0107624, 08USA2008/0107625), and in boiling AcOH (08USP2008/0194616, 08WOP2008/097991)] afforded 2-substituted and 2,3-disubstituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones. That of 3-methyl-2-aminopyridine (06USA206/0122206, 06WOP2006/061373) and 3-benzyloxy-2-aminopyridine (08WOP2008/128436) with 2-acetylbutyrolactone in POCl$_3$ at 90-100 ^{o}C for 5-18 h gave 2,9-dimethyl- and 2-methyl-9-benzyloxy-3-(2-chloroethyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones, respectively, in 31-35% yields. That of 5-fluoro-2-aminopyridine and ethyl (*R*)-4-(benzyloxycarbonylamino)-3-oxopentanoate in AcOH at 90 °C overnigth afforded 7-fluoro-2-[(1-benzyloxycarbonylamino)ethyl]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one in 28% yield (07WOP2007/002701).

Cyclocondenzation of 2-aminopyridine with **30** indole (06HCA2774) and **31** pyrimidine (07HCA1737) in boiling AcOH yielded **32** and **33** 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones, respectively.
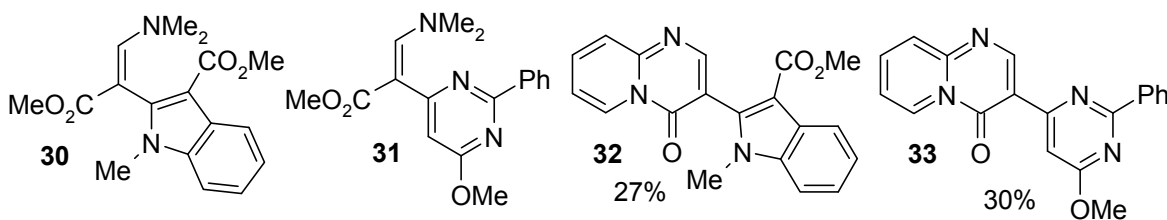
Cyclocondenzation of **11** enamine and 2-aminopyridines in boiling AcO$_2$H afforded **12** 3-substituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (09ARK137).
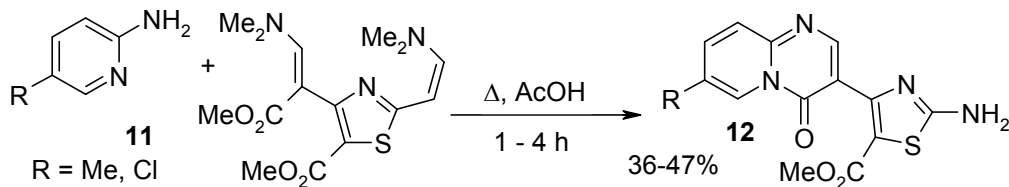
Reaction of 5-methyl-2-aminopyridine and diethyl ethoxymethylenemalonate in MeCN in the presence of DBU under microwave irradiation at 150 °C for 20 min gave ethyl 7-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate in 58% yield (06WOP2006/116713). Cyclocondenzation of 2-amino-3-hydroxypyridine and bis(2,4,6-trichlorophenyl) matonate in boiling bromobenzene for 3 h afforded 2,9-dihydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one in 98% yield (06WOP2006/109084).
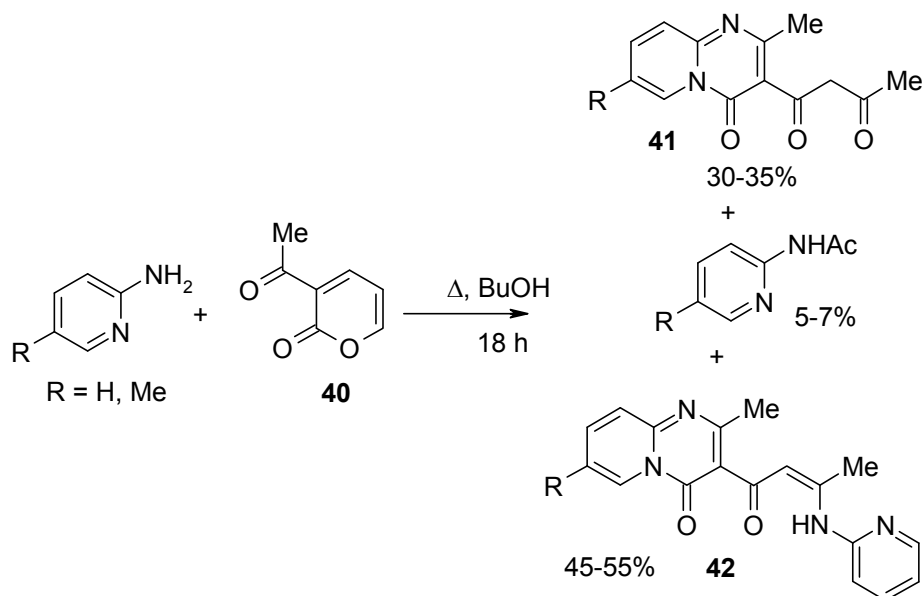
Reaction of 2-aminopyridines and compound **40** in boiling BuOH provided a mixtute of 2-acetamidopyridines, **41** and **42** 3-substituted-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidine-4-ones (05MI3).
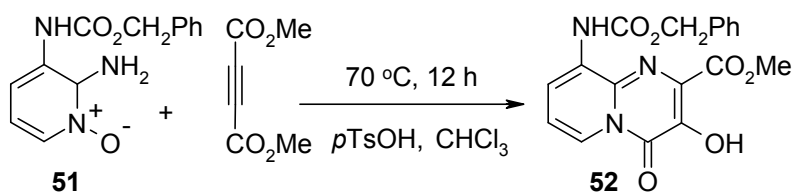
Reaction of **51** pyridine *N*-oxide with DMAD in the presence of *p*TsOH in CHCl₃ yielded **52** methyl 3-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate (07WOP2007/039218).

Michael addition of compound **36** to the ylidenic bond in compounds **35**, leading to the formation of acyclic intermediates **37** which cyclized into 6-imino-1,2,3,4,6,7-hexahydro-8*H*-pyrido[1,2-*a*]pyrimidine-7-carbonitriles **38** via nucleophilic attack of an NH group on a cyano group, followed by tautomerization to **39** 6-amino-1,2,3,4-tetrahydro-8*H*-pyrido[1,2-*a*]pyrimidine-7-carbonitriles (05CHE1525).
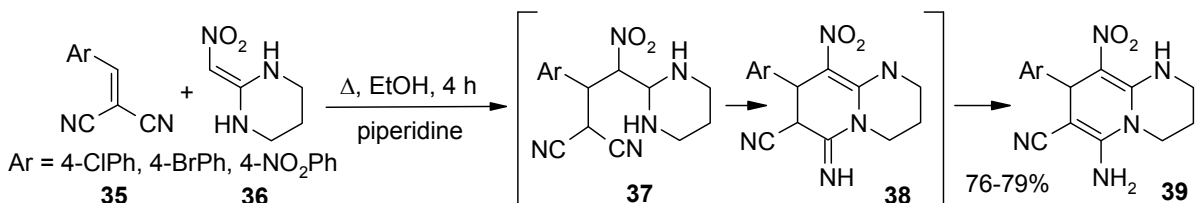
Cyclocondenzations of bis(methylthio)methylenemalonitrile and 2-(aroylmethylene)piperidines in boiling xylene for 4-8 h gave 6-imino-8-methylthio-9-aroyl-1,2,3,4-tetrahydro-6*H*-pyrido[1,2-*a*]pyrimidine-7-carbonitriles in 82-100 yields (07SL761). Reactions of **51** 2-aminopyridines and **52** 3-oxopropanethioamides in boiling AcOH gave **53** 2-methyl-4*H*-pyrido[1.2-*a*]pyrimidine-4-thiones (07RJO276).
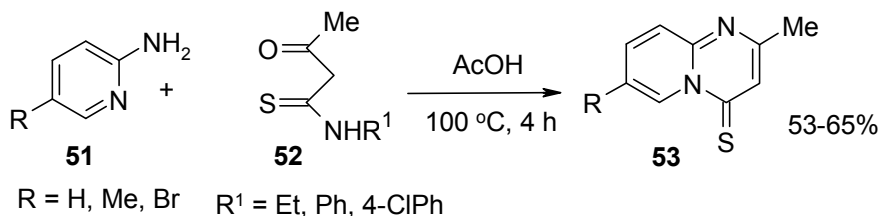
Reaction of 2-aminopyridine and **40** furo[2,3-*b*]quinoxaline in boiling AcOH provided **41** 2*H*-pyrido[1,2-*a*]pyrimidin-2-one (05AFF151).
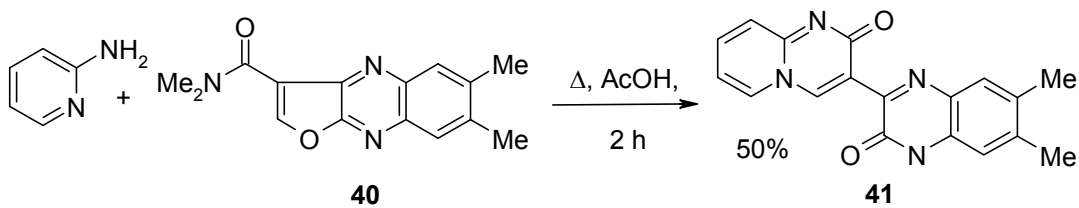
Reaction of 2-methylaminopyridine and 3-bromopropionic acid in MeCN at ambient temperature for 2 days gave 1-methyl-2-oxo-1,2,3,4-tetrahydropyrido[1,2-a]pyrimidinium bromide in 84% yield (07ARK55). Similar raction of 2-aminopyridine and 3-chloropropionic acid for 10 days provided 2-oxo-1,2-dihydropyrido[1,2-a]pyrimidinium chloride in 73% yield.

Cyclocondenzation of 2-aminopyridine, its 3- and 6-hydroxy derivatives with β-oxo esters in PPA at 100 °C for 1 h afforded 2-substituted 4H-pyrido[1,2-a]pyrimidin-4-ones in 35-97% yields (07JMC4917). Reaction of 2-amino-3-hydroxypyridine and 2-unsubstituted β-oxo esters in refluxing xylene for 16 h gave 3-unsubstituted 9-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-ones in 8-76% yields (09WOP2009/063901).

