Synthesis of Triflouromethylated Pyridinecarbonitriles

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Enaminonitriles **1** react in mild conditions with β-trifluoroacetylvinyl ethers **2** to give the pyridine derivatives **4**. The reaction involves the formation of the intermediate **3**, that can be isolated when enol ether **2a** is used.

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New methodologies have been developed recently for the synthesis of various trifluoromethylated heterocycles, since many kinds of these compounds are used in medicine and in agriculture [1,2]. For this reason reagents for the fluorination and trifluoromethylation of particular functional groups have received great attention. In particular β-trifluoroacetylvinyl ethers are a very interesting class of precursors for the preparation of a variety of substituted five- and six-membered heterocyclic compounds [3-6]. In this paper we describe an easy and convenient method for the synthesis of the pyridine bearing trifluoromethyl group by reaction of β-trifluoroacetylvinyl ethers **2** with enaminonitriles **1**, that are very reactive and versatile binucleophiles [7-9].

The reaction between enaminonitriles **1** and vinyl ethers **2** is carried out at reflux in acetonitrile to give good yields of 2-dialkylamino-6-trifluoromethyl-3-pyridinecarbonitriles **4** through the formation of the intermediate trifluoroacetyldienamine **3**. Adducts **3** are the main product of the reaction between the enaminonitriles **1** and enol ether **2a** when the reaction is carried out in chloroform at low temperatures (0-5°). In acetonitrile at room temperature, mixtures of adducts **3** and pyridines **4** are obtained in variable proportions depending on the enaminonitrile and the reaction times. Adduct **3a-d** obtained by nucleophilic substitution (*via* the α-carbon atom of enaminonitrile) undergo the intramolecular nucleophilic attack of the amino nitrogen on the carbonyl carbon of the trifluoroacetyl group to afford the 6-trifluoromethyl-3-pyridinecarbonitriles **4**.

The structure of the adducts **3a-d** was established by means of ^1H nmr spectra. The magnitude of the cou-

Table 1

Physical and Analytical Data of Compounds **3** and **4**

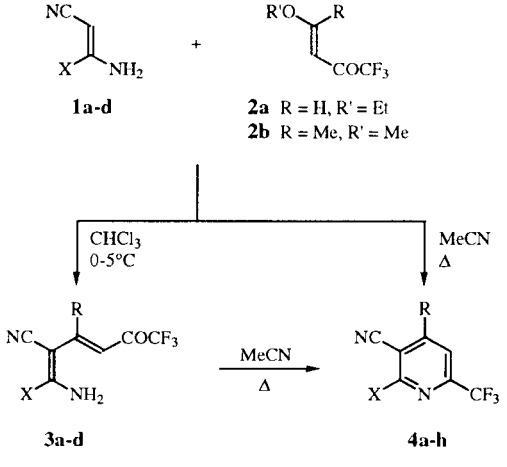
Compound No.	X	R	Yield (%)	Mp (°C)	Crystallization Solvent	Formula	Analysis % Calcd./Found C	H	N
3a	pyrrolidino	H	71	136-137	—	$C_{11}H_{12}F_3N_3O$	50.96	4.67	16.21
							50.90	4.68	16.24
3b	morpholino	H	68	181-182	—	$C_{11}H_{12}F_3N_3O_2$	48.00	4.40	15.27
							48.04	4.41	15.23
3c	4-methyl-piperazino	H	73	143-144	—	$C_{12}H_{15}F_3N_4O$	49.99	5.24	19.44
							50.04	5.23	19.47
3d	4-ethoxycarbonylpiperazino	H	76	149-150	—	$C_{14}H_{17}F_3N_4O_3$	48.55	4.95	16.18
							48.50	4.96	16.20
4a	pyrrolidino	H	79	45-46	petroleum ether	$C_{11}H_{10}F_3N_3$	54.77	4.18	17.42
							54.82	4.17	17.40
4b	morpholino	H	77	94-95	*n*-hexane	$C_{11}H_{10}F_3N_3O$	51.36	3.92	16.34
							51.41	3.91	16.36
4c	4-methyl-piperazino	H	68	218-219	2-propanol	$C_{12}H_{13}F_3N_4{\cdot}HCl$	46.99	4.27	18.27
							47.03	4.26	18.25
4d	4-ethoxycarbonylpiperazino	H	91	92-93	*n*-hexane	$C_{14}H_{15}F_3N_4O_2$	51.22	4.60	17.07
							51.18	4.61	17.04
4e	pyrrolidino	CH_3	86	114-115	2-propanol	$C_{12}H_{12}F_3N_3$	56.46	4.74	16.46
							56.50	4.73	16.44
4f	morpholino	CH_3	70	117-118	2-propanol	$C_{12}H_{12}F_3N_3O$	53.13	4.46	15.49
							53.09	4.42	15.52
4g	4-methyl-piperazino	CH_3	94	219-220	2-propanol	$C_{13}H_{15}F_3N_4{\cdot}HCl$	48.68	4.71	17.47
							48.73	4.70	17.44
4h	4-ethoxycarbonylpiperazino	CH_3	95	121-122	*n*-hexane	$C_{15}H_{17}F_3N_4O_2$	52.63	5.00	16.37
							52.68	5.01	16.33

