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Received April 3, 1996

Polyfunctionalized trifluoromethylpyridines **4**, **5** were readily synthesized from trifluoroacetylvinyl ether **3**, using *N*¹-acylacetamidrazones **1**, **2** as starting material.

J. Heterocyclic Chem., **33**, 1771 (1996).

In the recent years increasing interest has been paid to the chemistry of organic trifluoromethyl compounds due to their unique properties and their remarkable potential biological activities [1-3]. Few approaches for the preparation of trifluoromethyl heterocycles have been developed. Among these the use of easily available trifluoromethylated building blocks has often been found to be the best choice rather than conversion of a carboxy group into the trifluoromethyl or direct introduction of a trifluoromethyl group into heterocyclic systems [4].

In pursuit our researches in providing new methodologies in heterocyclic synthesis we have reported on the preparation of trifluoromethylated pyridines by reaction of enamionitriles with trifluoroacetylated vinyl ethers that are versatile synthones for convenient introduction of trifluoromethyl groups in heterocyclic compounds [5]. Now we wish to utilize these substrates in cyclization reactions with *N*¹-acylacetamidrazones that may serve as bis-nucleophiles to synthesize a wide variety of heterocyclic compounds by nucleophilic addition or substitution (*via* C-2)

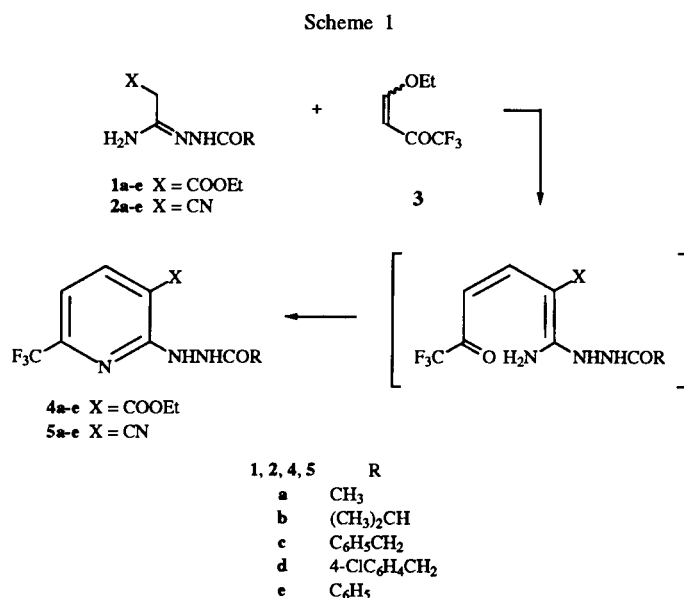


Table 1
Physical and Analytical Data of Compounds **4** and **5**

Compound No.	R	X	Yield (%)	mp (°C) (Recryst.Solvent)	Molecular Formula	Analysis (%)		
						Calcd./Found	C	H
4a	Me	COOEt	65	163-164	C ₁₁ H ₁₂ F ₃ N ₃ O ₃	45.37	4.15	14.43
				(Isopropyl ether)		45.31	4.17	14.40
4b	<i>i</i> -Pr	COOEt	78	151-152	C ₁₃ H ₁₆ F ₃ N ₃ O ₃	48.90	5.05	13.16
				(Isopropyl ether)		48.86	5.03	13.12
4c	PhCH ₂	COOEt	89	121-122	C ₁₇ H ₁₆ F ₃ N ₃ O ₃	55.59	4.39	11.44
				(Cyclohexane)		55.53	4.37	11.47
4d	4-ClC ₆ H ₄ CH ₂	COOEt	68	152-153	C ₁₇ H ₁₅ ClF ₃ N ₃ O ₃	50.82	3.76	10.46
				(Cyclohexane)		50.79	3.74	10.42
4e	Ph	COOEt	91	175-176	C ₁₆ H ₁₄ F ₃ N ₃ O ₃	54.39	3.99	11.89
				(Isopropyl ether)		54.43	3.98	11.92
5a	Me	CN	86	163-165	C ₉ H ₇ F ₃ N ₄ O	44.27	2.89	22.95
				(Benzene)		44.22	2.85	22.91
5b	<i>i</i> -Pr	CN	70	144-145	C ₁₁ H ₁₁ F ₃ N ₄ O	48.53	4.07	20.58
				(Benzene)		48.58	4.05	20.54
5c	PhCH ₂	CN	73	163-164	C ₁₅ H ₁₁ F ₃ N ₄ O	56.25	3.46	17.49
				(Isopropyl ether)		56.22	3.44	17.53
5d	4-ClC ₆ H ₄ CH ₂	CN	66	188-189	C ₁₅ H ₁₀ ClF ₃ N ₄ O	50.79	2.84	15.79
				(Benzene)		50.73	2.86	15.74
5e	Ph	CN	52	154-155	C ₁₄ H ₉ F ₃ N ₄ O	54.91	2.96	18.29
				(Benzene)		54.95	2.94	18.33