Methyl 2-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidine-8-carboxylate was prepared in the reaction of bis(2,4,6-trichlorophenyl) malonate and methyl 2-aminopyridine-4-carboxylate in boiling toluene for 1h in 51% yield (06BMC1993).

Cyclocondensation of 2-aminopyridines and 2-methyl-3,3-bis(methylthio)acrylate in EtOH in the presence of NaOEt and benzene in the presence of Et₃N afforded **32** 2-ethoxy- and **34** 2-methylthio-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carbonitriles, respectively (08MI10).

32 65-74%   NaOEt, Δ, EtOH, 3 h   R = H; 3(9)-; 4(8)-; 5(7)-Me; 5(7)-Cl; 3,5(7,9)-Br₂; 5(7)-NO₂   Et₃N, Δ, HPh, 3 h   **34** 64-74%
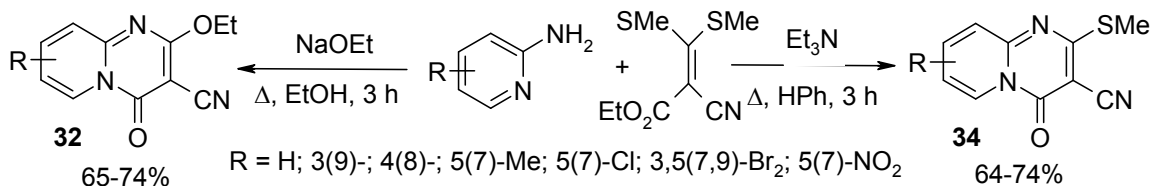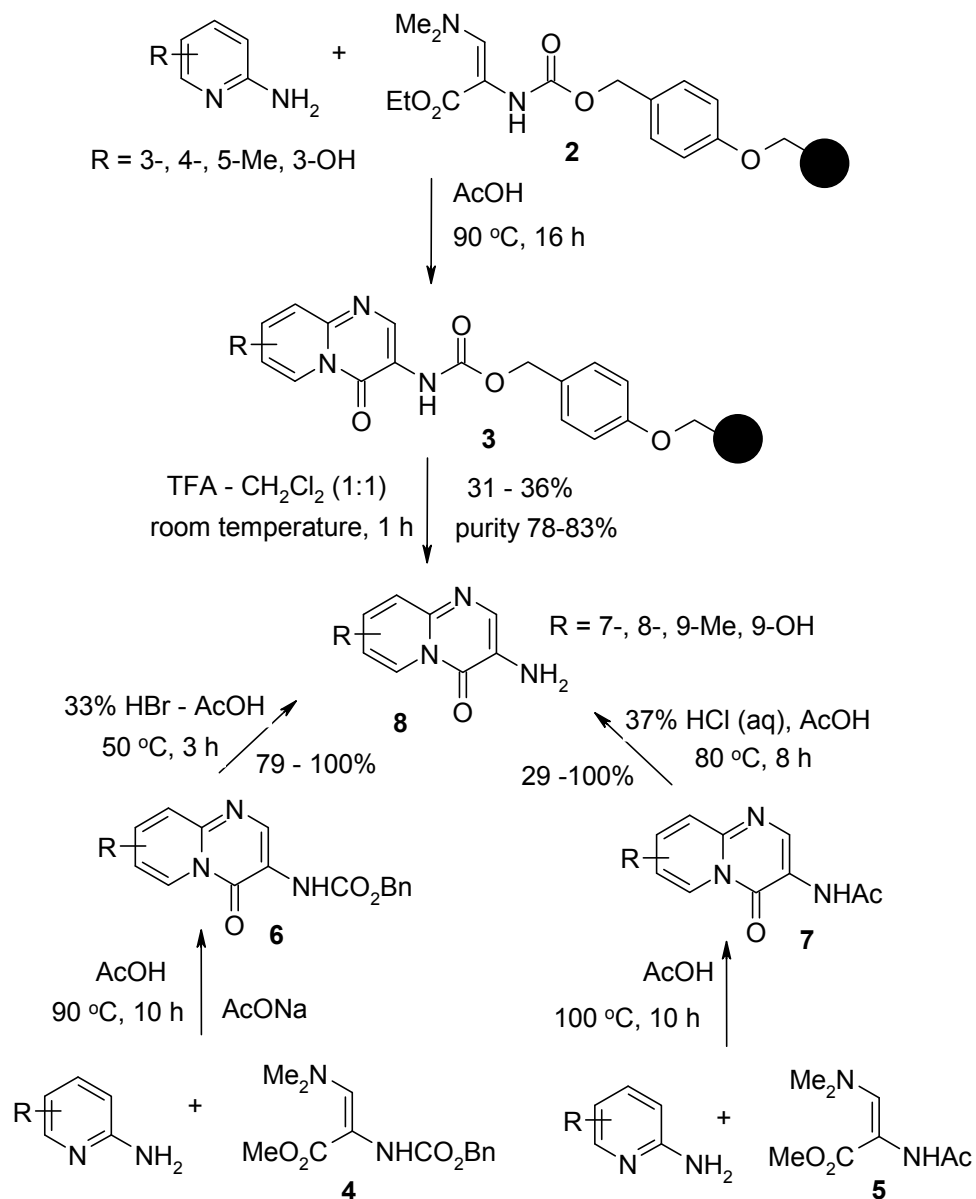
Scheme 1.

3-Amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**8**) were prepared by parallel solid-phase and solution-phase synthesis (Scheme1) (06JCO95). Polymer-bound (*Z*)-2-benzyloxycarbonylamino-3-(dimethylamino)prop-2-enoate (**2**) was reacted with 2-aminopyridine gave **3** polymer-bound 3-amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones, and **8** were cleaved by treatment with an 1:1 mixture TFA – CH$_2$Cl$_2$ at ambient temperature. The purity of **8** bicycles were 78-83%. Better yields were achieved by using parallel

solution-phase synthesis reacting 2-aminopyridines with **4** (*Z*)-2-benzyloxycarbonylamino-3-(dimethylamino)prop-2-enoate and **5** (*Z*)-2-acetylamino-3-(dimethylamino)prop-2-enoate.

Cyclocondenzation of 2-aminopyridine with **9** 3-dimethylaminoacrylate in boiling AcOH afforded **10** 3-benzyloxyamino-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (08H(75)2477).
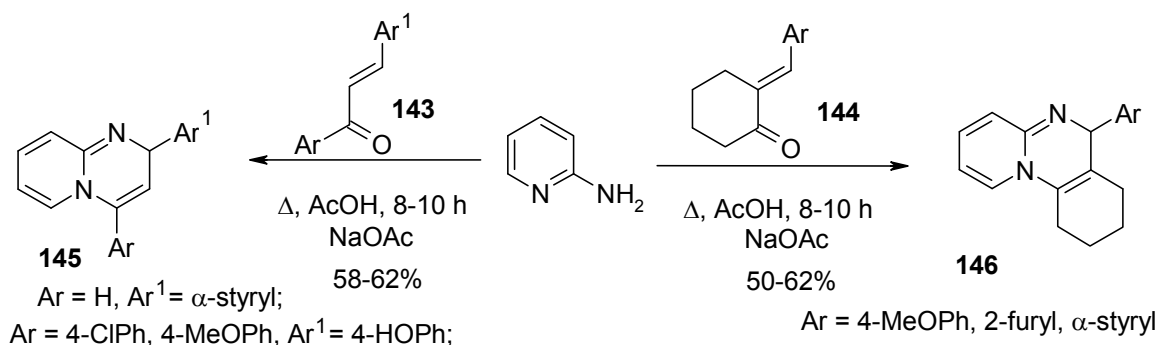
Reaction of 2-aminopyridine with **143** and **144** α,β-unsaturated ketones in boiling AcOH yielded **145** 2,4-disubstituted 2*H*-pyrido[1,2-*a*]pyrimidines and **146** 7,8,9,10-tetrahydro-6*H*-pyrido[1,2-*a*]quinazolines, respectively (06IJH39).

Base catalyzed cyclocondenzation of 2-iminopiperidine hydrochloride with **11** β-oxo ester yielded **12** tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one under microwave conditions (06WOP2006/008523). That of 2-amino-3,4,5,6-tetrahydropyridine and **111** β-oxo esters yielded **112** 2,3-disubstituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (06WOP2006/041968). Similarly **45** 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones were prepared from **43** amidine and **44** β-oxo esters (07WOP2007/057790, 08EPP1939187, 08WOP2008/078196). Starting from 2-amino-3-methyl-3-(1,3-dioxo-

2,3-dihydro-1*H*-isoindol-2-yl)-3,4,5,6-tetrahydropyridine and **44** (R = N) β-oxo ester

yielded 2-(4-pyrimidinyl)-9-methyl-9-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)6,7,8,9-

tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (08EPP1939187, 08WOP2008/078196).
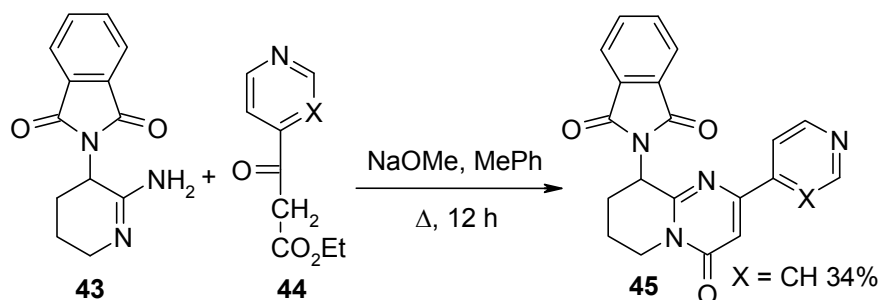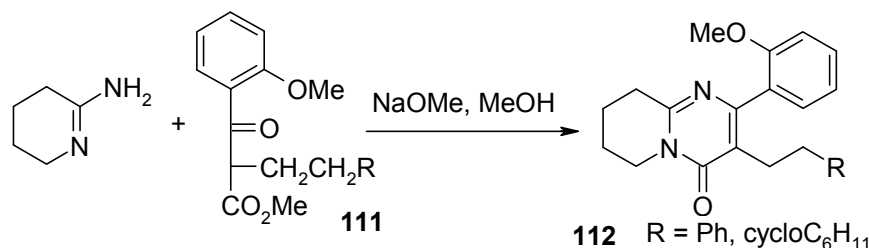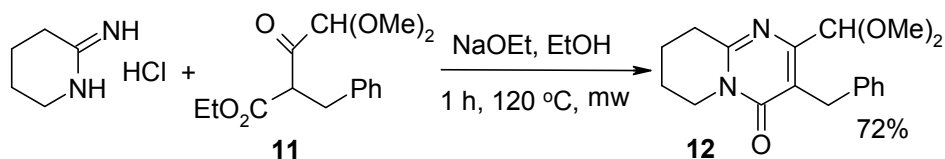
Methoxy group of 2-(2-methoxyphenyl)-3-substituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones

were demethylated by treatment with BBr$_3$ in CH$_2$Cl$_2$ (06WOP2006/041968).

