

Maria Teresa Cocco*, Cenzo Congiu and Valentina Onnis

Dipartimento Farmaco Chimico Tecnologico, Università, Via Ospedale No. 72, I-09124 Cagliari, Italy

Angela Maria Bernard and Pier Paolo Piras

Dipartimento di Scienze Chimiche, Università, Via Ospedale No. 72, I-09124 Cagliari, Italy

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The reaction between *N*¹-acylacetamidrazones **1** and enol ether **2** is described. Depending on the reaction conditions and on the substitution pattern of amidrazones 2-acylhydrazino-4-methyl-6-trifluoromethylpyridines **3** and/or 2-acylhydrazino-6-methyl-4-trifluoromethylpyridines **4** were obtained.

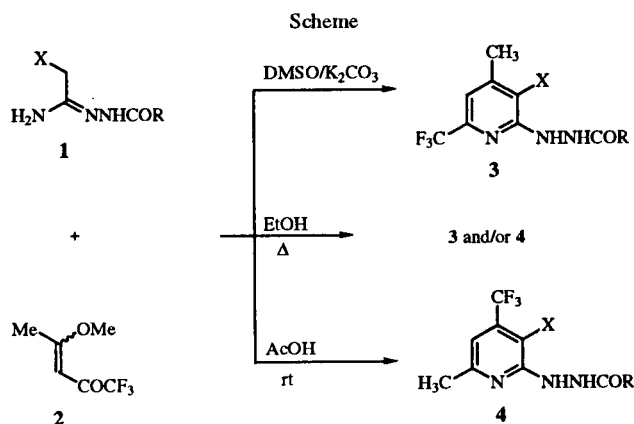
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In the course of our study on the reactivity of amidrazones we have reported on the reactions between *N*¹-acyl-2-(ethoxycarbonyl)acetamidrazones and enol ethers. With diethyl ethoxymethylenemalonate and ethyl ethoxymethylenecyanoacetate 1-acylaminopyridines and 2-acylhydrazinopyridines were respectively obtained depending on the starting acetamidrazones [1,2].

The observation that, aside from the reaction medium (neutral, slightly basic or acid), the postulated intermediate is originated by nucleophilic substitution to C-2 of amidrazones, implies that the nucleophilicity of C-2 is greater than that of nitrogen atoms in α -position and that the subsequent cyclization involves N² or N³ atoms.

Similar results were obtained in the reactions of amidrazones with 4-ethoxy-1,1,1-trifluoro-3-buten-2-one, where the 2-acylhydrazino-6-trifluoromethylpyridine derivatives [3] obtained show interesting functionalities for use in medicinal and agriculture fields [4].

As an extension and generalization of this work we now wish to study the reaction of 2-ethoxycarbonyl and 2-cyanoacetamidrazones **1** with 4-methoxy-1,1,1-trifluoro-3-penten-2-one **2**. Since the reactivity of the two electrophilic centres of **2** strongly differ, we became interested in studying the selectivity of the attack at the various nucleophilic centres of amidrazones **1**. To exam-



ine the regiochemistry of these cyclocondensation reactions a systematic study was carried out using amidrazones with different *N*¹-acyl substituents and changing the reaction conditions.

The reaction of equimolecular amounts of acetamidrazones **1** and 1,1,1-trifluoroacetylvinyl ether **2** in ethanol under reflux led to the isomeric 2-acylhydrazino-4-methyl-6-trifluoromethylpyridines **3** and/or 2-acylhydrazino-6-methyl-4-trifluoromethylpyridines **4** depending on the substitution pattern of the starting amidrazones (Tables 1, 2).

Table 1
Physical and Analytical Data of Compounds **3** and **4**

Compound No.	R	X	mp (°C) (Recryst. Solvent)	Formula	Analysis (%)		
					C	H	N
3a	Me	COOEt	120-121	C ₁₂ H ₁₄ F ₃ N ₃ O ₃	47.22	4.62	13.77
			(Isopropyl ether)		47.25	4.60	13.81
4a	Me	COOEt	139-140	C ₁₂ H ₁₄ F ₃ N ₃ O ₃	47.22	4.62	13.77
			(Isopropyl ether)		47.17	4.64	13.73
3b	<i>i</i> -Pr	COOEt	155-156	C ₁₄ H ₁₈ F ₃ N ₃ O ₃	50.45	5.44	12.61
			(Isopropyl ether)		50.40	5.46	12.65
4b	<i>i</i> -Pr	COOEt	138-139	C ₁₄ H ₁₈ F ₃ N ₃ O ₃	50.45	5.44	12.61
			(Isopropyl ether)		50.48	5.42	12.64

Table 1 (continued)