Table 2

Spectroscopic Data of Compounds **3** and **4**

Compound No.	IR ν cm^{-1}	^{1}H-NMR (solvent) δ (ppm), J (Hz)
3a	3360, 3160, 2190, 2180, 1670	(DMSO-d_6): 1.87, 3.47 (m, 8H pyrrolidinyl), 5.68 (d, 1H, $J_{3,4}$ = 13.2, =CH), 7.95 (d, 1H, $J_{3,4}$ = 13.2, =CH), 7.95 (br s, 2H, NH_2)
3b	3340, 3180, 2190, 1665	(DMSO-d_6): 3.50, 3.61 (m, 8H morpholinyl), 5.73 (d, 1H, $J_{3,4}$ = 13.7, =CH), 7.89 (d, 1H, $J_{3,4}$ = 13.7, =CH), 8.12, 8.59 (br s, 2H, NH_2)
3c	3330, 3160, 2200, 1660	(DMSO-d_6): 2.18 (s, 3H, CH_3), 2.38, 3.48 (m, 8H piperazinyl), 5.72 (d, 1H, $J_{3,4}$ = 13.7, =CH), 7.88 (d, 1H, $J_{3,4}$ = 13.7, =CH), 8.08, 8.56 (br s, 2H, NH_2)
3d	3600, 3510, 3180, 2200, 2190, 1695, 1670	(DMSO-d_6): 1.14 (t, 3H, CH_3), 3.43, 3.48 (m, 8H piperazinyl), 4.01 (q, 2H, CH_2), 5.72 (d, 1H, $J_{3,4}$ = 13.7, =CH), 7.89 (d, 1H, $J_{3,4}$ = 13.7, =CH), 8.11, 8.60 (br s, 2H, NH_2)
4a	2220, 1590, 1570	($CDCl_3$): 1.94, 3.73 (m, 8H pyrrolidinyl), 6.79 (d, 1H, $J_{4,5}$ = 7.8, H-5), 7.76 (d, 1H, $J_{4,5}$ = 7.8, H-4)
4b	2210, 1590, 1565	($CDCl_3$): 3.76 (m, 8H morpholinyl), 7.00 (d, 1H, $J_{4,5}$ = 7.8, H-5), 7.87 (d, 1H, $J_{4,5}$ = 7.8, H-4)
4c	2560, 2450, 2220, 1590	(DMSO-d_6): 2.74 (s, 3H, CH_3), 3.19, 3.45, 4.29 (m, 8H piperazinyl), 7.42 (d, 1H, $J_{4,5}$ = 7.8, H-5), 8.42 (d, 1H, $J_{4,5}$ = 7.8, H-4)
4d	2210, 1700, 1590, 1565	($CDCl_3$): 1.20 (t, 3H, CH_3), 3.57, 3.72 (m, 8H piperazinyl), 4.10 (q, 2H, CH_2), 7.02 (d, 1H, $J_{4,5}$ = 7.8, H-5), 7.88 (d, 1H, $J_{4,5}$ = 7.8, H-4)
4e	2210, 1580	($CDCl_3$): 1.93, 3.74 (m, 8H pyrrolidinyl), 2.43 (s, 3H, CH_3), 6.71 (s, 1H, H-5)
4f	2220, 1570	($CDCl_3$): 2.49 (s, 3H, CH_3), 3.71, 3.77 (m, 8H morpholinyl), 6.94 (s, 1H, H-5)
4g	2410, 2220, 1585, 1565	(DMSO-d_6): 2.50 (s, 3H, CH_3), 2.74 (s, 3H, CH_3), 3.11, 3.47, 4.20 (m, 8H piperazinyl), 7.48 (s, 1H, H-5)
4h	2220, 1700, 1570	($CDCl_3$): 1.21 (t, 3H, CH_3), 2.48 (s, 3H, CH_3), 3.58, 3.66 (m, 8H piperazinyl), 4.10 (q, 2H, CH_2), 6.94 (s, 1H, H-5)