Reaction of **13** organorhenium(I) derivative with 2-aminopyridine (5 mol equiv.) in

CH$_2$Cl$_2$ at room temperature for 3 h gave **14** pyrido[1,2-*a*]pyridinium salt (06OM416).

15 Base was liberated from **14** by treatment with MeONa in THF.

[Re] = {[MeC(CH$_2$PPh$_2$)$_3$](CO2) Re}
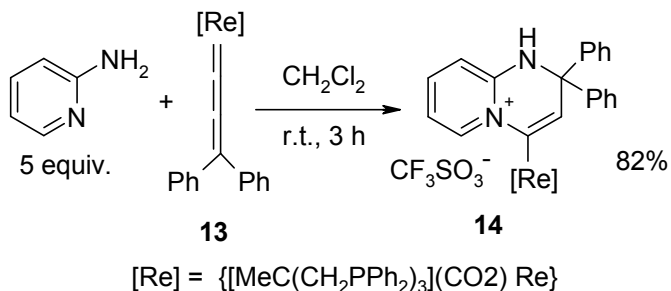
While the reaction of 2-aminopyridine and its 3-, 4-, and 5-methyl derivatives with **16** gave **17** bicycles, its 6-methyl derivative yielded only **18** condensation product (04RCB2060).
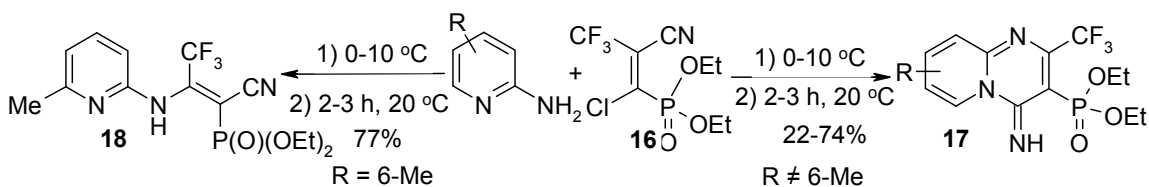
Reaction of 2-aminopyridine and **28** 4-methoxy-1,1,1-trichloro-3-buten-2-ones in boiling EtOH provided **29** 2-substituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (06JHC231).
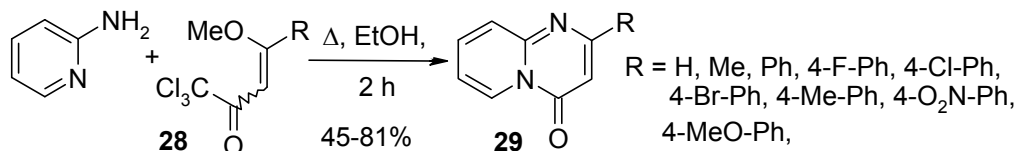
Cyclocondenzation of 2-aminopyridine and **30** enamino ester in boiling AcOH gave **31** 4*H*-pyrido[1,2-*a*]pyrimidin-4-one (05H(66)207). Under similar conditions 3-benzoyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**43**) was prepared in the reaction of 2-aminopyridine and **42** benzoyl derivative (05JCM440).
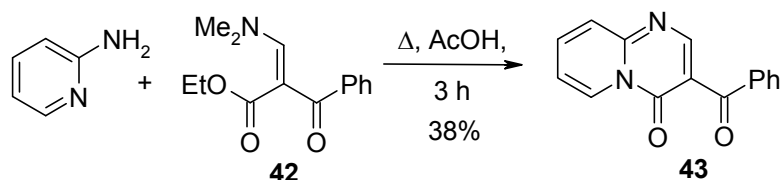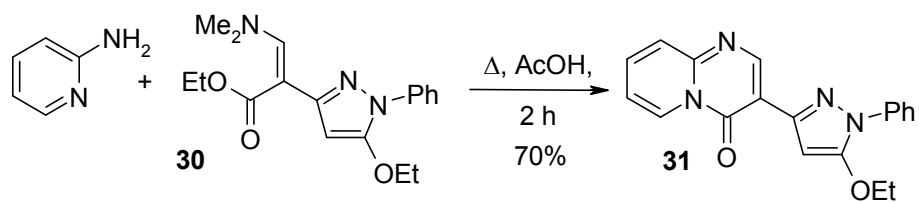
32 6*H*-Pyrido[1,2-*a*]pyrimidin-6-ones were prepared in the reaction of 2-phenylethynylpyrimidine and **31** dimethyl malonates in diglyme in the presence of NaH at 150 °C (06H(67)523).
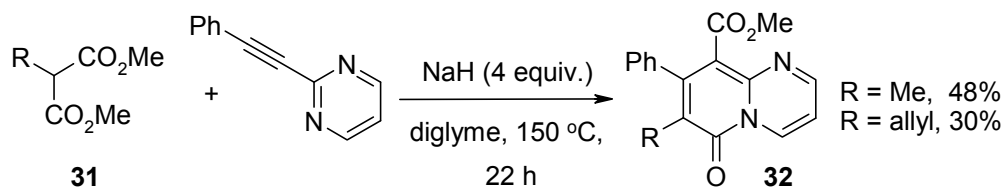
Reactions of **133** acrylamides and **134** 2-(aroylmethylene)perhydropyrimidine in the presence of Et₃N in MeCN afforded **124** 1,2,3,4,7,8-hexahydro-6*H*-pyrido[1,2-*a*]pyrimidin-6-ones (09MIP2).


R = Ph, 4-MeOPh;   Ar = Ph, 4-ClPh, 4-FPh, 4-MeOPh;
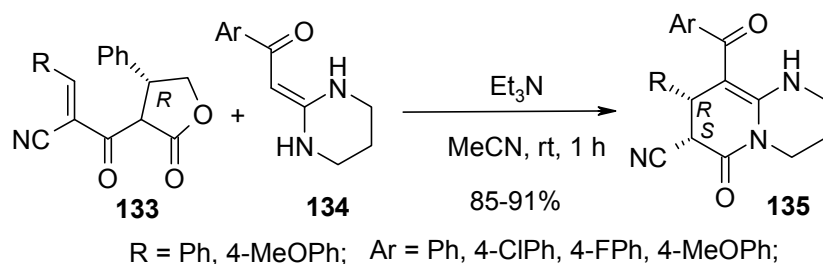
Reaction of 2-aminopyridine and **33** 2-arylmethylene-β-oxo esters in boiling benzene usually yielded a mixture of **34** and **35** 4*H*-pyrido[1,2-*a*]pyrimidines (05RCB2841).

33	Ar	R	R^1	34	35
	Ph	CF$_2$H	Et	42%	47%
	Ph	CF$_3$	Et	38%	25%
	4-MeOPh	CF$_3$	Et	30%	48%
	Ph	(CF$_2$)$_2$H	Me		56%
	4-MeOPh	(CF$_2$)$_2$H	Me		52%
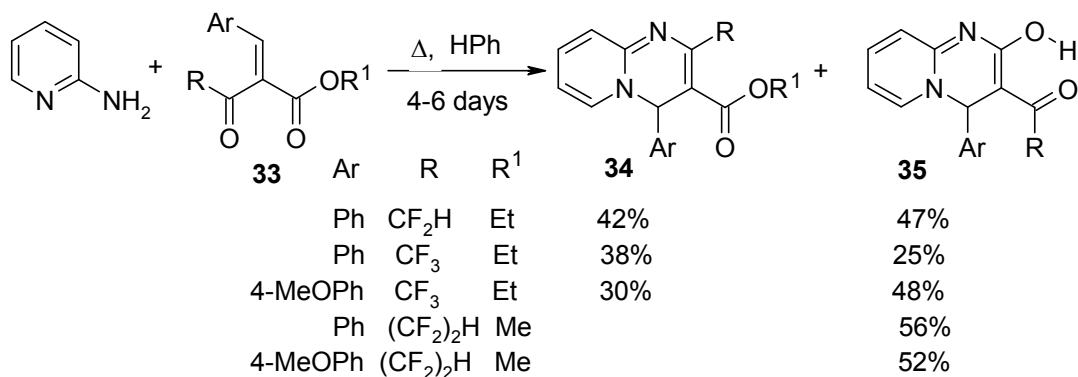
Reaction of 2-aminotetrahydropyridine and **88** 2-hydroxy-3-benzyloxyfumarete in MeOH in the presence of DBU yielded **89** 3-benzyloxy-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate (07TL6552).
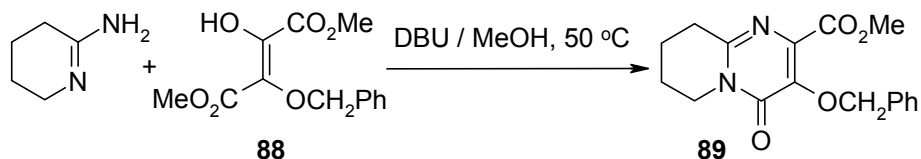

