Synthesis and Azannulation of Pyridinylaminohexadienones

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4-(2-Pyridinylamino)-1,1,1-trifluoro-3-penten-2-ones 3, obtained from the reaction of commercially available 2-aminopyridine derivatives and 4-methoxy-1,1,1-trifluoro-3-penten-2-one 2, were converted to 6-(dimethylamino)-4-(2-pyridinylamino)-3,5-hexadien-2-ones 4 by treatment with dimethylformamide dimethyl acetal. Azannulation of hexadienones 4 afforded 4-(2-pyridinylamino)-2-trifluoromethylpyridines 5 and 2-(trifluoroacetylmethylene)pyrido[1,2-*a*]pyrimidines 6, classes of compounds particularly interesting from a chemical and biological point of view.

Key words trifluoroacetyl vinyl ethers; annulation; aminopyridine; pyridopyrimidine

4-Aminopyridine and pyrido[1,2-*a*]pyrimidine derivatives have received much attention due to their important and different biological functions. The *N*-aryl-4-pyridinamines have been proposed as an adrenergic cognitive enhancer,[1,2] cardiovascular antihypertensive[3] and diuretic agents.[4] The pyrido[1,2-*a*]pyrimidines have been shown to possess psychotropic,[5—7] antiatherosclerotic, antipyretic and analgesic properties.[8]

The introduction of a lipophilic CF_3 group into a biomolecule has sometimes resulted in improvement of its biological activity.[9] Besides, to the best of our knowledge, few examples of the synthesis of 2-trifluoromethyl substituted 4-aminopyridine[10—12] and pyrido[1,2-*a*]pyrimidine derivatives not bearing an oxo or imino group[13—15] have been reported. These facts prompted us to elaborate an inexpensive and efficient synthetic route to these compounds.

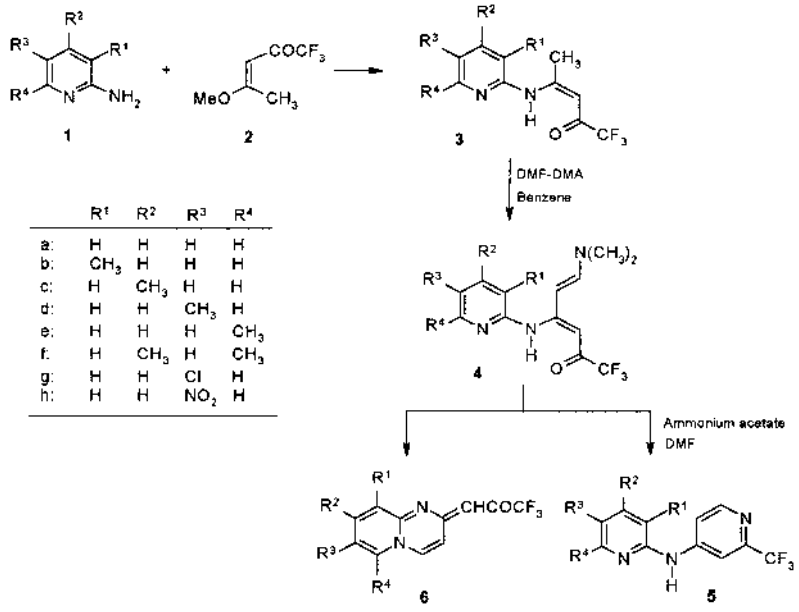
Among the building blocks for introducing the CF_3 group into organic compounds the CF_3 containing enol ethers are widely used.[16,17] We have recently reported the preparation of trifluorinated hexadienones from 4-methoxy-1,1,1-trifluoro-3-penten-2-one (**2**) and we have outlined their utility in the synthesis of trifluoromethylated benzoxazepines and arylaminopyridines.[18,19] In this paper we have focused our attention on 4-(pyridinylamino)-1,1,1-trifluoro-3,5-hexadienones **4** and their transformation into fluorinated 4-(2-pyridinylamino)pyridines **5** and pyrido[1,2-*a*]pyrimidines **6**.

Results and Discussion

The O–N exchange reaction between 4-methoxy-1,1,1-trifluoro-3-penten-2-one (**2**) with commercially available 2-aminopyridines easily gave 4-(2-pyridinylamino)-1,1,1-trifluoro-3-penten-2-ones **3**. As shown in Chart 1 the preparation of enaminones **3a**—**g** was achieved in 88—96% yields by refluxing equimolecular amounts of 2-aminopyridines **1a**—**g** and enol ether **2** in acetonitrile.

Under the same conditions 5-nitro-2-pyridinamine (**1h**) did not give the desired product but the starting materials were recovered even if the reaction time was increased. Enaminone **3h** was instead obtained in 93% yield by heating a mixture of 5-nitro-2-pyridinamine (**1h**) and enol ether **2** in 1 : 1.5 molar ratio. The *Z* configuration of enaminones **3** was established by comparison of their ^{1}H-NMR spectra with those of analogous compounds.[19]

Dimethylaminoformylation of enaminones **3** utilizing *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) afforded 6-(dimethylamino)-4-(2-pyridinylamino)-3,5-hexadien-2-ones **4**.