Compound No.	R	X	mp (°C) (Recryst. Solvent)	Formula	Analysis (%)		
					C	Calcd./Found H	N
3c	PhCH ₂	COOEt	135-136 (Isopropyl ether)	C ₁₈ H ₁₈ F ₃ N ₃ O ₃	56.69 56.74	4.76 4.80	11.02 10.98
4c	PhCH ₂	COOEt	114-115 (Benzene)	C ₁₈ H ₁₈ F ₃ N ₃ O ₃	56.69 56.63	4.76 4.74	11.02 11.05
3d	4-ClC ₆ H ₄ CH ₂	COOEt	160-161 (Isopropyl ether)	C ₁₈ H ₁₇ ClF ₃ N ₃ O ₃	52.00 52.04	4.12 4.13	10.11 10.08
4d	4-ClC ₆ H ₄ CH ₂	COOEt	137-138 (Benzene)	C ₁₈ H ₁₇ ClF ₃ N ₃ O ₃	52.00 51.95	4.12 4.10	10.11 10.14
3e	4-MeOC ₆ H ₄ CH ₂	COOEt	109-110 (Isopropyl ether)	C ₁₉ H ₂₀ F ₃ N ₃ O ₄	55.46 55.43	4.90 4.91	10.22 10.19
4e	4-MeOC ₆ H ₄ CH ₂	COOEt	113-114 (Isopropyl ether)	C ₁₉ H ₂₀ F ₃ N ₃ O ₄	55.46 55.51	4.90 4.88	10.22 10.25
3f	4-NO ₂ C ₆ H ₄ CH ₂	COOEt	180-181 (2-Propanol)	C ₁₈ H ₁₇ F ₃ N ₄ O ₅	50.71 50.76	4.02 4.00	13.14 13.10
4f	4-NO ₂ C ₆ H ₄ CH ₂	COOEt	174-175 (Acetone)	C ₁₈ H ₁₇ F ₃ N ₄ O ₅	50.71 50.67	4.02 4.03	13.14 13.18
3g	Ph	COOEt	89-90 (Methanol)	C ₁₇ H ₁₆ F ₃ N ₃ O ₃	55.59 55.54	4.39 4.41	11.44 11.40
4g	Ph	COOEt	124-125 (Isopropyl ether)	C ₁₇ H ₁₆ F ₃ N ₃ O ₃	55.59 55.62	4.39 4.37	11.44 11.47
3h	4-MeC ₆ H ₄	COOEt	164-165 (Isopropyl ether)	C ₁₈ H ₁₈ F ₃ N ₃ O ₃	56.69 56.73	4.76 4.77	11.02 10.97
4h	4-MeC ₆ H ₄	COOEt	134-135 (Isopropyl ether)	C ₁₈ H ₁₈ F ₃ N ₃ O ₃	56.69 56.63	4.76 4.74	11.02 11.04
3i	4-MeOC ₆ H ₄	COOEt	137-138 (Isopropyl ether)	C ₁₈ H ₁₈ F ₃ N ₃ O ₄	54.41 54.44	4.57 4.55	10.57 10.54
4i	4-MeOC ₆ H ₄	COOEt	142-143 (Isopropyl ether)	C ₁₈ H ₁₈ F ₃ N ₃ O ₄	54.41 54.37	4.57 4.58	10.57 10.60
3j	4-NO ₂ C ₆ H ₄	COOEt	189-190 (Isopropyl ether)	C ₁₇ H ₁₅ F ₃ N ₄ O ₅	49.52 49.46	3.67 3.66	13.59 13.56
4j	4-NO ₂ C ₆ H ₄	COOEt	214-215 (Acetonitrile)	C ₁₇ H ₁₅ F ₃ N ₄ O ₅	49.52 49.55	3.67 3.65	13.59 13.63
3k	4-pyridyl	COOEt	165-166 (Isopropyl alcohol)	C ₁₇ H ₁₅ F ₃ N ₄ O ₃ Cl	48.99 49.03	3.87 3.86	13.44 13.41
4k	4-pyridyl	COOEt	150-151 (Isopropyl ether)	C ₁₇ H ₁₅ F ₃ N ₄ O ₃	53.69 53.72	3.98 4.00	14.73 14.70
3l	4-ClC ₆ H ₄	COOEt	157-158 (Isopropyl ether)	C ₁₇ H ₁₅ ClF ₃ N ₃ O ₃	50.82 50.87	3.76 3.75	10.46 10.42
4l	4-ClC ₆ H ₄	COOEt	149-150 (Isopropyl ether)	C ₁₇ H ₁₅ ClF ₃ N ₃ O ₃	50.82 50.78	3.76 3.78	10.46 10.50
3m	OEt	COOEt	64-65 (Hexane)	C ₁₃ H ₁₆ F ₃ N ₃ O ₄	46.57 46.62	4.81 4.83	12.53 12.48
4m	OEt	COOEt	104-105 (Hexane)	C ₁₃ H ₁₆ F ₃ N ₃ O ₄	46.57 46.53	4.81 4.79	12.53 12.56
3n	Me	CN	196-197 (2-Propanol)	C ₁₀ H ₉ F ₃ N ₄ O	46.52 46.56	3.51 3.49	21.70 21.75
4n	Me	CN	184-186 (2-Propanol)	C ₁₀ H ₉ F ₃ N ₄ O	46.52 46.47	3.51 3.53	21.70 21.66
3o	<i>i</i> -Pr	CN	168-169 (Isopropyl ether)	C ₁₂ H ₁₃ F ₃ N ₄ O	50.35 50.32	4.58 4.56	19.57 19.60
4o	<i>i</i> -Pr	CN	164-165 (Benzene)	C ₁₂ H ₁₃ F ₃ N ₄ O	50.35 50.40	4.58 4.60	19.57 19.61
3p	PhCH ₂	CN	117-118 (Isopropyl ether)	C ₁₆ H ₁₃ F ₃ N ₄ O	57.49 57.45	3.92 3.95	16.76 16.73
4p	PhCH ₂	CN	169-170 (Toluene)	C ₁₆ H ₁₃ F ₃ N ₄ O	57.49 57.53	3.92 3.90	16.76 16.73
3q	4-ClC ₆ H ₄ CH ₂	CN	175-176 (Isopropyl ether)	C ₁₆ H ₁₂ ClF ₃ N ₄ O	52.12 52.08	3.28 3.26	15.19 15.16
4q	4-ClC ₆ H ₄ CH ₂	CN	197-198 (2-Propanol)	C ₁₆ H ₁₂ ClF ₃ N ₄ O	52.12 52.16	3.28 3.26	15.19 15.23
3r	4-MeOC ₆ H ₄ CH ₂	CN	152-153	C ₁₇ H ₁₅ F ₃ N ₄ O ₂	56.04	4.15	15.38