Heating a mixture of **90** 3-formylchromanone and **91** pyridinone in the presence of TMSCl in DMF in a sealed tube on water bath yielded **92** 4*H*-pyrido[1,2-*a*]pyrimidin-4-one (08S1069).
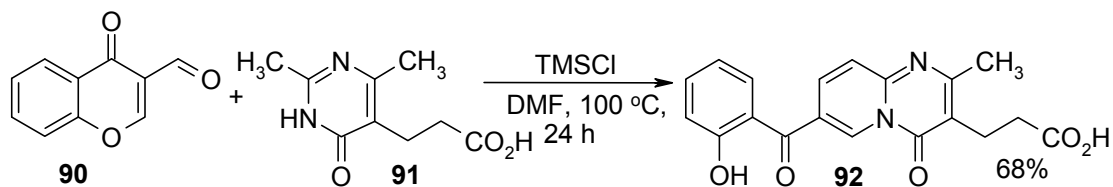
Cyclocondenzation of acrylaldehide and **11** piperidine afforded **12** 6*H*-1,2,3,4,7,8-hexahydropyrido[1,2-*a*]pyrimidine (06WOP2006/056108).
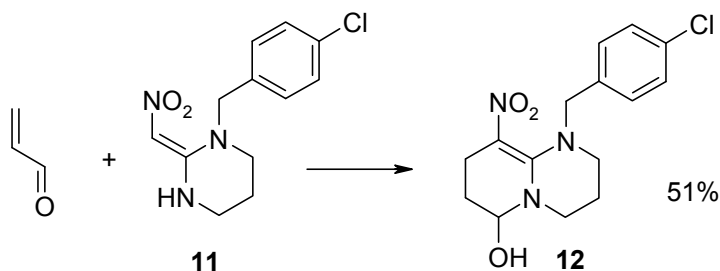
Reaction of **13** acrylates and **14** piperidines in the presence of AcOH catalyst gave **15** hexahydropyrido[1,2-*a*]pyrimodin-6-ones (07MIP4).
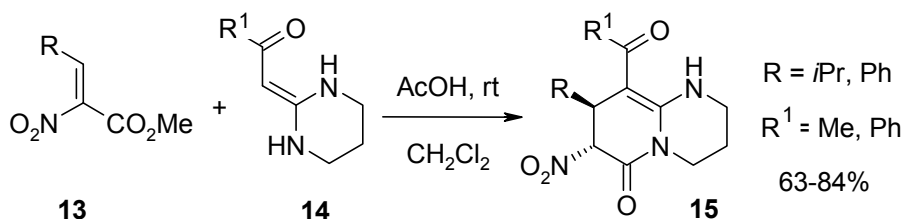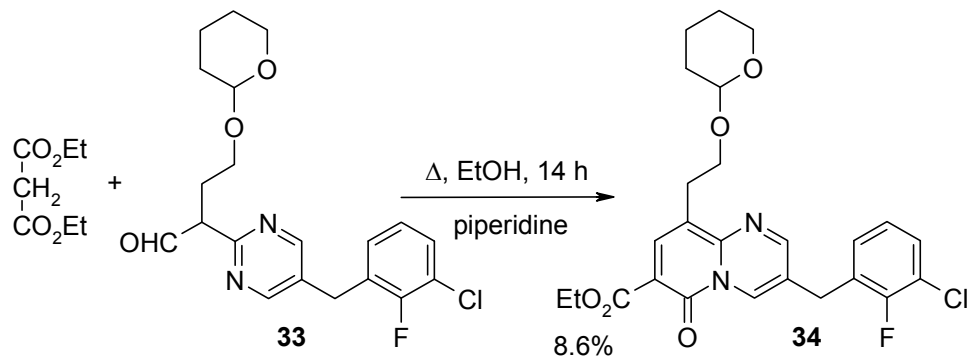

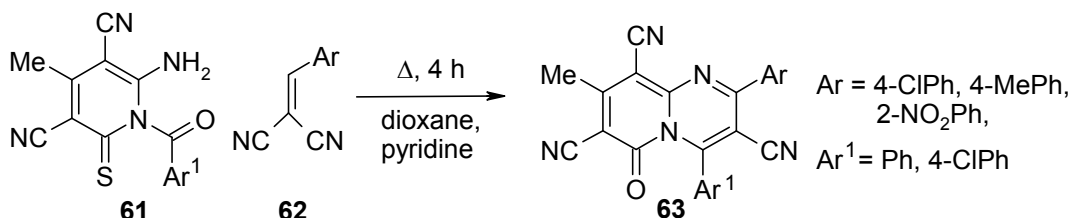5. By Formation of Two Bond from [4+2] Atom Fragments

Compound **13,** prepared from 3-amino-3-phenylpropionic acid with SOCl$_2$, was reacted with 2-piperidone under reflux in toluene for 2 h. to afforded **14** hexahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (05MCR347).
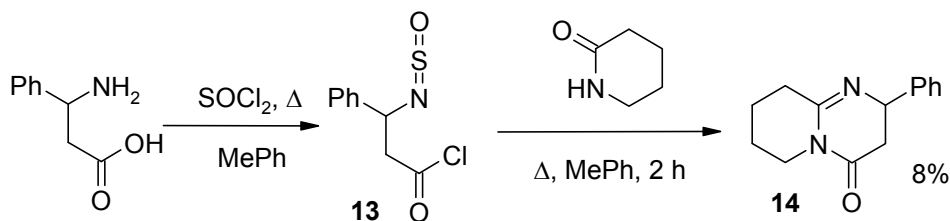
Reaction of diethyl malonate and **33** pyrimidine in the presence of piperidine in boiling EtOH yielded **34** 6-oxo-6*H*-pyrido[1,2-*a*]pyrimidine-7-carboxylate (06WOP2006/033422).
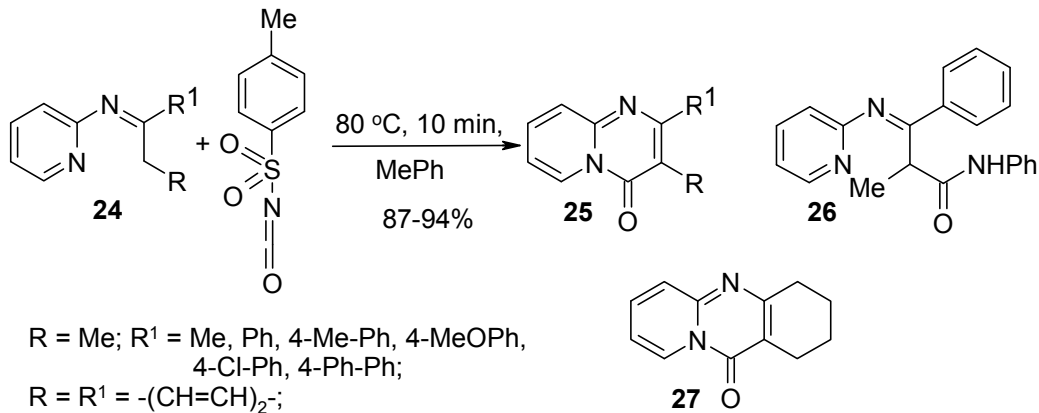
Cyclocondenzation of **61** pyridine-2-thiones with **62** arylidenemalononitriles in boiling dioxane in the presence of few drops of piperidine afforded **63** 6*H*-pyrido[1,2-*a*]pyrimidine-6-thiones (06JSF293).
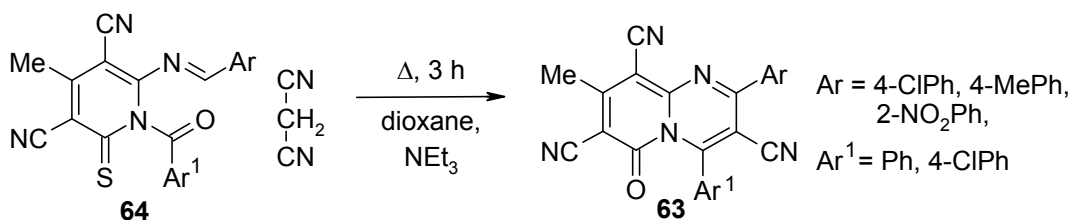

6. By Formation of Two Bond from [5+1] Atom Fragments

By the reaction of **24** ketimines with 2 mol equiv. of **25** isocyanates **26** 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones were obtained in excellent yields (06OBC203). The reaction did not occur with cyclohexylisocyanate, and (2,6-dimethylphenyl)isocyanate gave only 6% of **25** (R = Me, R^1 = cyclohexyl). Only 22% of **25** (R = Me, R^1 = Ph) was obtained from **24** (R = Me, R^1 = Ph), when 1 equiv. of tosylisocyanate was applied. Reaction of **24** ketimine (R = Me, R^1 = Ph) and phenylisocyanate in boiling toluene for 24 h provided a mixture of **25** 4*H*-pyrido[1,2-*a*]pyrimidin-4-one (R = Me, R^1 = Ph) (29%) and **26** pyridine (70%). **26** Pyridine could be cyclized into **25** 4*H*-pyrido[1,2-*a*]pyrimidin-4-one (R = Me, R^1 = Ph). Reaction of with **24** ketimine [R = R^1 = -(CH=CH)$_2$-] in boiling toluene for 1 h gave 75% of 1,2,3,4-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-one.