	R^1	R^2	R^3	R^4
a:	H	H	H	H
b:	CH_3	H	H	H
c:	H	CH_3	H	H
d:	H	H	CH_3	H
e:	H	H	H	CH_3
f:	H	CH_3	H	CH_3
g:	H	H	Cl	H
h:	H	H	NO_2	H

Chart 1

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Table 1. Reactions of 2-Aminopyridines **1** with 4-Methoxy-1,1,1-trifluoro-3-penten-2-one (**2**)

Run	Substrate **1**	Solvent	Conditions[a)]	Yield of **3** (%)
1	**a**	MeCN	Reflux 1 h, then r.t. 24 h	96
2	**b**	MeCN	Reflux 1 h, then r.t. 24 h	88
3	**c**	MeCN	Reflux 1 h, then r.t. 24 h	88
4	**d**	MeCN	Reflux 1 h, then r.t. 24 h	92
5	**e**	MeCN	Reflux 1 h, then r.t. 24 h	96
6	**f**	MeCN	Reflux 1 h, then r.t. 24 h	93
7	**g**	MeCN	Reflux 1 h, then r.t. 24 h	93
8	**h**	None	100 °C, water bath, 30 min	88

a) r.t., room temperature.

Table 2. Intramolecular Heterocyclization of 6-(Dimethylamino)-4-(2-pyridinylamino)-3,5-hexadien-2-ones **4** to Pyrido[1,2-*a*]pyrimidines **6**

Run	Substrate **4**	Solvent	Conditions	Yield of **6** (%)
1	**a**	Toluene	Reflux, 1 h	70
2	**b**	Toluene	Reflux, 1 h	74
3	**c**	Toluene	Reflux, 1 h	98
4	**d**	Toluene	Reflux, 1 h	90
5	**e**	Toluene	Reflux, 1 h	71
6	**f**	Toluene	Reflux, 1 h	91
7	**g**	AcOH	Reflux, 30 min	92
8	**h**	AcOH	Reflux, 30 min	77

The reaction is regioselective and the (3*Z*,5*E*)-dieneaminone **4** was exclusively obtained. The stereochemistry was confirmed by ^{1}H-NMR spectral data. The large coupling constant (about 13 Hz) of the H-5 and H-6 olefinic protons suggest the *E* configuration of the newly formed double bond in dieneamines **4**. The signal for H-3 appeared as a single peak showing the presence of only one stereoisomer. The highly deshielded NH resonance at δ 13.23—13.68 is characteristic of an amino group which participates in a strong hydrogen bond with an oxygen of a carbonyl in a six-membered, planar chelate, a fact which is supported by the presence of a carbonyl stretch at 1645—1625 cm^{-1} in the IR spectra. Thus a *Z* configuration can be attributed to the C(3)=C(4) double bond.

Our initial effort to cyclize dieneamines **4** with NH_3 by heating in MeCN solution did not give the desired 4-(2-pyridinylamino)-2-trifluoromethylpyridines **5**. When the cyclization was performed by mild heating of a DMF solution of dieneamines **4** and ammonium acetate, pyridines **5** were obtained in good yields. The ^{1}H-NMR spectra of compounds **5** display a pair of doublets at δ 7.75—7.95 (H-5, J=5 Hz) and 8.36—8.54 (H-6, J=5 Hz) and a singlet at δ 8.08—8.25 due to H-3 which are consistent with the assigned structure.

Polyfunctionalized dieneamines **4** are precursors for the synthesis of pyrido[1,2-*a*]pyrimidines **6** also. When hexadienones **4a**—**f** were heated under reflux in toluene intramolecular condensation readily proceeded to give pyrido[1,2-*a*]pyrimidines **6a**—**f** as a sole isomer.

Dieneamines **4g** and **4h**, bearing electron-withdrawing groups on the pyridine ring, cannot be transformed into their corresponding products **6** under these conditions. Treatment of **4g** and **4h** with acetic acid at reflux for few minutes afforded the pyridopyrimidines **6g** and **6h** in good yields. In the ^{1}H-NMR of **6** a singlet at 5.53—5.75 ppm relative to the exocyclic methyne proton accounts for the formation of a single diastereomeric product. Furthermore the two doublets at 8.29—8.46 ppm and 8.38—8.57 ppm (J=6.3 Hz) due to H-3 and H-4 confirmed the assigned structure.

Conclusion

In summary we devised an easy method of accessing CF_3-containing pyridine and pyrido[1,2-*a*]pyrimidines which are otherwise difficult to obtain. The principal advantages of this method are its simplicity and the great variety of substituents available.

Experimental

Melting points were taken on a Stuart Scientific SMP1 apparatus and are uncorrected. IR spectra were measured in Nujol mulls with a Perkin Elmer 398 spectrophotometer, while NMR spectra were recorded with a Varian Unity 300 instrument operating at 300 MHz: chemical shifts are expressed in ppm (δ) and coupling constants in Hertz (Hz). Elemental analyses were obtained with a Carlo Erba model 1106 Elemental Analyzer. All solvents were purified and dried by standard techniques; petroleum ether refers to the fraction of bp 40—60 °C.

General Procedure for the Preparation of Enaminones 3 A solution of 2-aminopyridine **1a**—**g** (0.02 mol) and enol ether **2** (0.02 mol) in dry acetonitrile (20 ml) was refluxed with stirring for 1 h, then allowed to cool for 24 h. The solvent was removed *in vacuo* and the residue was purified from crystallization to give enaminones **3a**—**g**.