Table 1 (continued)

Compound No.	R	X	mp (°C) (Recryst. Solvent)	Formula	Analysis (%)		
					C	H	N
			(Isopropyl ether)		56.10	4.17	15.42
4r	4-MeOC ₆ H ₄ CH ₂	CN	146-147	C ₁₇ H ₁₅ F ₃ N ₄ O ₂	56.04	4.15	15.38
			(Benzene)		55.99	4.13	15.33
3s	4-NO ₂ C ₆ H ₄ CH ₂	CN	201-202	C ₁₆ H ₁₂ F ₃ N ₅ O ₃	50.67	3.19	18.46
			(2-Propanol)		50.62	3.20	18.42
4s	4-NO ₂ C ₆ H ₄ CH ₂	CN	208-209	C ₁₆ H ₁₂ F ₃ N ₅ O ₃	50.67	3.19	18.46
			(Acetonitrile)		50.64	3.17	18.50
3t	Ph	CN	182-183	C ₁₅ H ₁₁ F ₃ N ₄ O	56.25	3.46	17.49
			(Benzene)		56.22	3.48	17.46
4t	Ph	CN	175-176	C ₁₅ H ₁₁ F ₃ N ₄ O	56.25	3.46	17.49
			(Isopropyl ether)		56.30	3.44	17.53
3u	4-MeC ₆ H ₄	CN	181-182	C ₁₆ H ₁₃ F ₃ N ₄ O	57.49	3.92	16.76
			(Isopropyl ether)		57.52	3.90	16.79
4u	4-MeC ₆ H ₄	CN	137-138	C ₁₆ H ₁₃ F ₃ N ₄ O	57.49	3.92	16.76
			(Benzene)		57.43	3.93	16.73
3v	4-OMeC ₆ H ₄	CN	193-194	C ₁₆ H ₁₃ F ₃ N ₄ O ₂	54.86	3.74	15.99
			(Isopropyl ether)		54.90	3.72	15.97
4v	4-OMeC ₆ H ₄	CN	155-157	C ₁₆ H ₁₃ F ₃ N ₄ O ₂	54.86	3.74	15.99
			(Benzene)		54.81	3.75	16.03
3w	4-NO ₂ C ₆ H ₄	CN	188-189	C ₁₅ H ₁₀ F ₃ N ₅ O ₃	49.32	2.76	19.17
			(2-Propanol)		49.37	2.78	19.14
4w	4-NO ₂ C ₆ H ₄	CN	214-215	C ₁₅ H ₁₀ F ₃ N ₅ O ₃	49.32	2.76	19.17
			(Ethanol)		49.35	2.75	19.20
4x	4-pyridyl	CN	176-178	C ₁₄ H ₁₀ F ₃ N ₅ O	52.34	3.14	21.80
			(Benzene)		52.37	3.13	21.78

As a matter of fact 2-cyanoacetamidrazones afforded pyridines **4**, except for **1n,u,v** which gave a mixture of pyridines **3** and **4**. On the other hand 2-ethoxycarbonyl-

acetamidrazones gave, in most cases, an isomeric mixture. Only pyridines **4** were obtained from the reactions of amidrazones **1e,j,k**.