R = Me; R[1] = Me, Ph, 4-Me-Ph, 4-MeOPh,
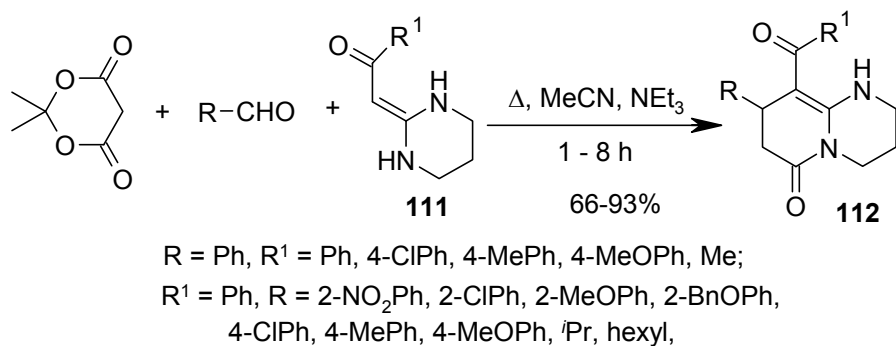4-Cl-Ph, 4-Ph-Ph;
R = R[1] = -(CH=CH)$_2$-;

Cyclocondenzation of **64** pyridine-2-thiones with malononitrile in boiling dioxane in the presence of few amounts of NEt$_3$ gave **63** 6*H*-pyrido[1,2-*a*]pyrimidine-6-thiones (06JSF293).
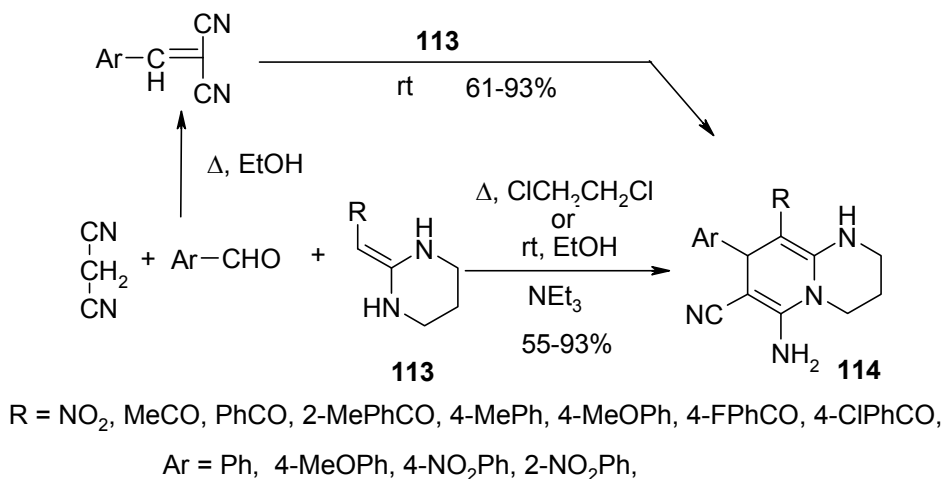

7. By Formation of Three Bond from [3+2+1] Atom Fragments

6-Amino-8-aril-9-nitro-1,2,3,4-tetrahydro-8*H*-pyrido[1,2-*a*]pyrimidine-7-carbonitriles (**39**) were prepared by one-pot reaction of 2-nitromethylenepiperidine (**36**), CH$_2$(CN)$_2$ and aromatic aldehydes in boiling EtOH in the presence of piperidine for 4 h (05CHE1525).

R = Ph, R¹ = Ph, 4-ClPh, 4-MePh, 4-MeOPh, Me;
R¹ = Ph, R = 2-NO₂Ph, 2-ClPh, 2-MeOPh, 2-BnOPh,
4-ClPh, 4-MePh, 4-MeOPh, iPr, hexyl,

Three-component reactions of Meldrum's acid, aldehyde and **111** ketene aminal in the presence of NEt₃ boiling MeCN gave **112** 1,2,3,4,7,8-hexahydro-6*H*-pyrido[1,2-*a*]pyrimidin-6-ones (06SL1835, 07MIP58). In the case of **111** (R¹ = iPr and hexyl) longer reaction period (24-96 h) was necessary for good yields. When ketone (as carbonyl reactant) or dialkyl malonates (instead of Meldrum's acid) were used, the reactions were usually very slow and resulted in a complicated mixture of products.

R = NO₂, MeCO, PhCO, 2-MePhCO, 4-MePh, 4-MeOPh, 4-FPhCO, 4-ClPhCO,
Ar = Ph, 4-MeOPh, 4-NO₂Ph, 2-NO₂Ph,

Tree-component reactions of malononitril, aromatic aldehydes and **113** perhydropiperidines yielded **114** 9-substituted 6-amino-8-aryl-1,2,3,4-tetrahydro-8H-pyrido[1,2-*a*]pyrimidine-7-carbonitriles (07MIP3).

One-pot, three-component reactions of **121** isocyanides, **122** dialkyl acetylenedicarboxylate and **123** *N*-(2-pyridylamines under mild reaction conditions

yielded **124** 2-amino-4*H*-pyrido[1,2-*a*]pyrimidine-3,4-dicarboxylates (07TL4195, 07T11135).

R = *t*Bu, cyclohexyl; R^1 = Me, Et; R^2 = OEt, CO$_2$Et; R^3 = H, 7(5)-Me, 8(4)-Me
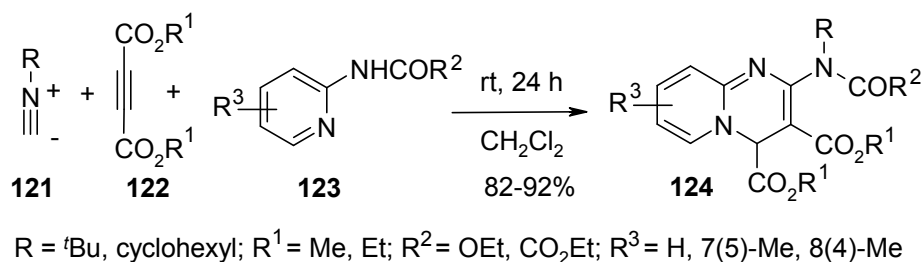
8. By Formation of Three Bond from [4+1+1] Atom Fragments

3-Ethyl-2-hetaryl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**103**) were obtained by [2+2] carbonylative cycloaddition of **101** imines with allyl bromide under CO pressure in the presence of Pd(OAc)$_2$, PPh$_3$ and Et$_3$N in THF (06T12064). In the first step**102** β-lactams formed, which then rearranged into **103** 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones on the action of NEt3. The proposed reaction mechanism is depicted in Scheme 1.


Ar = 4-methylthiazol -2-yl, 98%

benzothiazol -2-yl,   40%
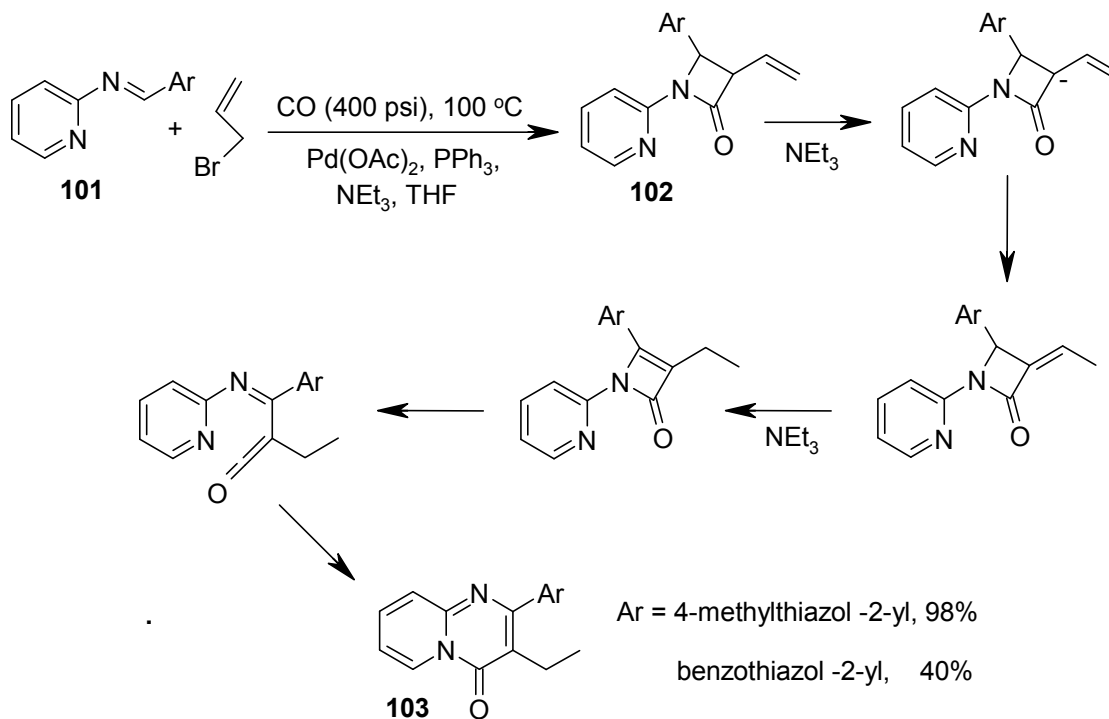
9. Ring Transformation

Rearrangenent of *N*-(2-pyridyl)-3-oxoheptanamide in cc H_2SO_4 at ambient temperature for 48 h afforded 2-butyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one in 29% yield (08USP2008/0194616, 08WOP2008/097991).