Table 2
Ir and ¹H-nmr Data of Compounds 4 and 5

Compound No.	IR ν (cm ⁻¹)		¹ H NMR δ (ppm)		
			H-4, H-5	R	X NH - NH
4a	3360, 3330, 3200, 1695, 1655	[a]	7.22, 8.35 (d), J = 7.8	1.88 (s)	1.29 (t), 4.32 (q), J = 7.1 9.39, 10.09 (s)
4b	3300, 3270, 1685, 1655	[b]	6.94, 8.21 (d) J = 7.8	1.13 (d), 2.46 (hept), J = 7.3	1.31 (t), 4.30 (q), J = 7.3 8.16, 9.59 (d), J = 4.4
4c	3340, 3200, 1690, 1660	[b]	6.98, 8.24 (d), J = 7.8	3.66 (s), 7.32 (m)	1.33 (t), 4.32 (q), J = 6.8 7.93, 9.71 (d), J = 4.9,
4d	3330, 3280, 1695, 1665	[b]	7.00, 8.25 (d), J = 7.8	3.61 (s), 7.27 (m)	1.33 (t), 4.32 (q), J = 7.3 7.92, 9.69 (d), J = 4.4
4e	3320, 3170, 1685, 1630	[a]	7.25, 8.41 (d), J = 7.8	7.52, 7.94 (m)	1.33 (t), 4.36 (q), J = 6.8 9.64, 10.75 (s)
5a	3280, 2220, 1655	[b]	7.22, 8.25 (d), J = 7.8	1.88 (s)	— 9.62, 10.11 (s)
5b	3250, 2220, 1675, 1600	[a]	7.18, 8.23 (d), J = 7.8	1.04 (d), 2.49 (hept), J = 6.8	— 9.60, 10.02 (s)
5c	3240, 2200, 1645	[a]	7.23, 8.31 (d), J = 7.8	3.40 (s), 7.30 (m)	— 9.75, 10.42 (s)
5d	3310, 3260, 2230, 1665, 1595	[a]	7.27, 8.31 (d), J = 7.8	3.55 (s), 7.33 (m)	— 9.73, 10.40 (s)
5e	3300, 2220, 1645	[a]	7.27, 8.30 (d), J = 7.8	7.51, 7.86 (m)	— 9.85, 10.76 (s)

[a] In DMSO-d₆ solution, [b] In deuteriochloroform solution.