Table 2
Yields of Compounds **3** and **4**

Substrate	Method A: Ethanol/Δ Products (Yield)		Method B: DMSO/potassium carbonate Products (Yield)	Method C: Acetic Acid/rt Products (Yield)
1a	3a (28)	4a (42)	3a (60)	4a (45)
1b		3b (70)	3b (68)	4b (24)
1c	3c (13)	4c (56)	3c (53)	4c (28)
1d	3d (10)	4d (65)	3d (60)	4d (55)
1e		4e (78)	3e (59)	4e (56)
1f	3f (23)	4f (38)	3f (66)	4f (28)
1g		3g (78)	3g (80)	4g (33)
1h	3h (53)	4h (40)	3h (92)	4h (33)
1i	3i (39)	4i (34)	3i (91)	4i (46)
1j		4j (70)	3j (90)	4j (42)
1k		4k (70)	3k (49)	4k (36)
1l	3l (59)	4l (26)	3l (89)	4l (64)
1m		3m (73)	3m (70)	4m (36)
1n	3n (59)	4n (14)	3n (55)	
1o		4o (43)	3o (55)	
1p		4p (73)	3p (99)	
1q		4q (62)	3q (66)	
1r		4r (55)	3r (99)	
1s		4s (40)	3s (99)	
1t		4t (73)	3t (57)	
1u	3u (53)	4u (40)	3u (85)	4u (87)
1v	3v (39)	4v (34)	3v (99)	4v (63)
1w		4w (60)	3w (70)	4w (60)
1x		4x (93)		

The structure of compounds **3** and **4** was deduced from microanalyses, ir, ^1H nmr and ^{13}C nmr spectra (Tables 3 and 4). Whereas the ^1H -nmr spectra differ slightly in the chemical shift of the C-5 and CH_3 protons, the ^{13}C nmr spectra allowed unambiguous structure identification on the basis of characteristic chemical shifts values, multiplicities and J_{CF}

values. The ^{13}C nmr spectra of pyridines **3** and **4** show great difference in C-4 and C-6 chemical shifts. The trifluoromethyl group deshields the pyridine point of attachment giving a characteristic quadruplet at 143-147 ppm, with a coupling to ^{19}F of 34 Hz for the C-6 of pyridines **3**, while in the regioisomer **4** the C-4 quadruplet resonates at higher