(3*Z*)-4-(2-Pyridinylamino)-1,1,1-trifluoro-3-penten-2-one (**3a**): Crystallized from petroleum ether, mp 77—78 °C; yield 96%; IR (Nujol) cm^{-1}: 1620, 1600, 1580; ^{1}H-NMR ($CDCl_3$/tetramethylsilane TMS) δ: 2.50 (3H, s, CH_3), 5.48 (1H, s, H-3), 6.89—8.30 (4H, m, pyridinyl), 12.81 (1H, s, NH, D_2O exchangeable). *Anal.* Calcd for $C_{10}H_9F_3N_2O$: C, 52.18; H, 3.94; N, 12.17. Found: C, 52.19; H, 3.91; N, 12.13.

(3*Z*)-4-[(3-Methyl-2-pyridinyl)amino]-1,1,1-trifluoro-3-penten-2-one (**3b**): Crystallized from petroleum ether, mp 82—83 °C; yield 88%; IR (Nujol) cm^{-1}: 1630, 1615,1585; ^{1}H-NMR ($CDCl_3$/TMS) δ: 2.28 (3H, s, CH_3), 2.51 (3H, s, CH_3), 5.70 (1H, s, H-3), 7.11—8.23 (3H, m, pyridinyl), 12.60 (1H, s, NH, D_2O exchangeable). *Anal.* Calcd for $C_{11}H_{11}F_3N_2O$: C, 54.10; H, 4.54; N, 11.47. Found: C, 54.13; H, 4.49; N, 11.49.

(3*Z*)-4-[(4-Methyl-2-pyridinyl)amino]-1,1,1-trifluoro-3-penten-2-one (**3c**): Crystallized from petroleum ether, mp 37—39 °C; yield 88%; IR (Nujol) cm^{-1}: 1610, 1555; ^{1}H-NMR ($CDCl_3$/TMS) δ: 2.27 (3H, s, CH_3), 2.50 (3H, s, CH_3), 5.47 (1H, s, H-3), 6.75—8.16 (3H, m, pyridinyl), 12.78 (1H, s, NH, D_2O exchangeable). *Anal.* Calcd for $C_{11}H_{11}F_3N_2O$: C, 54.10; H, 4.54; N, 11.47. Found: C, 54.04; H, 4.51; N, 11.51.

(3*Z*)-4-[(5-Methyl-2-pyridinyl)amino]-1,1,1-trifluoro-3-penten-2-one (**3d**): Crystallized from petroleum ether, mp 73—74 °C; yield 92%; IR (Nujol) cm^{-1}: 1610, 1580; ^{1}H-NMR ($CDCl_3$/TMS) δ: 2.24 (3H, s, CH_3), 2.47 (3H, s, CH_3), 5.47 (1H, s, H-3), 6.83—8.14 (3H, m, pyridinyl), 12.82 (1H, s, NH, D_2O exchangeable). *Anal.* Calcd for $C_{11}H_{11}F_3N_2O$: C, 54.10; H, 4.54; N, 11.47. Found: C, 54.12; H, 4.48; N, 11.44.

(3*Z*)-4-[(6-Methyl-2-pyridinyl)amino]-1,1,1-trifluoro-3-penten-2-one (**3e**): Crystallized from petroleum ether, mp 68—70 °C; yield 96%; IR (Nujol) cm^{-1}: 1635, 1610, 1580; ^{1}H-NMR ($CDCl_3$/TMS) δ: 2.42 (3H, s, CH_3), 2.52 (3H, s, CH_3), 5.47 (1H, s, H-3), 6.72—7.54 (3H, m, pyridinyl), 12.78 (1H, s, NH, D_2O exchangeable). *Anal.* Calcd for $C_{11}H_{11}F_3N_2O$: C, 54.10; H, 4.54; N, 11.47. Found: C, 54.14; H, 4.50; N, 11.50.

(3*Z*)-4-[(4,6-Dimethyl-2-pyridinyl)amino]-1,1,1-trifluoro-3-penten-2-one (**3f**): Crystallized from ethanol, mp 35—36 °C; yield 93%; IR (Nujol) cm^{-1}: 1620, 1595, 1560; ^{1}H-NMR ($CDCl_3$/TMS) δ: 2.22 (3H, s, CH_3), 2.36 (3H, s, CH_3), 2.49 (3H, s, CH_3), 5.45 (1H, s, H-3), 6.56 (1H, s, pyridinyl), 6.72 (1H, s, pyridinyl), 12.74 (1H, s, NH, D_2O exchangeable). *Anal.* Calcd for $C_{12}H_{13}F_3N_2O$: C, 55.81; H, 5.07; N, 10.85. Found: C, 55.83; H, 5.09; N, 10.87.

(3*Z*)-4-[(5-Chloro-2-pyridinyl)amino]-1,1,1-trifluoro-3-penten-2-one (**3g**): Crystallized from petroleum ether, mp 94—95 °C; yield 93%; IR (Nujol) cm^{-1}: 1610, 1585; ^{1}H-NMR ($CDCl_3$/TMS) δ: 2.50 (3H, s, CH_3), 5.51 (1H, s, H-3), 6.86—8.26 (3H, m, pyridinyl), 12.83 (1H, s, NH, D_2O exchangeable). *Anal.* Calcd for $C_{10}H_8ClF_3N_2O$: C, 45.39; H, 3.05; N, 10.59 . Found: C, 45.43; H, 3.03; N, 10.60.