Table 3
¹³C nmr Data of Compounds 4 and 5

Compound No.		C-2	C-3	C-4	C-5	C-6	CF ₃	NHCO	X	R
4a	[a]	155.6	108.0	140.3	108.0	146.8 J = 34.2	119.0 J = 274.7	166.4	11.9, 59.7, 163.5	18.33
4b	[b]	156.5	110.0	141.3	109.6	149.8 J = 34.8	120.6 J = 274.7	175.5	13.8, 61.5, 165.1	18.9, 33.25
4c	[b]	156.3	109.8	141.3	109.5	149.8 J = 34.8	120.6 J = 275.3	169.4	13.7, 61.5, 165.1	40.8, 126.7, 128.3, 129.1, 134.1
4d	[b]	156.2	110.0	141.4	109.8	149.8 J = 34.8	120.5 J = 275.3	168.8	13.8, 61.6, 165.0	40.2, 128.5, 130.4, 132.3, 132.8
4e	[a] [c]	156.1	108.5	140.3	108.3	146.9 J = 34.2	119.0 J = 274.7	164.3	11.9, 59.7, 163.2,	125.5, 126.4, 129.7, 130.9
5a	[a]	157.3	91.0	144.8	108.0	146.3 J = 34.2	118.70 J = 275.3	167.3	113.5	18.1
5b	[a]	157.2	91.5	144.2	108.0	146.4 J = 34.8	118.7 J = 275.3	174.1	113.3	17.0, 30.2
5c	[a]	157.1	91.6	144.3	108.2	146.5 J = 34.2	118.8 J = 275.3	168.2	113.4	124.5, 126.2, 127.3, 133.4
5d	[a]	157.0	91.5	144.4	108.2	146.4 J = 34.2	118.7 J = 275.3	167.7	113.4	37.0, 126.1, 129.1, 129.3, 132.4
5e	[a]	157.5	91.4	144.9	108.3	146.4 J = 34.8	118.8 J = 275.3	164.5	113.5	125.7, 126.5, 130.0, 130.2

[a] In DMSO-d₆ solution, [b] In deuteriochloroform solution, [c] The signals for COOEt and NHCO groups are interchangeable.

and cyclocondensation (via NH₂ or NH) reaction sequences [6,7]. In this paper we examined the reactivity of N¹-acyl-2-(ethoxycarbonyl)acetamidrazones 1 as well as N¹-acyl-2-cyano acetamidrazones 2, that were readily obtained by usual procedure [8] starting from 3-amino-3-ethoxypropenenitrile and acylhydrazines, towards 4-ethoxy-1,1,1-trifluoro-3-buten-2-one 3 in order to afford new trifluoromethylpyridines.

By reacting acetamidrazones 1, 2 with 3 in ethanol at reflux 2-acylhydrazino-6-trifluoro methylpyridines 4, 5 are obtained in good yields (Scheme 1). We suggest that the mechanism of heterocyclization probably involves an initial nucleophilic substitution at C-2 of amidrazones 1, 2 to give a C-adduct, which undergoes cyclization by nucleophilic attack of the amino nitrogen onto the carbonyl carbon of trifluoroacetyl group to afford pyridines 4, 5.

The physical characteristics and spectroscopic data of the new pyridines **4**, **5** are listed in Tables 1-3. For the pyridine protons, ^1H nmr spectroscopy shows an AB system with doublets at 7.18-7.27 ppm and 8.23-8.31 ppm respectively, with $J_{4,5} = 7.8$ Hz. Complete ^{13}C nmr spectral characterization provides further confirmation for the proposed structure of **4**, **5**. The ^{13}C nmr spectra of compounds **4**, **5** consist of up to five signals corresponding to quaternary and two to tertiary carbons and the appropriate number of substituents group signals. Furthermore ^{13}C nmr spectra are characterized by two quartets, the one at 146.3-146.5 ppm was attributed to C-6 ($^2J_{\text{CF}}$ about 34 Hz) and the other at 118.7-120.6 ppm to CF_3 ($^1J_{\text{CF}}$ about 275 Hz).

These results indicated a novel route to polyfunctionalized trifluoromethylpyridines that can be further elaborated to provide fused trifluoromethyl heterocycles.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage and are uncorrected. The ir spectra were determined in Nujol with a Perkin-Elmer 398 spectrophotometer. The ^1H and ^{13}C nmr spectra were recorded on a Varian Unity 300 spectrometer; the chemical shift are given in δ downfield from internal standard hexamethyldisiloxane. Elemental analyses were carried out with a Carlo Erba Model 1106 Elemental Analyzer. Compounds **1a-e** [8], **3** [9] were prepared according to literature procedures.

General Procedure for the Synthesis of Compounds **2a-e**.

A solution of 3-amino-3-ethoxypropenenitrile (1.1 g, 0.01 mole) and the appropriate hydrazine (0.01 mole) in dry ethanol (20 ml) was heated at 70° for 5 minutes and then left overnight at room temperature. The formed precipitate was filtered off, washed with diethyl ether and recrystallized from the solvent indicated.

N^1 -Acetyl-2-cyanoacetamidrazone (**2a**).