Table 3
IR and ^1H -NMR Data of Compounds **3** and **4**

Compound No.	IR	H-5	CH_3	^1H NMR R	X	NHNH
3a	3350, 3240, 1695, 1650	[a] 7.12 (s)	2.28 (s)	1.81 (s)	1.27 (t), 4.29 (q)	8.75, 9.75 (s)
3b	3250, 1670	[b] 6.85 (s)	2.49 (s)	1.17 (d), 2.40 (m)	1.36 (t), 4.36 (q)	8.06, 9.40 (d), $J = 5.6$
3c	3320, 3210, 1700, 1645	[a] 7.11 (s)	2.28 (s)	3.43 (s), 7.26 (m)	1.24 (t), 4.28 (q)	8.81, 10.07 (s)
3d	3330, 3200, 1690, 1645	[b] 6.84 (s)	2.47 (s)	3.55 (s), 7.22 (m)	1.33 (t), 4.33 (q)	8.28, 9.40 (s)
3e	3330, 3200, 1700, 1640	[b] 6.84 (s)	2.49 (s)	3.60 (s), 3.76 (s), 6.86, 7.23 (m)	1.36 (t), 4.36 (q)	8.00, 9.46 (s)
3f	3320, 3260, 1680, 1655	[a] 7.11 (s)	2.28 (s)	3.62 (s), 7.56, 8.10 (m)	1.24 (t), 4.29 (q)	8.85, 10.18 (s)
3g	3280, 1685, 1640	[b] 6.88 (s)	2.53 (s)	7.42, 7.79 (m)	1.40 (t), 4.41 (q)	9.06, 9.96 (s)
3h	3300, 3170, 1675, 1605	[b] 6.87 (s)	2.53 (s)	2.36 (s), 7.22, 7.70 (m)	1.41 (t), 4.41 (q)	9.02, 9.93 (s)
3i	3350, 3280, 1670, 1650	[b] 6.85 (s)	2.52 (s)	3.79 (s), 6.90, 7.77 (m)	1.39 (t), 4.39 (q)	8.99, 9.88 (s)
3j	3300, 3190, 1670, 1615	[b] 6.90 (s)	2.54 (s)	7.96, 8.23 (m)	1.40 (t), 4.41 (q)	9.30, 9.96 (s)
3k	3340, 3190, 2460, 1690, 1600	[a] 7.20 (s)	2.33 (s)	8.22, 9.04 (m)	1.24 (t), 4.26 (q)	9.19, 11.20 (s)
3l	3290, 3170, 1680, 1605	[b] 6.92 (s)	2.57 (s)	7.36, 7.79 (m)	1.45 (t), 4.45 (q)	9.36, 9.85 (s)
3m	3370, 3240, 1720, 1675	[b] 6.88 (s)	2.48 (s)	1.20 (t), 4.12 (q)	1.34 (t), 4.35 (q)	6.64, 8.79 (s)
3n	3260, 3080, 3030, 2210, 1680	[a] 7.25 (s)	2.45 (s)	1.87 (s)		9.47, 10.05 (s)
3o	3300, 3240, 2220, 1675	[b] 7.11 (s)	2.60 (s)	1.28 (d), 2.58 (m)		7.37, 7.72 (s)
3p	3190, 2220, 1680	[b] 7.06 (s)	2.55 (s)	3.71 (s), 7.33, 7.36 (m)		7.66, 8.37 (s)
3q	3290, 2210, 1650	[b] 7.06 (s)	2.53 (s)	3.66 (s), 7.30 (m)		7.24, 7.56 (s)
3r	3300, 3240, 2220, 1645	[b] 7.10 (s)	2.59 (s)	3.70 (s), 3.86 (s), 6.96, 7.33 (m)		7.40, 7.67 (s)
3s	3290, 2200, 1650	[b] 7.05 (s)	2.51 (s)	3.75 (s), 7.50, 8.17 (d)		7.22, 7.60 (s)
3t	3300, 3280, 2220, 1665	[a] 7.28 (s)	2.49 (s)	7.50, 7.92 (m)		9.74, 10.76 (s)
3u	3310, 3290, 2220, 1680	[b] 7.04 (s)	2.53 (s)	2.38 (s), 7.24, 7.72 (m)		7.60, 8.33 (s)
3v	3310, 3290, 2220, 1660	[b] 7.03 (s)	2.52 (s)	3.82 (s), 6.93, 7.79 (d)		7.55, 8.24 (s)
3w	3250, 2220, 1645	[a] 7.31 (s)	2.50 (s)	8.13, 8.36 (m)		9.85, 11.07 (s)
4a	3340, 3240, 1710, 1655	[a] 6.96 (s)	2.38 (s)	1.81 (s)	1.22 (t), 4.25 (q)	8.54, 9.72 (s)
4b	3340, 3240, 1700, 1640	[b] 6.81 (s)	2.41 (s)	1.18 (d), 2.47 (m)	1.31 (t), 4.31 (q)	8.01, 8.80 (s)
4c	3200, 1730, 1650	[b] 6.80 (s)	2.34 (s)	3.64 (s), 7.32 (m)	1.30 (t), 4.32 (q)	8.04, 8.83 (d), $J = 4.4$
4d	3350, 3240, 1690, 1600	[b] 6.99 (s)	2.37 (s)	3.49 (s), 7.37 (m)	1.24 (t), 4.29 (q)	8.67, 10.08 (s)
4e	3310, 3210, 1690, 1630	[b] 6.79 (s)	2.34 (s)	3.57 (s), 3.74 (s), 6.86, 7.21 (m)	1.29 (t), 4.35 (q)	8.03, 8.81 (s)
4f	3320, 3240, 1685, 1600	[a] 6.96 (s)	2.33 (s)	3.63 (s), 7.60, 8.15 (d)	1.21 (t), 4.26 (q)	8.67, 10.14 (s)
4g	3320, 3220, 1695, 1630	[b] 6.83 (s)	2.42 (s)	7.44, 7.81 (m)	1.32 (t), 4.34 (q)	9.04, 9.23 (s)
4h	3320, 3190, 1700, 1615	[b] 6.91 (s)	2.48 (s)	2.41 (s), 7.24, 7.80 (d)	1.41 (t), 4.42 (q)	9.25, 9.36 (s)
4i	3290, 3200, 1705, 1620	[b] 6.90 (s)	2.47 (s)	3.85 (s), 6.91, 7.87 (d)	1.40 (t), 4.41 (q)	9.18, 9.41 (s)
4j	3310, 3180, 1685, 1620	[a] 7.01 (s)	2.36 (s)	8.08, 8.33 (m)	1.15 (t), 4.18 (q)	9.07, 10.73 (s)
4k	3320, 3180, 1690, 1625	[a] 7.01 (s)	2.36 (s)	7.76, 8.74 (m)	1.14 (t), 4.16 (q)	8.88, 10.70 (s)
4l	3300, 3200, 1710, 1630	[b] 6.93 (s)	2.49 (s)	7.41, 7.84 (d)	1.41 (t), 4.42 (q)	9.26, 9.43 (s)
4m	3350, 3260, 1710, 1690	[b] 6.91 (s)	2.49 (s)	1.27 (t), 4.20 (q)	1.37 (t), 4.38 (q)	7.20, 8.28 (s)
4n	3260, 3210, 3040, 2220, 1680	[a] 7.11 (s)	2.42 (s)	1.87 (s)		9.44, 10.05 (s)
4o	3300, 3210, 2220, 1655	[a] 7.06 (s)	2.40 (s)	1.05 (d), 2.50 (sept)		9.41, 9.98 (s)
4p	3260, 2220, 1675, 1605	[a] 7.08	2.40 (s)	3.56 (s), 7.23 (m)		9.57, 10.35 (s)
4q	3290, 3230, 2200, 1655	[a] 7.15 (s)	2.41 (s)	3.53 (s), 7.36 (m)		9.57, 10.34 (s)
4r	3240, 2200, 1645	[b] 6.87 (s)	2.43 (s)	3.60 (s), 3.75 (s), 6.85, 7.23 (m)		7.33, 7.58 (s)
4s	3310, 3240, 2220, 1660	[a] 7.23 (s)	2.48 (s)	3.79 (s), 7.68, 8.26 (m)		9.68, 10.50 (s)
4t	3150, 2210, 1650	[a] 7.18 (s)	2.45 (s)	7.50, 7.89 (m)		9.68, 10.73 (s)
4u	3150, 2200, 1640	[b] 6.91 (s)	2.46 (s)	2.37 (s), 7.23, 7.73 (d)		7.64, 8.37 (s)
4v	3130, 2200, 1630	[b] 6.92 (s)	2.48 (s)	3.82 (s), 6.94, 7.81 (m)		7.62, 8.30 (s)
4w	3150, 2210, 1650	[a] 7.21 (s)	2.45 (s)	8.12, 8.36 (m)		9.82, 11.07 (s)
4x	3140, 2220, 1660	[b] 6.97 (s)	2.50 (s)	7.68, 8.77 (m)		7.66, 8.68 (s)

[a] In $\text{DMSO}-d_6$ solution. [b] In deuteriochloroform solution.