Preparation of (3*Z*)-4-[(5-Nitro-2-pyridinyl)amino]-1,1,1-trifluoro-3-penten-2-one (3h) A mixture of 2-amino-5-nitropyridine **1h** (2.8 g, 0.02 mol) and enol ether **2** (5.0 g, 0.03 mol) was stirred with heating from a

boiling water bath for 30 min. After cooling the resulting solid was collected and crystallized to give enaminone **3h**. Crystallized from isopropyl ether, mp 107—108 °C; yield 88%; IR (Nujol) cm^{-1}: 1625, 1595; ^{1}H-NMR ($CDCl_3$/TMS) δ: 2.71 (3H, s, CH_3), 5.72 (1H, s, H-3), 7.04—9.21 (3H, m, pyridinyl), 12.93 (1H, s, NH, D_2O exchangeable). *Anal.* Calcd for $C_{10}H_8F_3N_3O_3$: C, 43.65; H, 2.93; N, 15.27. Found: C, 43.70; H, 2.94; N, 15.25.

General Procedure for the Preparation of Hexadienones 4 A solution of enaminone **3** (0.02 mol) and DMF-DMA (0.06 mol) in dry benzene (40 ml) was refluxed with stirring for 30 min, then allowed to cool for 24 h. The solvent was removed *in vacuo* and the residue purified from crystallization to give hexadienones **4a**,**d**—**h**.

In the case of hexadienones **4b**,**c**, after removing the solvent, the residue was collected and washed with a small amount of isopropyl ether, dried and utilized without further purification.

(3*Z*,5*E*)-6-(Dimethylamino)-4-(2-pyridinylamino)-1,1,1-trifluoro-3,5-hexadien-2-one (**4a**): Crystallized from isopropyl ether, mp 131—132 °C; yield 87%; IR (Nujol) cm^{-1}: 1630, 1595; ^{1}H-NMR ($CDCl_3$/TMS) δ: 2.93, 3.06 (6H, br s, CH_3), 5.56 (1H, s, H-3), 6.74 (1H, d, J=13.2 Hz, H-5), 6.91, 7.56, 8.27 (4H, m, pyridinyl), 7.45 (1H, d, J=13.2 Hz, H-6), 13.48 (1H, s, NH, D_2O exchangeable). *Anal.* Calcd for $C_{13}H_{14}F_3N_3O$: C, 54.74; H, 4.95; N, 14.73. Found: C, 54.68; H, 4.94; N, 14.76.

(3*Z*,5*E*)-6-(Dimethylamino)-4-[(3-methyl-2-pyridinyl)amino]-1,1,1-trifluoro-3,5-hexadien-2-one (**4b**): mp 143—145 °C; yield 82%; IR (Nujol) cm^{-1}: 1645, 1605; ^{1}H-NMR hexadeuterio dimethylsulphoxide (DMSO-d_6/TMS) 2.26 (3H, s, CH_3), 2.86 (3H, s, CH_3), 3.18 (3H, s, CH_3), 5.83 (1H, s, H-3), 6.97 (1H, d, J=13.2 Hz, H-5), 6.98, 7.61, 8.18 (3H, m, pyridinyl), 8.06 (1H, d, J=13.2 Hz, H-6), 13.23 (1H, s, NH, D_2O exchangeable). *Anal.* Calcd for $C_{14}H_{16}F_3N_3O$: C, 56.18; H, 5.39; N, 14.04. Found: C, 56.24; H, 5.40; N, 14.00.

(3*Z*,5*E*)-6-(Dimethylamino)-4-[(4-methyl-2-pyridinyl)amino]-1,1,1-trifluoro-3,5-hexadien-2-one (**4c**): mp 150—152 °C; yield 88%; IR (Nujol) cm^{-1}: 1625, 1590; ^{1}H-NMR (DMSO-d_6/TMS) δ: 2.24 (3H, s, CH_3), 2.85 (3H, s, CH_3), 3.17 (3H, s, CH_3), 5.76 (1H, s, H-3), 6.59 (1H, d, J=12.9 Hz, H-6), 6.88, 8.16 (3H, m, pyridinyl), 8.01 (1H, d, J=12.9 Hz, H-6), 13.31 (1H, s, NH, D_2O exchangeable). *Anal.* Calcd for $C_{14}H_{16}F_3N_3O$: C, 56.18; H, 5.39; N, 14.04. Found: C, 56.23; H, 5.38; N, 14.07.

(3*Z*,5*E*)-6-(Dimethylamino)-4-[(5-methyl-2-pyridinyl)amino]-1,1,1-trifluoro-3,5-hexadien-2-one (**4d**): Crystallized from petroleum ether; mp 158—159 °C; yield 95%; IR 1635, 1605; ^{1}H-NMR ($CDCl_3$/TMS) δ: 2.21 (3H, s, CH_3), 2.97 (6H, br s, $2CH_3$), 5.54 (1H, s, H-3), 6.59 (1H, d, J=12.9 Hz, H-5), 6.85, 7.39, 8.10 (3H, m, pyridinyl), 7.42 (1H, d, J=12.9 Hz, H-6), 13.41 (1H, s, NH, D_2O exchangeable). *Anal.* Calcd for $C_{14}H_{16}F_3N_3O$: C, 56.18; H, 5.39; N, 14.04. Found: C, 56.15; H, 5.41; N, 14.08.