This compound was obtained using acetylhydrazine in a yield of 92%, mp $174-175^\circ$ (1-propanol); ir: ν 3340, 3160, 3050, 2230, 1685, 1660, 1600 cm^{-1} ; ^1H nmr (DMSO- d_6): δ 1.84 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 3.46 (s, 2H, CH_2), 6.38 (s, 2H, NH_2), 9.46, 9.53 (s, 1H, NH).

Anal. Calcd. for $\text{C}_5\text{H}_8\text{N}_4\text{O}$: C, 42.85; H, 5.75; N, 39.98. Found: C, 42.92; H, 5.76; N, 39.94.

N^1 -Isobutryl-2-cyanoacetamidrazone (**2b**).

This compound was obtained using isobutrylhydrazine in a yield of 90%, mp $169-170^\circ$ (acetonitrile); ir: ν 3410, 3220, 3040, 2270, 1660, 1610 cm^{-1} ; ^1H nmr (DMSO- d_6): δ 1.01 (d, 6H, $J = 6.8$ Hz, CH_3), 2.50 (m, 1H, CH), 3.44 (s, 2H, CH_2), 6.35 (s, 2H, NH_2), 9.38 (d, 1H, $J = 7.3$ Hz, NH).

Anal. Calcd. for $\text{C}_7\text{H}_{12}\text{N}_4\text{O}$: C, 49.98; H, 7.19; N, 33.31. Found: C, 50.03; H, 7.17; N, 33.35.

N^1 -(Phenylacetyl)-2-cyanoacetamidrazone (**2c**).

This compound was obtained using (phenylacetyl)hydrazine in a yield of 83%, mp $167-168^\circ$ (acetonitrile); ir: ν 3420, 3300, 3180, 2260, 1645, 1595 cm^{-1} ; ^1H nmr (DMSO- d_6): δ 3.36, 3.43, 3.47 (s, 5H, CH_2 and CH), 3.75 (s, 1H, CH), 6.35, 6.41 (s, 2H, NH_2), 7.24 (m, 5H, Ar), 9.63, 9.66 (s, 1H, NH).

Anal. Calcd. for $\text{C}_{11}\text{H}_{12}\text{N}_4\text{O}$: C, 61.09; H, 5.59; N, 25.91. Found: C, 61.13; H, 5.61; N, 25.88.

N^1 -(4-Chlorophenylacetyl)-2-cyanoacetamidrazone (**2d**).

This compound was obtained using 4-(chlorophenylacetyl)hydrazine in a yield of 80%, mp $158-160^\circ$ (acetonitrile); ir: ν 3560, 3320, 3240, 2260, 1640, 1610, 1590 cm^{-1} ; ^1H nmr (DMSO- d_6): δ 3.40, 3.45, 3.49 (s, 5H, CH_2 and CH), 3.77 (s, 1H, CH), 6.40, 6.46 (s, 2H, NH_2), 7.30 (m, 4H, Ar), 9.71 (s, 1H, NH).

Anal. Calcd. for $\text{C}_{11}\text{H}_{11}\text{ClN}_4\text{O}$: C, 52.70; H, 4.42; N, 22.35. Found: C, 52.65; H, 4.44; N, 22.38.

N^1 -Benzoyl-2-cyanoacetamidrazone (**2e**).

This compound was obtained using benzoylhydrazine in a yield of 90%, mp $184-185^\circ$ (1-propanol); ir: ν 3400, 3200, 2230, 1670, 1645, 1630, 1610 cm^{-1} ; ^1H nmr (DMSO- d_6): δ 3.54 (s, 2H, CH_2), 6.66 (s, 2H, NH_2), 7.47, 7.84 (m, 5H, Ar), 9.96 (s, 1H, NH).

Anal. Calcd. for $\text{C}_{10}\text{H}_{10}\text{N}_4\text{O}$: C, 59.39; H, 4.98; N, 27.71. Found: C, 59.43; H, 5.00; N, 27.67.

General Procedure for the Preparation of 6-Trifluoromethylpyridine Derivatives **4**, **5**.

A solution of **1**, **2** (0.005 mole) and **3** (0.84 g, 0.005 mole) in anhydrous ethanol (30 ml) was refluxed for 2 hours. After removal of the solvent the residue was collected and recrystallized to give compounds **4**, **5** (Table 1).

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