Table 4
¹³C-NMR Data of Compounds 3 and 4

Compound No.	C-2	C-3	C-4	C-5	C-6	CH ₃	CF ₃	NHCO	X	R
3a [a]	154.9	113.0	147.5	110.2	143.4 <i>J</i> = 33.6	17.5	119.3 <i>J</i> = 274.7	167.2	11.7, 59.6, 164.2	18.3
3b [a]	154.7	112.9	147.6	110.9	143.5 <i>J</i> = 33.6	17.8	119.3 <i>J</i> = 274.7	174.1	11.8, 59.7, 164.0	17.1, 30.1
3c [a]	154.5	113.1	147.6	111.1	143.4 <i>J</i> = 33.6	17.7	122.7 <i>J</i> = 274.7	167.9	11.9, 59.8, 164.0	124.4, 126.1, 127.1, 133.7
3d [b]	156.2	111.0	153.3	114.3	147.5 <i>J</i> = 34.2	22.9	120.1 <i>J</i> = 274.7	168.1	13.9, 61.8, 166.2	40.5, 128.7, 130.5, 132.2, 133.0
3e [b]	155.9	110.9	153.2	114.1	147.5 <i>J</i> = 34.8	22.8	120.7 <i>J</i> = 274.7	168.6	13.9, 61.7, 166.1	40.6, 55.0, 114.1, 125.5, 130.3, 158.7
3f [a]	154.3	113.1	147.7	111.2	143.3 <i>J</i> = 34.2	17.7	120.2 <i>J</i> = 274.7	166.9	11.9, 59.8, 163.9	121.2, 128.4, 141.9, 144.3
3g [a]	155.0	113.4	147.4	111.0	143.4 <i>J</i> = 34.2	17.5	119.3 <i>J</i> = 274.7	164.5	11.7, 59.7, 164.1	125.5, 126.4, 127.0, 129.8
3h [b]	155.3	110.9	153.3	113.8	147.6 <i>J</i> = 34.8	22.7	120.7 <i>J</i> = 274.7	166.0	13.9, 61.8, 164.1	21.2, 126.8, 129.1, 129.3, 142.1
3i [b]	155.8	110.9	153.1	113.8	147.4 <i>J</i> = 34.2	22.7	120.7 <i>J</i> = 274.7	166.1	13.8, 61.7, 164.3	55.0, 113.5, 124.2, 128.7, 162.2
3j [b]	155.4	111.0	153.7	114.5	147.6 <i>J</i> = 34.8	22.9	120.6 <i>J</i> = 274.7	166.2	13.9, 62.0, 162.4	123.6, 128.0, 137.8, 149.5
3k [a] [c]	153.9	113.4	144.4	111.6	143.4 <i>J</i> = 33.6	17.8	119.2 <i>J</i> = 274.7	163.9	11.8, 59.9, 161.0	122.7, 142.0, 148.0
3l [b]	155.7	110.9	153.4	114.1	147.5 <i>J</i> = 34.8	22.9	120.7 <i>J</i> = 274.7	166.2	13.9, 61.9, 163.8	128.3, 128.6, 130.5, 137.8
3m [a]	154.9	113.2	147.2	110.6	143.3 <i>J</i> = 33.6	17.3	119.3 <i>J</i> = 274.7		11.7, 58.5, 154.9	12.4, 59.6, 164.1
3n [a]	157.7	91.5	155.5	109.7	145.5 <i>J</i> = 34.2	18.3	118.9 <i>J</i> = 275.3	167.2	112.4	18.2
3o [a]	157.7	91.9	155.1	109.7	145.6 <i>J</i> = 34.2	18.2	119.0 <i>J</i> = 274.7	174.0	112.2	17.1, 30.2
3p [a]	157.5	92.0	155.2	109.9	145.7 <i>J</i> = 34.2	18.3	119.0 <i>J</i> = 275.3	168.0	112.3	38.4, 124.5, 126.2, 127.2, 133.5
3q [a]	157.5	92.0	155.2	109.9	145.6 <i>J</i> = 34.2	18.3	118.9 <i>J</i> = 275.3	167.6	112.3	37.2, 126.1, 129.0, 129.3, 132.5
3r [a]	157.6	91.9	155.2	109.8	145.7 <i>J</i> = 34.2	18.2	119.0 <i>J</i> = 275.3	168.3	112.3	53.0, 111.6, 125.4, 128.2, 156.0
3s [a]	157.5	92.2	155.5	110.2	145.7 <i>J</i> = 34.2	18.5	119.1 <i>J</i> = 275.3	167.1	112.4	121.4, 128.7, 141.8, 144.5
3t [a]	158.1	91.9	155.5	109.9	145.6 <i>J</i> = 34.2	18.3	118.9 <i>J</i> = 275.3	164.5	112.4	125.7, 126.5, 129.9, 130.5
3u [a]	158.5	92.2	155.7	110.1	145.9 <i>J</i> = 34.2	18.6	119.2 <i>J</i> = 275.3	164.7	112.6	19.3, 126.0, 127.3, 127.9, 140.2
3v [a]	158.4	91.9	155.5	109.8	145.7 <i>J</i> = 34.2	18.3	119.0 <i>J</i> = 274.7	164.1	112.4	53.4, 111.7, 122.5, 127.7, 160.2
3w [a]	157.6	92.1	155.6	110.2	145.6 <i>J</i> = 34.2	18.4	118.9 <i>J</i> = 275.3	163.0	112.3	121.8, 127.1, 136.0, 147.5
4a [a]	154.6	104.3	134.1 <i>J</i> = 31.7	107.5	158.2	22.0	120.7 <i>J</i> = 274.7	167.2	11.4, 59.9, 163.2	18.3
4b [a]	155.5	104.4	138.9 <i>J</i> = 32.4	111.1	161.6	24.4	122.2 <i>J</i> = 274.0	174.6	13.3, 62.1, 165.5	19.1, 33.4
4c [a]	154.0	104.4	133.9 <i>J</i> = 31.7	107.5	158.3	22.1	120.7 <i>J</i> = 274.7	168.0	11.6, 60.1, 163.1	38.1, 124.5, 126.1, 127.2, 133.8
4d [a]	153.9	104.4	134.1 <i>J</i> = 31.7	107.6	158.4	22.1	120.7 <i>J</i> = 274.7	167.6	11.5, 60.0, 163.1	37.3, 126.1, 129.0, 129.3, 132.8
4e [b]	158.7	104.3	138.9 <i>J</i> = 31.7	111.1	161.6	24.4	122.2 <i>J</i> = 274.7	168.7	13.3, 62.1, 165.4	40.6, 54.9, 114.0, 125.7, 130.3, 155.2
4f [a]	153.8	104.4	134.0 <i>J</i> = 32.4	107.6	158.4	22.0	120.6 <i>J</i> = 274.7	166.9	11.5, 60.1, 163.0	121.2, 128.5, 141.9, 144.4
4g [b]	155.4	104.6	139.0 <i>J</i> = 33.0	111.2	161.7	24.4	122.2 <i>J</i> = 274.7	165.4	13.3, 62.2, 164.7	126.9, 128.3, 131.7, 131.9
4h [b]	155.5	104.6	139.0 <i>J</i> = 33.0	111.2	161.7	24.4	122.2 <i>J</i> = 274.7	165.5	13.4, 62.2, 164.7	21.2, 126.9, 129.0, 129.1, 142.2