(3*Z*,5*E*)-6-(Dimethylamino)-4-[(6-methyl-2-pyridinyl)amino]-1,1,1-trifluoro-3,5-hexadien-2-one (**4e**): Crystallized from isopropyl ether; mp 177—178 °C; yield 95%; IR (Nujol) cm^{-1}: 1635, 1600; ^{1}H-NMR ($CDCl_3$/TMS) δ: 2.40 (3H, s, CH_3), 3.03 (6H, br s, $2CH_3$), 5.54 (1H, s, H-3), 6.72, 6.76, 7.43 (3H, m, pyridinyl), 6.95 (1H, d, J=13.2 Hz, H-5), 7.44 (1H, d, J=13.2 Hz, H-6), 13.43 (s, 1H, NH, D_2O exchangeable). *Anal.* Calcd for $C_{14}H_{16}F_3N_3O$: C, 56.18; H, 5.39; N, 14.04. Found: C, 56.22; H, 5.39; N, 14.06.

(3*Z*,5*E*)-6-(Dimethylamino)-4-[(4,6-dimethyl-2-pyridinyl)amino]-1,1,1-trifluoro-3,5-hexadien-2-one (**4f**): Crystallized from isopropyl ether; mp 130—132 °C; yield 95%; IR (Nujol) cm^{-1}: 1640, 1620, 1595; ^{1}H-NMR ($CDCl_3$/TMS) δ: 2.18 (3H, s, CH_3), 2.36 (3H, s, CH_3), 2.98 (6H, br s, $2CH_3$), 5.54 (1H, s, H-3), 6.58, 6.61 (2H, s, pyridinyl), 6.97 (1H, d, J=12.9 Hz, H-5), 7.42 (1H, d, J=12.9 Hz, H-6), 13.41 (1H, s, NH, D_2O exchangeable). *Anal.* Calcd for $C_{15}H_{18}F_3N_3O$: C, 57.50; H, 5.79; N, 13.41. Found: C, 57.54; H, 5.80; N, 13.48.

(3*Z*,5*E*)-6-(Dimethylamino)-4-[(5-chloro-2-pyridinyl)amino]-1,1,1-trifluoro-3,5-hexadien-2-one (**4g**): Crystallized from benzene; mp 176—177 °C; yield 72%; IR (Nujol) cm^{-1}: 1635, 1605; ^{1}H-NMR ($CDCl_3$/TMS) δ: 2.92, 3.11 (6H, br s, $2CH_3$), 5.57 (1H, s, H-3), 6.67 (1H, d, J=12.9 Hz, H-5), 6.88, 7.52, 8.22 (3H, m, pyridinyl), 7.47 (1H, d, J=12.9 Hz, H-6), 13.58 (1H, s, NH, D_2O exchangeable). *Anal.* Calcd for $C_{13}H_{13}ClF_3N_3O$: C, 48.84; H, 4.10; N, 13.14. Found: C, 48.78; H, 4.09; N, 13.18.

(3*Z*,5*E*)-6-(Dimethylamino)-4-[(5-nitro-2-pyridinyl)amino]-1,1,1-trifluoro-3,5-hexadien-2-one (**4h**): Crystallized from 2-propanol; mp 218—220 °C; yield 82%; IR (Nujol) cm^{-1}: 1640, 1615, 1585; ^{1}H-NMR (DMSO-d_6/TMS) δ: 2.96 (3H, s, CH_3), 3.24 (3H, s, CH_3), 5.89 (1H, s, H-3), 6.81 (1H, d, J=12.5 Hz, H-5), 7.17, 8.44, 9.15 (3H, m, pyridinyl), 8.21 (1H, d, J=12.5 Hz, H-6), 13.68 (1H, br s, NH, D_2O exchangeable). *Anal.* Calcd for $C_{13}H_{13}F_3N_4O_3$: C, 47.28; H, 3.97; N, 16.96. Found: C, 47.33; H, 3.98; N, 16.92.

General Procedure for the Preparation of 2-Trifluoromethyl-4-pyridinamines 5 A solution of hexadienones **4** (0.005 mol) and ammonium acetate (0.01 mol) in dry DMF (5 ml) was gently refluxed for 1 h. After cooling, water (40 ml) was added and the resulting precipitate was filtered off, dried and crystallized to give compounds **5**.

N-(2-Pyridinyl)-2-trifluoromethyl-4-pyridinamine (**5a**): Crystallized from isopropyl ether/chloroform; mp 144—146 °C; yield 82%; IR (Nujol) cm^{-1}: 3290, 3190, 3100, 3020, 1630, 1620; ^{1}H-NMR (DMSO-d_6/TMS) δ: 6.91 (2H, m, H-3′, H-5′), 7.66 (1H, m, H-4′), 7.80 (1H, d, J=5.4 Hz, H-5), 8.18 (1H, s, H-3), 8.26 (1H, m, H-6′), 8.38 (1H, d, J=5.4 Hz, H-6), 9.94 (1H, s, NH, D_2O exchangeable). *Anal.* Calcd for $C_{11}H_8F_3N_3$: C, 55.23; H, 3.37; N, 17.57. Found: C, 55.17; H, 3.38; N, 17.59.

N-(3-Methyl-2-pyridinyl)-2-trifluoromethyl-4-pyridinamine (**5b**): Crystallized from hexane; mp 113—115 °C; yield 85%; IR (Nujol) cm^{-1}: 3470, 3330, 3180, 3090, 1610, 1590; ^{1}H-NMR (DMSO-d_6/TMS) δ: 2.28 (3H, s, CH_3), 6.93 (1H, m, H-5′), 7.56 (1H, m, H-4′), 7.95 (1H, m, H-5), 8.13 (1H, s, H-3), 8.14 (1H, d, J=5.9 Hz, H-6′), 8.40 (1H, d, J=6.1 Hz, H-6), 8.78 (1H, s, NH, D_2O exchangeable). *Anal.* Calcd for $C_{12}H_{10}F_3N_3$: C, 56.92; H, 3.98; N, 16.59. Found: C, 56.88; H, 3.99; N, 16.61.

