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Direct Synthesis of 3,4-Dihydro-2*H*-pyrido[1,2-*a*]pyrimidines, by Addition Reactions with 2-Aminopyridines

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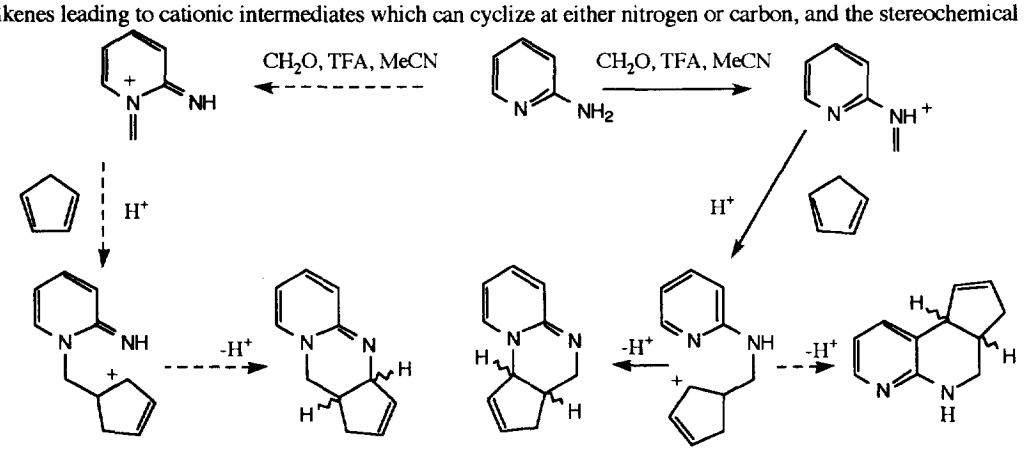
Abstract: Reaction of 2-aminopyridines with formaldehyde and electron rich alkenes permits synthesis of pyridopyrimidines by formation of imines and subsequent addition to the alkenes in a formal aza Diels Alder reaction. The structure of the cyclic amidine products is confirmed by single crystal X-ray analysis on a neutral amidine isolated from an aminopyridine substituted with an electron withdrawing trifluoromethyl group and of a trifluoroacetate salt of an amidine obtained from 2-aminopyridine, formaldehyde and indene. These structural studies permit the regio- and stereo-chemical outcome of these additions to be defined and compared with related processes.

In a series of papers we have elaborated the initial discovery of Grieco and Bahsas[1] that cyclopentadiene and formaldehyde react with anilines to give tetrahydroquinolines. We have applied the reaction to the synthesis of azasteroids[2] from aminotetralones, polycyclic quinones[3] from aminoanthraquinones and modified benzodiazepines[4] from o-phenylenediamines, and have established[5] with different electron rich alkenes that reaction is via a multi-step sequence. The general application of the procedure to aminoheterocycles promises a new route to many interesting heterocyclic skeletons. However as illustrated in the Scheme for reaction with 2-aminopyridine the outcome of the procedure is unclear. The major uncertainties concern the initial site of reaction of formaldehyde with 2-aminopyridine, the step-wise reaction with cyclopentadiene or other electron rich alkenes leading to cationic intermediates which can cyclize at either nitrogen or carbon, and the stereochemical

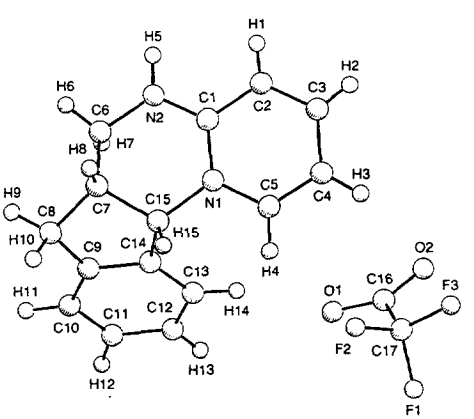


Scheme

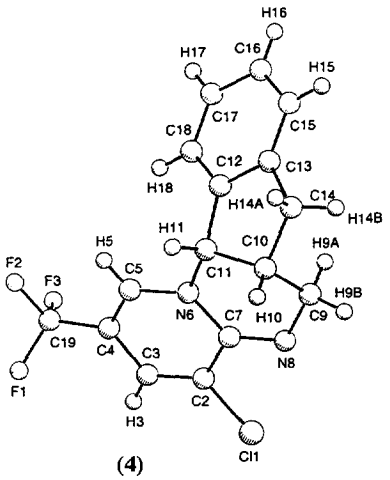
outcome of cyclisation. In this paper we establish unequivocally, based upon single crystal X-ray analyses the outcome of reactions of 2-aminopyridines with formaldehyde and electron rich alkenes, which afford diverse dihydropyrido[1,2-*a*]pyrimidines. In the following paper we extend the protocol to the synthesis of a range of

novel cyclic amidine and isothiourea skeletons.