Reaction of **88** furochromone-6-aldehyde and 2-aminopyridine in alcoholic KOH yielded **89** 3-substituted 9*aH*-pyrido[1,2-*a*]pyrimidine (09BML2420).
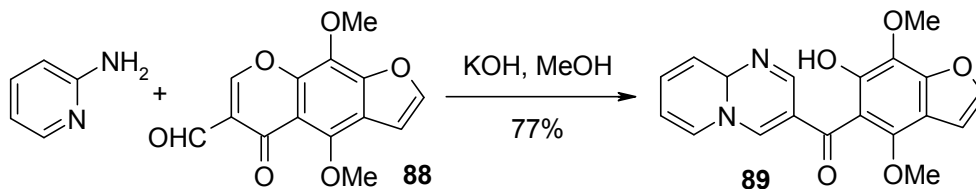
Heating **90** bicyclic 1,2,4-oxadiazoline in *o*-xylene yielded **91** 3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate (07TL6552).
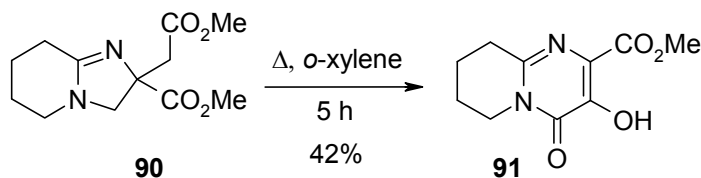
Diastereomeric mixtures of **101** betaine, obtained in the reaction of 2-aminopyridines and methylglyoxal, was identified as high-affinity inhibitiors of cystic fibrosis transmembrane conductance regulator chloride channels (07MI4).
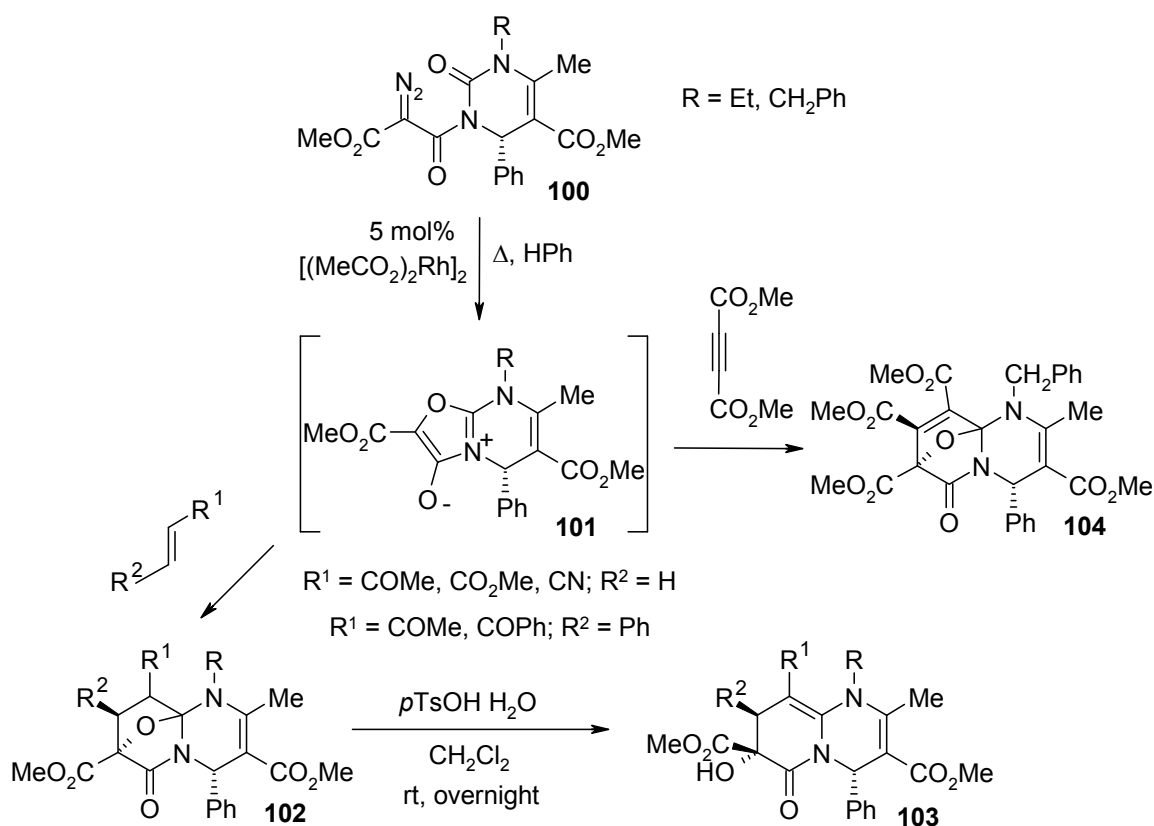
Rh(II)-mediated dipolar cycloaddition of **101** isomünchnone dipole, formed in situ from **100** pyrimidin-2-one in the presence of rhodium(II) acetate dimer in boiling benzene, with dipolarophiles gave **102** oxygen-bridged bicyclic compounds, which could be transformed into **103** 1,4,7,8-tetrahydro-6H-pyrido[1,2-a]pyrimidin-6-ones by treatment with TsOH (07JOC9998). Dimethyl acetylenedicarboxylate yielded compound **104**.

10. Rearrangement

Rearrangement/cyclization of **10** pyridine-N-oxides, obtained in the reaction of 2-aminopyridine N-oxides and DMAD in CHCl$_3$, by heating in boiling o-xylene gave **11** 3-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidin-2-carboxylates, which were purified through ester formation (07WOP2007/039218, 08TL6556). 9-Benzyloxyamino derivative of **11**

(R = NHCO$_2$CH$_2$Ph) was obtained from **13** pyridine-*N*-oxide in the reaction of DMAD in the presence of *p*TsOH in boiling CHCl$_3$ (08TL6556).
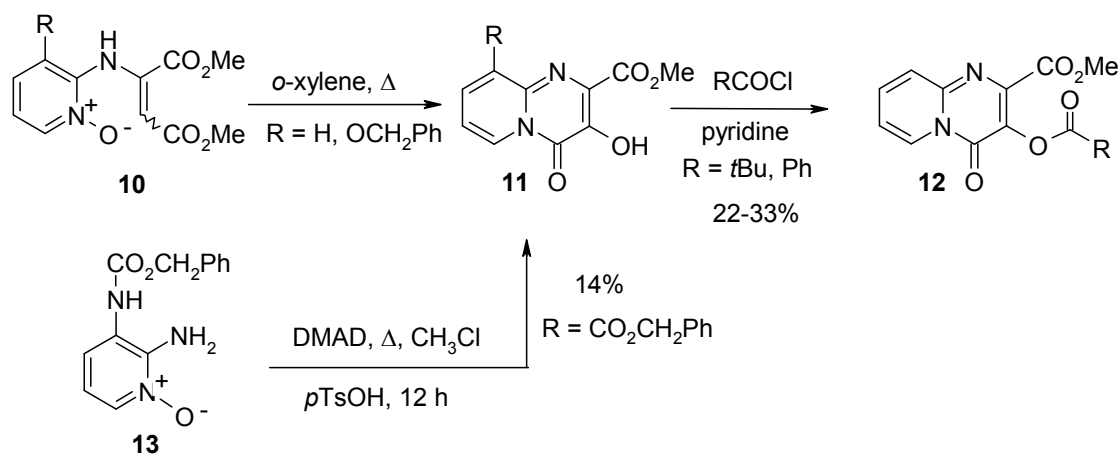

11. Miscellaneous

The tandem-cyclization of **17** β-amino acid containing dipeptides in boiling toluene in the presence of *p*-TsOH afforded **18** (6*S*,9*aR*)-perhydropyrido[1,2-*a*]pyrimidine-6-carboxylates in high diastereoselectivity (06OL239).

17a (*S*)-3-Ph
17b (*R*)-3-Ph

18a (*S*)-2-Ph dr = 19:1
18b (*R*)-2-Ph dr > 99:1
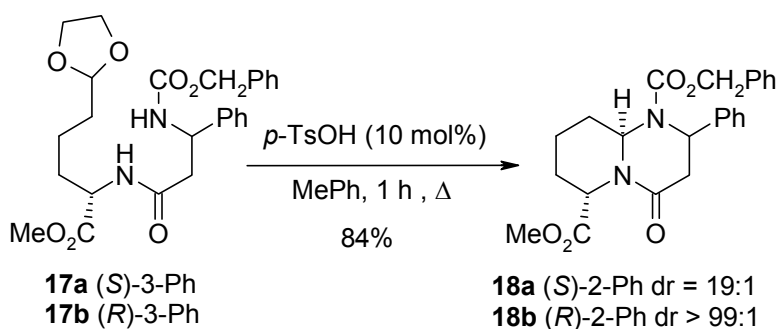
Cyclohydrocarbonylation of **20** dipeptide catalyzed by Rh-BIPHEPHOS complex gave **21** 4-oxoperhydropyrido[1,2-*a*]pyrimidine-6-carboxylate with high regioselectively (07JOC1871).
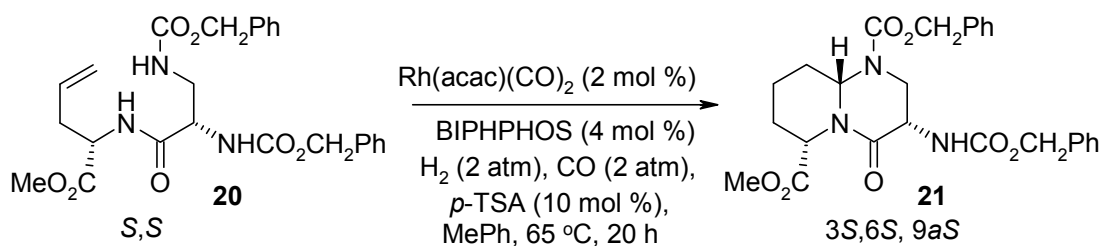
Perhydropyrido[1,2-a]pyrimidin-6-one **18** was obtained when its **7** precursor was split from resin (07JCC1060).
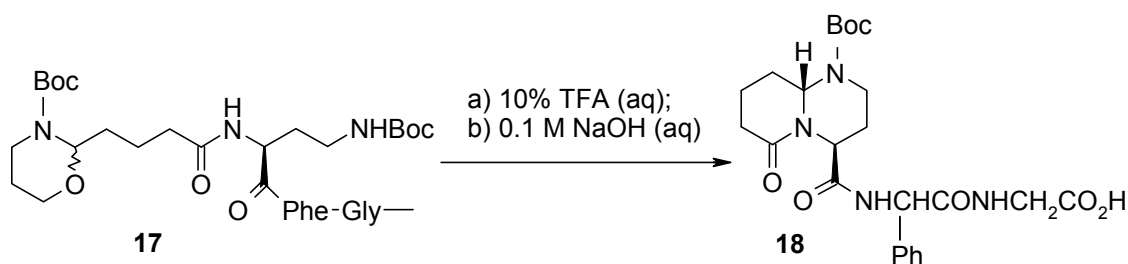

D. Applications and Important Compounds

3-Aroyl-3,3-dihydro-2*H*-pyrido[1,2-a]pyrimidinium perclorates (**16**) exhibited promising nitric oxide synthases inhibitory activities (09EJM2877). Compound **44** is a potent phosphoinositide 3-kinase γ (PI3Kγ) inhibitor (06EJM558). R107474 is a potent and relatively selective α2-adrenoceptor antagonist (06BMC4526). Its radiolabeled derivative might be a suitable PET ligand for human use.
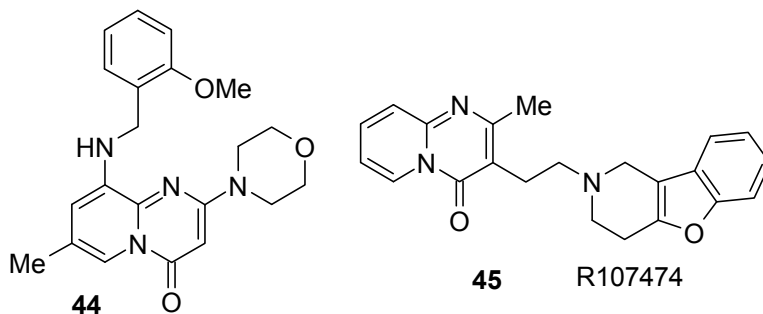
Compound **102** had a high passive permeability, the highest bioavailability of compounds **100**, **101**, and **102**; and a high colonic bioavailability relative to risperidone (06JPS883).