N-(4-Methyl-2-pyridinyl)-2-trifluoromethyl-4-pyridinamine (**5c**): Crystallized from ligroin; mp 137—138 °C; yield 68%; IR (Nujol) cm^{-1}: 3300, 3180, 3100, 1630, 1610, 1595; ^{1}H-NMR (DMSO-d_6/TMS) δ: 2.23 (3H, s, CH_3), 6.71 (1H, s, H-3′), 6.76 (1H, d, J=5.4 Hz, H-5′), 7.79 (1H, dd, J=5.4, 2.0 Hz, H-5), 8.12 (1H, d, J=5.4 Hz, H-6′), 8.18 (1H, d, J=2.0 Hz, H-3), 8.38 (1H, d, J=5.4 Hz, H-6), 9.84 (1H, s, NH, D_2O exchangeable). *Anal.* Calcd for $C_{12}H_{10}F_3N_3$: C, 56.92; H, 3.98; N, 16.59. Found: C, 56.96; H, 4.00; N, 16.54.

N-(5-Methyl-2-pyridinyl)-2-trifluoromethyl-4-pyridinamine (**5d**): Crystallized from isopropyl ether/chloroform; mp 178—180 °C; yield 83%; IR (Nujol) cm^{-1}: 3280, 3180, 3100, 3040, 1630, 1610; ^{1}H-NMR (DMSO-d_6/TMS) δ: 2.16 (3H, s, CH_3), 6.83 (1H, d, J=8.3 Hz, H-3′), 7.48 (1H, dd, J=8.3, 1.9 Hz, H-4′), 7.75 (1H, m, 5-H), 8.09 (1H, s, H-6′), 8.12 (1H, d, J=1.9 Hz, H-3), 8.36 (1H, d, J=5.4 Hz, H-6), 9.82 (1H, s, NH, D_2O exchangeable). *Anal.* Calcd for $C_{12}H_{10}F_3N_3$: C, 56.92; H, 3.98; N, 16.59. Found: C, 56.87; H, 3.97; N, 16.62.

N-(6-Methyl-2-pyridinyl)-2-trifluoromethyl-4-pyridinamine (**5e**): Crystallized from ethyl acetate/ligroin; mp 176—177 °C; yield 89%; IR (Nujol) cm^{-1}: 3290, 3190, 3110, 3020, 1630, 1615, 1590, 1580; ^{1}H-NMR (DMSO-d_6/TMS) δ: 2.38 (3H, s, CH_3), 6.74 (2H, m, H-3′, H-5′), 7.54 (1H, m, H-4′), 7.82 (1H, d, J=5.9 Hz, H-5), 8.25 (1H, s, H-3), 8.38 (1H, d, J=5.9 Hz, H-6), 9.86 (1H, s, NH, D_2O exchangeable). *Anal.* Calcd for $C_{12}H_{10}F_3N_3$: C, 56.92; H, 3.98; N, 16.59. Found: C, 56.95; H, 3.98; N, 16.58.

N-(4,6-Dimethyl-2-pyridinyl)-2-trifluoromethyl-4-pyridinamine (**5f**): Crystallized from ligroin; mp 158—160 °C; yield 89%; IR (Nujol) cm^{-1}: 3290, 3180, 3110, 1630, 1610, 1595; ^{1}H-NMR (DMSO-d_6/TMS) δ: 2.18 (3H, s, CH_3), 2.33 (3H, s, CH_3), 6.52, 6.60 (2H, s, H-3′, H-5′), 7.81 (1H, d, J=5.9 Hz, H-5), 8.24 (1H, s, H-3), 8.37 (1H, d, J=5.9 Hz, H-6), 9.76 (1H, s, NH, D_2O exchangeable). *Anal.* Calcd for $C_{13}H_{12}F_3N_3$: C, 58.43; H, 4.53; N, 15.72. Found: C, 58.38; H, 4.51; N, 15.75.

N-(5-Chloro-2-pyridinyl)-2-trifluoromethyl-4-pyridinamine (**5g**): Crystallized from ethyl acetate/ligroin; mp 187—188 °C; yield 98%; IR (Nujol) cm^{-1}: 3290, 3180, 3090, 1630, 1605, 1580; ^{1}H-NMR (DMSO-d_6/TMS) δ: 6.92 (1H, d, J=8.8 Hz, H-3′), 7.74 (1H, d, J=8.8 Hz, H-4′), 7.76 (1H, d, J=5.9 Hz, H-5), 8.08 (1H, s, H-3), 8.27 (1H, s, H-6′), 8.41 (1H, d, J=5.9 Hz, H-6), 10.08 (1H, s, NH, D_2O exchangeable). *Anal.* Calcd for $C_{11}H_7ClF_3N_3$: C, 48.28; H, 2.58; N, 15.36. Found: C, 48.33; H, 2.57; N, 15.33.