In all the examples described in the Table reactions were conducted in acetonitrile in the presence of trifluoroacetic acid. Typically the amine, formaldehyde and the alkene were kept at reflux for 1 hour. Under the reaction conditions used for synthesis of tetrahydroquinolines using acetonitrile as solvent and trifluoroacetic acid as catalyst the anticipated product is an amidine trifluoroacetate salt. Basification might afford the neutral amidines Products were isolated by extraction with dichloromethane from a solution of the reaction mixture basified by aqueous sodium bicarbonate solution, followed by chromatography. In the case of reaction of 2-aminopyridine with cyclopentadiene the product (**1**) was isolated as a trifluoroacetate salt. In contrast in a similar reaction with 2-amino-5-nitropyridine and cyclopentadiene the product (**2**) was isolated as a neutral amidine. The nature of the product isolated is a reflection of the basicity of the appropriate amidine. In the Table all 8 reactions carried out with 2-aminopyridine and diverse aminopicolines afforded the trifluoroacetate salts of adducts with electron rich alkenes. In contrast the 8 examples shown in the Table of reaction of aminopyridines having electron withdrawing substituents afforded neutral amidine adducts under the same work up conditions. In those cases where trifluoroacetate salts were isolated, it was observed that the neutral amidines were unstable and much more prone to decomposition than their trifluoroacetate salts. Although the structures of the products shown in the Table could be deduced from spectroscopic observations, rigorous confirmation of structures was obtained by single crystal X-ray analysis of the trifluoroacetate (**3**)[6] from reaction of 2-aminopyridine with indene, and of the neutral amidine (**4**)[7], the product of reaction of 2-amino-3-chloro-5-trifluoromethylpyridine with indene. A number of interesting points emerge from these structural studies.



(3)



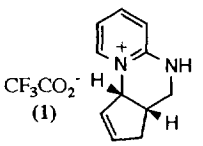
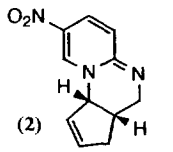
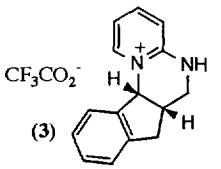
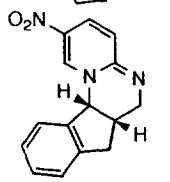
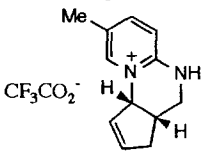
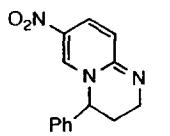
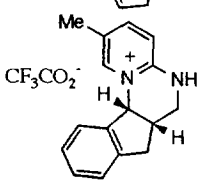
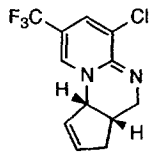
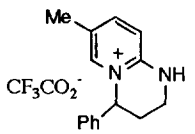
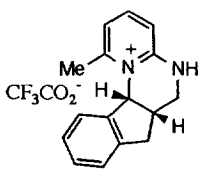
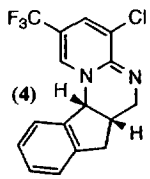
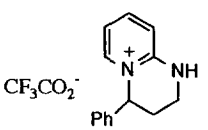
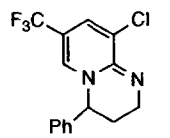
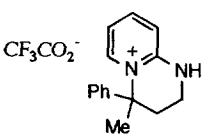
(4)

Molecular structures with numbering schemes adopted

First the regiochemistry is dictated by the reaction of formaldehyde at the primary amino site, in spite of previous studies which show that 2-aminopyridines can react with electrophiles at both nitrogen centres[8]. No products in our study originate other than by reaction of formaldehyde at the primary amino site. Again we observe a regioselectivity in the cyclisation, whereby only pyrido[1,2-*a*]pyrimidines are obtained as products. Although cyclisation at carbon affording naphthyridines (see Scheme) has literature precedent[8], under our reaction conditions it is unimportant. Finally the X-ray analyses establish that cyclisations afford the cis bicyclic