Table 4 (continued)

Compound No.	C-2	C-3	C-4	C-5	C-6	CH ₃	CF ₃	NHCO	X	R
4i [b]	155.9	104.8	139.0 <i>J</i> = 33.0	111.2	161.7	24.3	122.2 <i>J</i> = 274.7	165.5	13.3, 62.1, 164.6	44.9, 113.5, 124.0, 128.8, 162.3
4j [a] [c]	156.2	104.6	134.3 <i>J</i> = 31.7	107.8	158.5	22.1	120.6 <i>J</i> = 274.7	163.1	11.3, 60.0, 162.9	121.6, 126.9, 136.3, 147.3
4k [a] [c]	154.1	104.7	134.2 <i>J</i> = 31.7	107.8	158.4	22.1	120.6 <i>J</i> = 274.7	163.1	11.3, 60.0, 162.9	119.3, 137.7, 148.4
4l [b]	155.4	104.7	139.1 <i>J</i> = 33.0	111.5	161.8	24.4	122.2 <i>J</i> = 274.7	165.6	13.3, 62.3, 163.9	128.0, 128.4, 128.6 138.0
4m [b]	157.0	104.7	138.8 <i>J</i> = 33.0	111.5	161.7	24.4	122.2 <i>J</i> = 274.7		13.2, 61.6, 161.7	14.2, 62.0, 165.8
4n [a]	158.5	78.9	139.2 <i>J</i> = 31.7	108.5	162.7	22.7	119.8 <i>J</i> = 274.7	167.1	111.4	18.2
4o [a]	158.5	79.4	139.1 <i>J</i> = 31.7	108.3	162.5	22.6	119.8 <i>J</i> = 274.7	173.9	112.2	17.1, 30.1
4p [a]	158.3	79.4	139.0 <i>J</i> = 31.7	108.5	162.7	22.7	120.0 <i>J</i> = 274.7	167.9	111.3	38.0, 125.9, 126.1, 127.3, 133.5
4q [a]	158.2	79.4	139.0 <i>J</i> = 31.7	108.6	162.7	22.7	120.0 <i>J</i> = 274.7	167.6	111.3	37.2, 126.1, 129.1, 129.4, 132.5
4r [a]	158.3	79.3	139.2 <i>J</i> = 31.7	108.6	162.7	22.7	119.9 <i>J</i> = 275.1	168.3	111.4	53.0, 111.6, 125.4, 128.3, 156.1
4s [a]	158.0	79.4	139.0 <i>J</i> = 31.7	108.7	162.8	22.7	119.9 <i>J</i> = 274.7	166.9	111.3	121.3, 128.6, 141.6, 144.4
4t [a]	158.8	79.4	139.3 <i>J</i> = 31.7	108.7	162.7	22.8	119.9 <i>J</i> = 274.7	164.3	111.4	125.7, 126.5, 129.9, 130.3
4u [a]	158.9	79.2	139.2 <i>J</i> = 31.7	108.8	162.8	22.8	119.9 <i>J</i> = 274.7	164.2	111.4	19.1, 125.7, 127.1, 127.4, 140.0
4v [a]	159.0	79.2	139.2 <i>J</i> = 31.7	108.7	162.7	22.4	119.9 <i>J</i> = 275.3	163.7	111.2	53.5, 111.8, 122.4, 127.6, 160.2
4w [a]	158.4	79.6	139.2 <i>J</i> = 31.7	108.9	162.9	22.8	119.8 <i>J</i> = 274.7	162.9	111.4	121.7, 127.2, 136.0, 147.5
4x [a] [d]	158.4	79.5	139.2 <i>J</i> = 31.7	109.1	162.9	22.9	119.9 <i>J</i> = 274.7	163.0	111.4	119.5, 137.4, 148.5