N-(5-Nitro-2-pyridinyl)-2-trifluoromethyl-4-pyridinamine (**5h**): Crystallized from 2-propanol; mp 238 °C (dec.); yield 80%; IR (Nujol) cm^{-1}: 3340, 3230, 1625, 1580; ^{1}H-NMR (DMSO-d_6/TMS) δ: 7.04 (1H, d, J=8.8 Hz, H-3′), 7.92 (1H, d, J=5.4 Hz, H-5), 8.21 (1H, s, H-3), 8.41 (1H, d, J=8.8 Hz, H-4′), 8.54 (1H, d, J=5.4 Hz, H-6), 9.12 (1H, s, H-6′), 10.74 (1H, s, NH, D_2O exchangeable). *Anal.* Calcd for $C_{11}H_7F_3N_4O_2$: C, 46.49; H, 2.48; N, 19.71. Found: C, 46.53; H, 2.47; N, 19.74.

General Procedure for the Preparation of Pyrido[1,2-*a*]pyrimidines 6a—f A solution of hexadienones **4** (0.005 mol) in dry toluene (5 ml) was refluxed for 30 min with stirring. After cooling the resulting precipitate was filtered off and purified from crystallization to give pyridopyrimidines **6**.

2-(Trifluoroacetylmethylene)pyrido[1,2-*a*]pyrimidine (**6a**): Crystallized from acetonitrile; mp 244—246 °C; yield 70%; IR (Nujol) cm^{-1}: 3030, 1650, 1590; ^{1}H-NMR (DMSO-d_6/TMS) δ: 5.60 (1H, s, H-1′), 7.21, 7.46, 7.88, 8.39 (4H, m, Ar), 8.42, 8.50 (2H, 2d, J=7.8 Hz, H-3, H-4). *Anal.* Calcd for $C_{11}H_7F_3N_2O$: C, 55.01; H, 2.94; N, 11.66. Found: C, 55.08; H, 2.93; N, 11.62.

9-Methyl-2-(trifluoroacetylmethylene)pyrido[1,2-*a*]pyrimidine (**6b**): Crystallized from acetonitrile; mp 240—242 °C; yield 74%; IR (Nujol) cm^{-1}: 3040, 1655, 1560; ^{1}H-NMR (DMSO-d_6/TMS) δ: 2.34 (3H, s, CH_3), 5.59 (1H, s, H-1′), 7.08, 7.72, 8.23 (3H, m, Ar), 8.37, 8.44 (2H, d, J=7.3 Hz, H-3, H-4). *Anal.* Calcd for $C_{12}H_9F_3N_2O$: C, 56.70; H, 3.57; N, 11.02. Found: C, 56.77; H, 3.56; N, 11.07.

8-Methyl-2-(trifluoroacetylmethylene)pyrido[1,2-*a*]pyrimidine (**6c**): Crystallized from acetonitrile; mp 248—250 °C; yield 98%; IR (Nujol) cm^{-1}: 3040, 1655, 1575 cm^{-1}; ^{1}H-NMR (DMSO-d_6/TMS) δ: 2.37 (3H, s, CH_3), 5.54 (1H, s, H-1′), 7.08, 7.28, 8.28 (3H, m, Ar), 8.36, 8.42 (2H, d, J=7.8 Hz, H-3, H-4). *Anal.* Calcd for $C_{12}H_9F_3N_2O$: C, 56.70; H, 3.57; N, 11.02. Found: C, 56.76; H, 3.56; N, 11.05.

7-Methyl-2-(trifluoroacetylmethylene)pyrido[1,2-*a*]pyrimidine (**6d**): Crystallized from ethanol; mp 300 °C (dec.); yield 90%; IR (Nujol) cm^{-1}: 3030, 1650, 1585; ^{1}H-NMR (DMSO-d_6/TMS) δ: 2.25 (3H, s, CH_3), 5.55 (1H, s, H-1′), 7.41, 7.77, 8.24 (3H, m, Ar), 8.38, 8.42 (2H, d, J=7.3 Hz, H-3, H-4). *Anal.* Calcd for $C_{12}H_9F_3N_2O$: C, 56.70; H, 3.57; N, 11.02. Found: C, 56.74; H, 3.58; N, 11.06.

6-Methyl-2-(trifluoroacetylmethylene)pyrido[1,2-*a*]pyrimidine (**6e**): Crystallized from 2-propanol; mp 250—252 °C; yield 71%; IR (Nujol) cm^{-1}: 3040, 1640, 1600; ^{1}H-NMR (DMSO-d_6/TMS) δ: 2.64 (3H, s, CH_3), 5.58 (1H, s, H-1′), 7.14, 7.38, 7.81 (3H, m, Ar), 8.46, 8.57 (2H, d, J=7.8 Hz, H-3, H-4). *Anal.* Calcd for $C_{12}H_9F_3N_2O$: C, 56.70; H, 3.57; N, 11.02. Found: C, 56.65; H, 3.59; N, 10.98.

6,8-Dimethyl-2-(trifluoroacetylmethylene)pyrido[1,2-*a*]pyrimidine (**6f**): Crystallized from ethanol; mp 300 °C (dec.); yield 91%; IR (Nujol) cm^{-1}: 3090, 1650, 1580; ^{1}H-NMR (DMSO-d_6/TMS) δ: 2.33 (3H, s, CH_3), 2.59 (3H, s, CH_3), 5.53 (1H, s, H-1′), 7.03, 7.22 (2H, s, Ar), 8.40, 8.50 (2H, d, J=7.8 Hz, H-3, H-4). *Anal.* Calcd for $C_{13}H_{11}F_3N_2O$: C, 58.21; H, 4.13; N, 10.44. Found: C, 58.26; H, 4.16; N, 10.39.