|		
100	R = H,	R^1 = Cl
101	R = Me,	R^1 = Cl
102	R = Me,	R^1 = Br
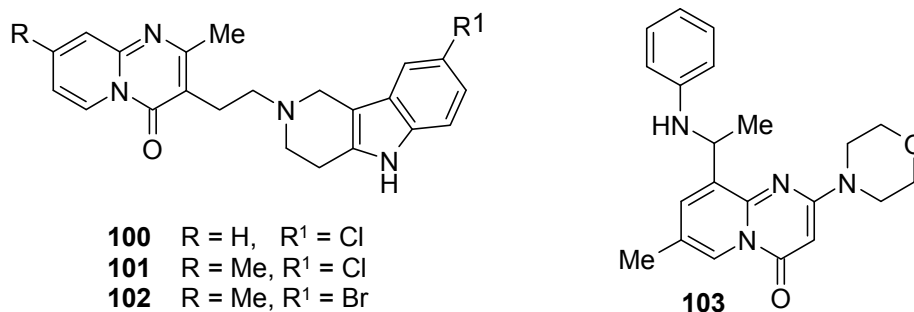
Pyridopyrimidinone **103** (TGX-221) is a phosphoinositide 3-kinase β specific inhibitor (08BJ383), which exhibits antithrombotic activity (06CCT339, 08MI3), and inhibits platelet aggregation and platelet-granulocyte binding (08MI4). 3,8-Dibromo-9-hydroxy-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one was identified as selective hit in a neural cell model of Huntington disease (07NCB99).
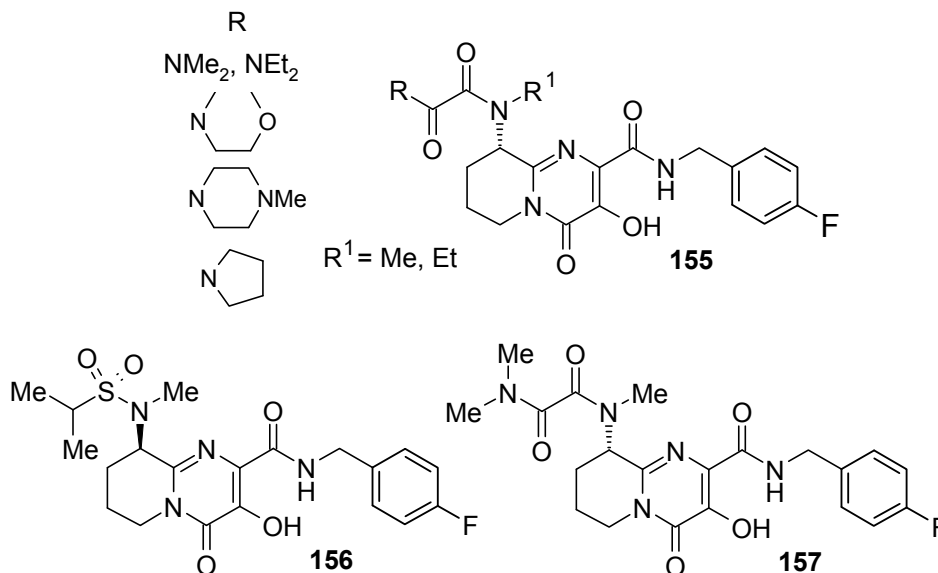
4-Oxo-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxamides **155** (09BML1930), 6,7,8,9-tetrahydro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxamides **156** and **157** (08JMC861)**,**

and their derivatives (09DND873) exhibited a good pharmacological profile and they are potent and orally active HIV-1 integrase inhibitors.
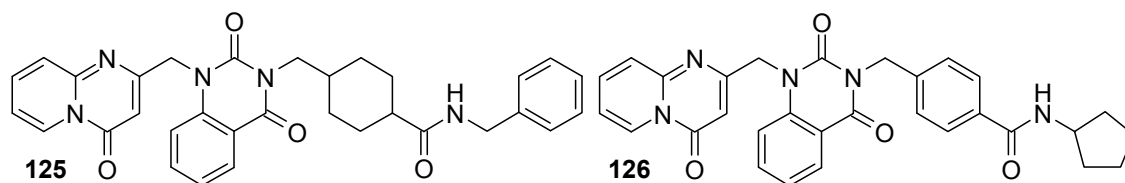
4*H*-Pyrido[1,2-*a*]pyrimidin-4-ones **125** and **126** were identified as inhibitors of cancerous Wnt/β-catenin pathway (09NCB100).

7-Dimethyl-3-nitro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one has a good immunopharmacological profile on different in vitro and in vivo models, and it exhibited antihistaminic, anti-inflammatory and bronchorelaxant activities (08MI2).

A novel polymorph of risperidone (02MIP1) was patented. Polymorphic forms of paliperidone were also patented (09USA2009/0061005, 09WOP2009/016653). Different 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones were patented as effective compounds inhibiting neuronal cell death (07USA2007/0027164) and as a part of recording layers of optical recording materials (07JP2007001095).
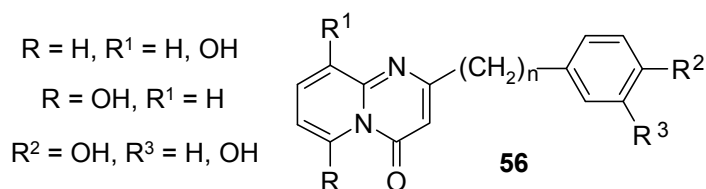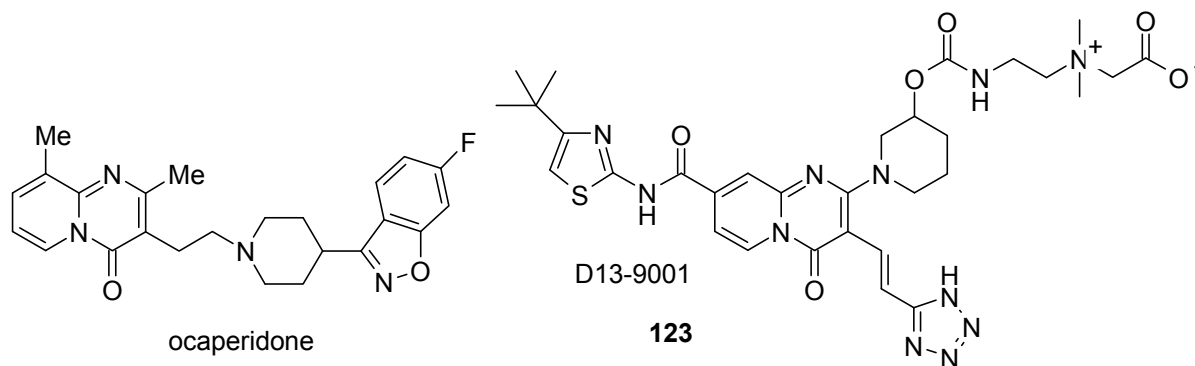

4*H*-Pyrido[1,2-*a*]pyrimidin-4-ones **56** exhibited selective aldose reductase inhibitory activity (07JMC4917).

Pemirolast was also used to develop an electrophysiologic method for predicting corneal epithelial breakdown by antiallergic eye drops (08MI7). Ophthalmic compositions

(*Chem. Abstr*. **151**, 470200 (2009) and antiallergic tablets (09MIP3) of pemirolast were patented.

A composition comprising ocaperidone, an antipsychotic drug, as an active substance and an effective amount of water-soluble polymers to increase solubility of ocaperidone was patented (06EUP1690540). Different salts (e.g. with pyroglutamic acid, N-(2-carboxyphenyl)glycine acid, orotic acid, galactic acid) of ocaperidone were patented (06WOP2006/090285). The highly soluble **123** 4*H*-pyrido[1,2-*a*]pyrimidin-4-one (D13-9001) has good potency in vitro and displayed excellent MexAB-OprM specific efflux pump inhibitory activity in vivo in a rat pneumonia model of *Pseudomonas aeruginosa* (07BMC7087).

2-Piperidino-4*H*-pyrido[1,2-*a*]pyrimidin-4-one exhibited in vitro inhibitory activities on human platelet aggregation induced in platelet-rich plasma by adenosine diphosphate, collagen and A23187 (07JMC2886).
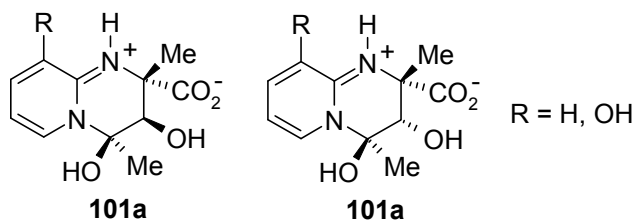
Diastereomeric mixtures of **101** betaines, obtained in the reaction of 2-aminopyridines and methylglyoxal, were identified as high-affinity inhibitiors of cystic fibrosis transmembrane conductance regulator chloride channels (07MI4).

3,4-Dihydro-2*H*-pyrido[1,2-*a*]pyrimidine could be used as acid scavenger in the esterification and amination of alkyl and aryl carboxylic acids and also in glycosylation of 2-amino-2-deoxy sugar (01MI1), but it did not show activity as an acylation catalyst …. (07OL37).

IV. Benzologs of pyrido[1,2-*a*]pyrimidines

   A. Structure

   1. Thermodynamic Aspects

   2. Theoretical Calculations

   3. UV Spectroscopy

   4. IR and RamanSpectroscopy

   5. NMR Spectroscopy

   6. Mass Spectrometry

7. X-Ray Investigations

B. Reactivity

1. Ring Opening

2. Oxidation, Dehydrogenation

3. Hydrogenation, Reduction

4. Reactivity of the Ring Carbon Atoms

Brominatiom of 2-butyl-4*H*-pyrimido[2,1-*a*]isoquinolin-4-one with Br_2 in AcOH gave 3-bromo derivative (08USP2008/0194616, 08WOP2008/097991).