Scheme



1, 3, 4	X	R
a	pyrrolidino	H
b	morpholino	H
c	4-methylpiperazino	H
d	4-ethoxyc arbonylpiperazino	H
e	pyrrolidino	Me
f	morpholino	Me
g	4-methylpiperazino	Me
h	4-ethoxycarbonylpiperazino	Me

pling constant $J_{3,4}$ = 13.4 Hz of the olefinic protons suggests an *E* configuration. The non equivalence of the protons of the amino group suggests an interaction of the group with CN.

EXPERIMENTAL

Melting points were determined on a Köfler hot stage and are uncorrected. The ir spectra were determined in Nujol with a Perkin-Elmer 398 spectrophotometer. The ^{1}H nmr spectra were recorded on a Varian Unity 300 spectrometer; the chemical shifts are given in δ downfield from the internal standard hexamethyldisiloxane (HMDSO). Elemental analyses were carried out with a Carlo Erba Model 1106 Elemental Analyzer. Compounds **1a-d** [7], **2a,b** [4,10] were prepared according to the literature procedures.

6-Amino-5-cyano-6-(dialkylamino)-1,1,1-trifluoro-3,5-hexadien-2-ones **3**.

General Method.

β-Trifluoroacetylvinyl ether **2a** (10 mmoles) was added to a solution of enaminonitrile **1a-d** (10 mmoles) in dry chloroform (10 ml). The mixture was kept at 0-5° for 24 hours. The formed solid was then filtered off, washed with chloroform and dried to give compounds **3** (Table 1).

Thermal Cyclization of 1,1,1-Trifluoro-3,5-hexadien-2-one

Derivatives **3a-d**.

General Method.

A suspension of compound **3a-d** (5 mmoles) in dry acetonitrile (10 ml) was heated at reflux for 1 hour. The solvent was then evaporated *in vacuo* and the residue recrystallized from an appropriate solvent to give the pyridines **4a-d** in quantitative yields.

2-(Dialkylamino)-6-trifluoromethyl-3-pyridinecarbonitrile Derivatives **4**.

General Method.

β-Trifluoroacetylvinyl ether **2** (10 mmoles) was added to a solution of enaminonitrile **1** (10 mmoles) in dry acetonitrile (10 ml). The mixture was refluxed for 2 hours and then evaporated to dryness. The residue was recrystallized from an appropriate solvent to give compounds **4** (Table 2). In the case of compounds **4c** and **4g** the residue was first treated with excess cold 37% aqueous hydrochloric acid, triturated with isopropyl ether and then purified as described above.

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