General Procedure for the Preparation of Pyrido[1,2-*a*]pyrimidines 6g,h A solution of hexadienones **4g**,**h** (0.005 mol) in acetic acid (2 ml) was refluxed under stirring for 30 min. After cooling the resulting precipitate was filtered off and purified from crystallization to give pyridopyrimidines **6g**,**h**.

7-Chloro-2-(trifluoroacetylmethylene)pyrido[1,2-*a*]pyrimidine (**6g**): Crystallized from ethanol; mp 272—274 °C; yield 92%; IR (Nujol) cm^{-1}: 3020, 1660, 1645, 1600; ^{1}H-NMR (DMSO-d_6/TMS) δ: 5.60 (1H, s, H-1′), 7.44, 7.91, 8.70 (3H, m, Ar), 8.33, 8.38 (2H, d, J=7.3 Hz, H-3, H-4). *Anal.* Calcd for $C_{11}H_6ClF_3N_2O$: C, 48.11; H, 2.20; N, 10.20. Found: C, 48.16; H, 2.22; N, 10.16.

7-Nitro-2-(trifluoroacetylmethylene)pyrido[1,2-*a*]pyrimidine (**6h**): Crystallized from acetic acid; mp 252—254 °C; yield 77%; IR (Nujol) cm^{-1}: 3050, 1660, 1600; ^{1}H-NMR (DMSO-d_6/TMS) δ: 5.75 (1H, s, H-1′), 7.38, 8.49, 9.60 (3H, m, Ar), 8.29, 8.49 (2H, d, J=7.8 Hz, H-3, H-4). *Anal.* Calcd for $C_{11}H_6F_3N_3O_3$: C, 46.33; H, 2.12; N, 14.73. Found: C, 46.21; H, 2.18; N, 14.67.

References and Notes

1) Andreani A., Leoni A., Locatelli A., Morigi R., Rambaldi M., Pietra C., Villetti G., *Eur. J. Med. Chem*., **35**, 77—82 (2000).
2) Kester J. A., Moos W. H., Thomas A. J., U.S. Patent, 4855308 [*Chem. Abstr*., **112**, 48815*c* (1990)].
3) Takemoto T., Eda M., Hihara M., Okada T., Sakashita H., Eiraku M., Fukaya C., Nakamura N., Sugiura M., U.S. Patent, 5371086 [*Chem. Abstr*., **123**, 111854*j* (1995)].
4) Prous J. R., "The Year's Drug News," Prous Science S. A.: Barcelona and Philadelphia, 1995.
5) Effland R. C., Klein J. T., Martin L. L., Shutske G. M., Kapples K. J., Tomer J. D., IV, U.S. Patent, 5328920 [*Chem. Abstr*., **123**, 83210*a* (1995)].
6) Kozlovskaya M. M., Inozemtsev A. N., Nikitin S. V., Gochmuradov A., Yakushev R. A., Chabak-Gorbach R., *Byull. Eksp. Biol. Med*., **119**, 299—301 (1995) [*Chem. Abstr*., **124**, 76193*q* (1996)].
7) Vandenberk J., Kennis L., Edmond J., PCT Int. Appl. WO 95 14,691, 1995 [*Chem. Abstr*., **123**, 340172*c* (1995)].
8) Meszaros Z., *Kem. Kozl*., **50**, 173—190 (1978) [*Chem. Abstr*., **89**, 156994*a* (1978)].
9) Ishikawa, N., "Biologically Active Organofluorine Compounds," CMC Tokyo, 1990.
10) Katsuyama I., Funabiki K., Matsui M., Muramatsu H., Shibata K., *Tetrahedron Lett*., **37**, 4177—4178 (1996).
11) Webber S. E., Bleckman T. M., Attard J., Deal J. G., Kathardekar V., Welsh K. M., *J. Med. Chem*., **36**, 733—746 (1993).
12) Okada E., Masuda R., Hojo M., *Heterocycles*, **34**, 1927—1934 (1992).
13) Wamhoff H., Wintersohl H., Stoelben S., Paasch J., Zhu N.-J., Guo F., *Justus Liebigs Ann. Chem*., **1990**, 901—911.
14) Brel V. K., Abramkin E. V., Chekhlov A. N., Martynov I. V., *Dokl. Akad. Nauk. SSSR*, **312**, 619—622 (1990) [*Chem. Abstr*., **114**, 122513*n* (1991)].
15) Brel V. K., Abramkin E. V., *Izv. Akad. Nauk. SSSR, Ser. Khim.*, **1991**, 473—477 (1991) [*Chem. Abstr*., **114**, 247399*m* (1991)].
16) Lang S. A., Lin Y.-I., "Katritzky and Rees Comprehensive Heterocyclic Chemistry," ed. by Potts K. T., Pergamon Press, Oxford, 1984, pp. 61—66, 93, 94, 100—102.
17) Colla A., Martins M. A. P., Clar G., Krimmer S., Fischer P., *Synthesis*, **1991**, 483—486.
18) Cocco M. T., Congiu C., Onnis V., Bernard A. M., Piras P. P., *J. Heterocyclic Chem*., **34**, 1347—1350 (1997).
19) Cocco M. T., Congiu C., Onnis V., *Tetrahedron Lett*., **40**, 4407—4410 (1999).