TABLE 1

Synthesis of Cyclic Amidines by Reaction of 2-Aminopyridines with Formaldehyde and Alkenes

Substrates	Products (Yields %)		Substrates	Products (Yield %)[a]	
2-Aminopyridine Cyclopentadiene		46	2-Amino-5-nitropyridine Cyclopentadiene		88
2-Aminopyridine Indene		88	2-Amino-5-nitropyridine Indene		57
2-Amino-5-methyl pyridine Cyclopentadiene		42	2-Amino-5-nitropyridine Styrene		52
2-Amino-5-methyl pyridine Indene		76	2-Amino-3-chloro-5-trifluoromethylpyridine Cyclopentadiene		90
2-Amino-5-methyl pyridine Styrene		54	2-Amino-3-chloro-5-trifluoromethylpyridine Cyclohexadiene		85
2-Amino-6-methyl pyridine Indene		62	2-Amino-3-chloro-5-trifluoromethylpyridine Indene		88
2-Aminopyridine Styrene		36	2-Amino-3-chloro-5-trifluoromethylpyridine Styrene		70
2-Aminopyridine α-Methylstyrene		46	2-Amino-3-chloro-5-trifluoromethylpyridine 1-Phenylcyclohexene		70

a) All new compounds were fully characterised on the basis of their spectra and analytical data

products, in agreement with our observations in related cases. Hence the results shown in the Table establish a route to diverse pyrido[1,2-*a*]pyrimidines, cyclic amidines closely related to recently reported amidines[9] having anti-cancer activity and now in phase 1 clinical trials. The synthesis and pharmaceutical applications of pyrido [1,2-*a*]pyrimidines[8] have been reviewed. However just as importantly, by rigorous structural studies, the results provide the structural foundation for a more general elaboration of aminoheterocycles which is described in the following paper.

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6. X-Ray analysis of (**3**): $C_{17}H_{15}N_2O_2F_3$, M = 336.3, colourless block, 0.50 x 0.40 x 0.30mm, a = 10.859 (3), b = 12.316 (3), c = 11.413 (2) Å, β = 104.48 (2)^0 V = 1477.8 (6) Å^3, T = 150K, D_{calc} = 1.511gcm^{-3} Z = 4, monoclinic, $P2_1/n$, Rigaku AFC7S four -circle diffractometer, λ = 0.71073Å, ω–2θ scan-mode, 2884 reflections, 2735 unique (R_{int} = 0.038), 2164 observed reflections [I >3σ(I)], structure solved by direct methods (SHELXS-86: Program for Crystal Structure Solution, G. M. Sheldrick, University of Göttingen, 1986) and refined by iterative cycles of full-matrix least-squares (teXsan:Crystal Structure Analysis Package Molecular Structure Corporation, Texas, 1992), H-atoms located and then fixed, R = 0.042, R_w = 0.051 for 217 refined parameters [$w^{-1} = \sigma^2$ (F)] residual electron density = 0.33eÅ^3.In δH (270MHz) for (**3**) 5.67 (1H, d J 5.7, CH-N$^+$)
7. X-Ray analysis of (**4**): $C_{16}H_{12}ClN_2F_3$, M = 324.7, colourless block, 0.32 x 0.25 x 0.14mm, a = 9.384 (4), b = 15.995 (4), c = 9.561 (7) Å, β = 92.59(3)^0, V = 1433.6 (13) Å^3, T = 120K, D_{calc} = 1.505gcm^{-3}, Z = 4, monoclinic, $P2_1/c$, Enraf Nonius Fast System, λ = 0.71073Å, ω–scan-mode, 6094 reflections, 2257 unique (R_{int} = 0.055), 1787 observed reflections [I >2σ(I)], structure solved by direct methods (SHELXS- 86: Program for Crystal Structure Solution, G. M. Sheldrick, University of Göttingen, 1986) and refined by iterative cycles of full-matrix least-squares (SHELXL-93: Program for Crystal Structure Refinement G. M.Sheldrick, University of Göttingen, 1993) H-atoms located and then fixed, R_1 = 0.045, wR_2 = 0.1088 for 199 refined parameters [$w^{-1} = \sigma^2$ (F_O^2) + (0.0695P)^2] where P = (max(F_O^2,0) +2F_C^2)/3, residual electron density = 0.59eÅ^3. In δH (270MHz) for (**4**) 5.08 (1H, d J 6.0, CH-N)
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