5. Reactivity of the Ring Nitrogen Atom

6. Reactivity of Substituent Attached to a Ring Carbon Atom

7. Reactivity of Substituent Presents in a Side Chain

8. Rearrangement, Ring Transformation


9. Miscellaneous

C. Synthesis

1. By Formation of One Bond α to the Bridgehead Nitrogen Atom [6+0(α)]

2. By Formation of One Bond β to the Bridgehead Nitrogen Atom [6+0(β)]

3. By Formation of One Bond γ to the Bridgehead Nitrogen Atom [6+0(γ)]

4. By Formation of Two Bond from [3+3] Atom Fragments

Heating an 1 : 2 ratio of 2-aminoquinoline and bis(2,4,6-trichlorophenyl) 2-phenylmalonate at 250 °C for 15 min under solvent-free microwave reactor afforded 3-hydroxy-2-phenyl-1H-pyrimido[1,2-a]quinolin-1-one in 79% yield (07TL8250). Cyclocondenzation of 1-aminoisoquinoline and methyl 3-oxoheptanoate in boiling AcOH provided 2-butyl-4H-pyrimido[2,1-a]isoquinolin-4-one (08US2008/0194616, 08WOP2008/097991).
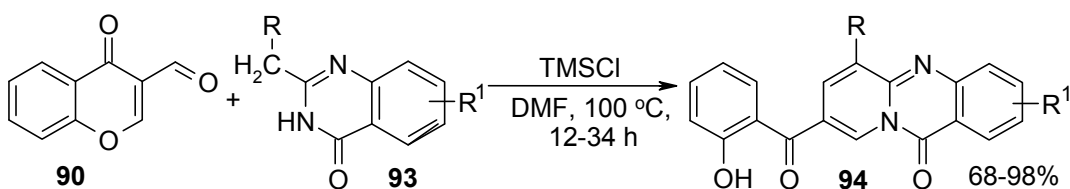

R = H, Cl, CN, CH₂CO₂H, CH₂CH₂CO₂H, 1-pirerazinil, 4-methyl-1-piperazinyl, 4-morpholinyl
R¹ = H, 4-Me, 2-Cl, 3-Cl, 3-CO₂H, 3-CO₂Me, 2,3-(OMe)₂

Heating mixtures of **90** 3-formylchromanone and **93** quinazolinones in the presence of TMSCl in DMF in a sealed tube on water bath yielded **94** 11H-pyrido[2,1-b]quinazolin-11-ones (08S1069).

5. By Formation of Two Bond from [4+2] Atom Fragments

Compound **113**, prepared from anthranilic acid with SOCl$_2$, was reacted with 2-piperidone to give **114** tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-one (05MCR347). Tricyclic compound 114 was also prepared under solvent free conditions from 2-piperidone and anthranilic acid on silica gel by microwave irradiation.
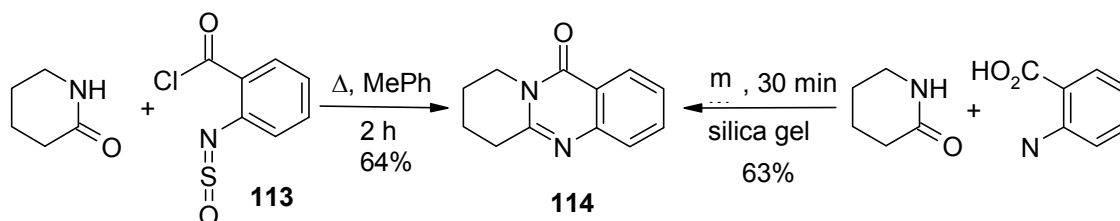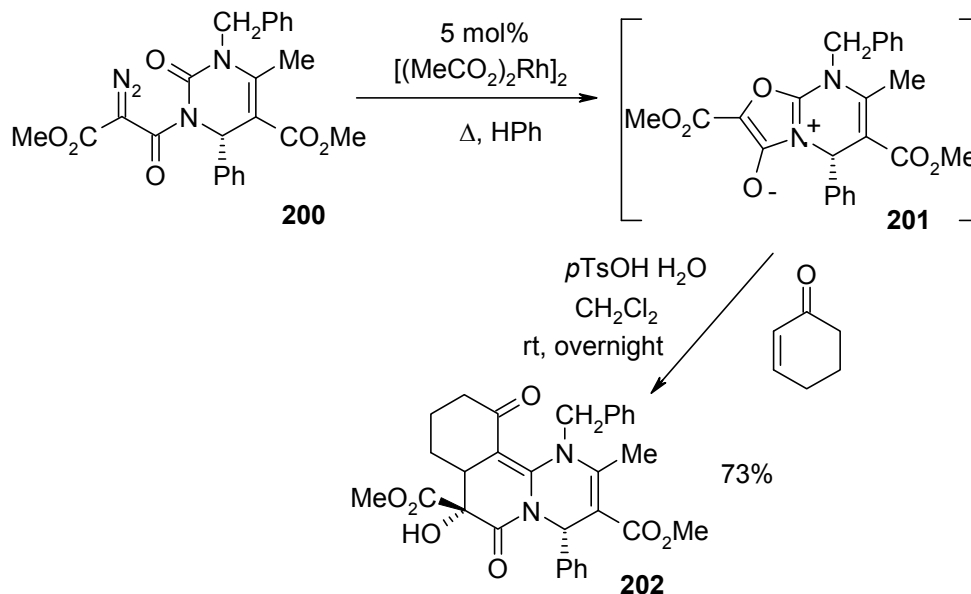

6. By Formation of Two Bond from [5+1] Atom Fragments

7. By Formation of Three Bond from [3+2+1] Atom Fragments

8. By Formation of Three Bond from [4+1+1] Atom Fragments

9. Ring Transformation

Rh(II)-mediated dipolar cycloaddition of **201** isomünchnone dipole, formed in situ from **200** pyrimidin-2-one in the presence of rhodium(II) acetate dimer in boiling benzene, with 2-cyclohexen-1-one gave **202** 1,4,7,8-tetrahydro-6*H*-pyrimido[1,2-*a*]isoquinoline-6,11-dione (07JOC9998).

10. Miscellaneous

Cyclization of **20** dipeptide in boiling toluene in the presence of *p*-TsOH catalyst gave a nearly 1:1 mixture of **21** tetrahydro and **22** hexahydropyrido[2,1-*b*]quinazoline-9-carboxylate. When the cyclization was carried out in CH_2Cl_2 with $BF_3 \cdot OEt_2$ a 4:1 diastereomeric mixture of **22** and **23** hexahydropyrido[2,1-*b*]quinazoline-9-carboxylates were obtained. The diastereomers were separated by preparative HPLC (06OL239).
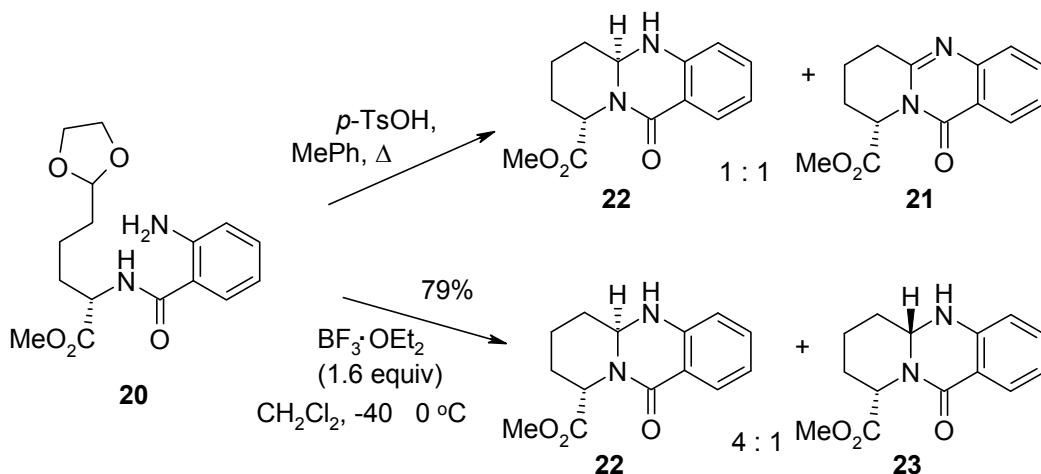
D. Applications and Important Compounds
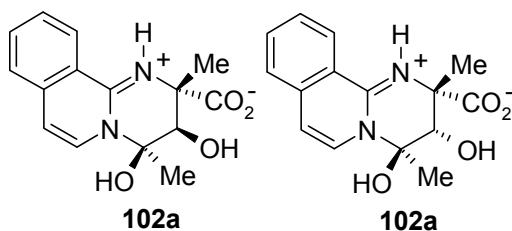
A diastereomeric mixture of **102** betaine, prepared by the reaction of 1-aminoisoquinoline and methylglyoxal, was identified as high-affinity inhibitors of cystic fibrosis transmembrane conductance regulator chloride channels (07MI4).

AcOH	Acetic acid
CDI	1,1'-Carbonylbis -1*H*-imidazole
CTAB	Cetyltrimethylammonium bromide
DBZA	Dibenzoylacetylene
DIAD	Diisopropyl azodiucarboxylate
DIBAL-H	Diizobutylaluminum hydride
DIPEA	*N,N*-Diisopropylethylamine
DMAD	Dimetyl acetylenedicarboxylate
DMAP	4-Dimethylaminopyridine
EDCI EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride MEGNEZNI
hERG	human *ether-a-go-go* related gene
HOBt	1-Hydroxybenzotriazole hydrate
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Pd(dppf)$_2$Cl$_2$	
Pd(dba)$_2$	
PET	positron emission tomography

PPTS	Pyridinium *p*-toluene sulfonate
pTsCl	p-toluenesulfonyl chloride
QSAR	Quantitative structure-activity relationships
TDAE	Tetrakis(dimethylamino)ethylene
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMSCl	Chlorotrimethylsilane
TsOH	*p*-Toluenesulfonic acid monohydrate