[a] In DMSO-*d*₆ solution. [b] In deuteriochloroform solution. [c] The signals for COOEt and NHCO groups are interchangeable. [d] The signals for C-6 and NHCO carbons are interchangeable.

field (133-139 ppm, with $J_{\text{C-F}} = 31$ Hz). Another interesting feature of the ¹³C nmr spectra of pyridines **3** and **4** is the net shielding due to the methyl group of C-4 (147-155 ppm) in compounds **3** and of C-6 (158-162 ppm) in **4**.

From the above it is evident that the formation of isomers **3** and **4** is affected by the ambident nature of the starting amidrazones **1** and the enol ether **2**. The reaction could potentially follow two pathways: by competitive nucleophilic substitution at C-2 or at NH₂ of amidrazones **1** by the enol group of **2** or by an initial electrophilic addition of the high reactive trifluoromethyl substituted carbonyl to C-2 of amidrazones and subsequent ring closure.

Furthermore *N*¹-acyl-2-(ethoxycarbonyl or cyano)-acetamidrazones are well known to exist as tautomeric species (amide hydrazone, hydrazide imide and enamine) [5]. When the amide hydrazone form is stabilized by -M or -I effect the electrophilic addition is favoured as a consequence of the enhanced nucleophilicity of C-2 and pyridines **4** were only obtained.

To confirm this when the reaction was performed in acetic acid at room temperature compounds **4** were obtained again even if in moderate yield. These results were taken to mean that acidic medium increased both the electrophilicity of the trifluoromethylcarbonyl group and nucleophilicity of C-2, the latter by *N*-protonation of the amidrazones.

In contrast, the reaction of **1** with **2** in dimethyl sulfoxide at room temperature and in the presence of an equimolecular amount of potassium carbonate produces pyridines **3**. These products are most likely formed by an initial nucleophilic substitution of the methoxy group by the C-2 of the amidrazones to give a C-adduct, which then undergoes cyclization by attack of the amino nitrogen onto the carbonyl carbon of trifluoroacetyl group.

When the reaction between compounds **1a-m** and enol ether **2** was carried out using an excess of potassium carbonate the 6-trifluoromethylpyridine derivatives **3** underwent cyclization to give good yields of the 4-methyl-6-trifluoromethyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-ol.

In conclusion the regioselectivity of the reactions of amidrazones **1** with **2** can be easily controlled by the choice of the reaction conditions and from the substitution pattern of **1**.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage and are uncorrected. The ir spectra were obtained in Nujol with a Perkin-Elmer 398 spectrophotometer. The ¹H and ¹³C-nmr spectra were recorded on a Varian Unity 300 spectrometer, the chemical shifts are given in δ (ppm) downfield from the internal standard hexamethyldisiloxane and coupling constants in Hz. Elemental analyses were carried out with a Carlo Erba Model 1106 Elemental Analyzer. Preparative separation were performed by column chromatography on silica gel (Acros, 0.2-0.5 mm, pore diameter 6 nm). The *N*¹-acylacetamidrazones **1a-d,g,j,m-q,t** and trifluoroacetylvinyl ether **2** were prepared by previously described procedures [3,5,6].

General Procedure for the Synthesis of *N*¹-Acylacetamidrazones **1**.

A solution of ethyl 3-amino-3-ethoxypropenoate or 3-amino-3-ethoxypropenenitrile (0.01 mole) and the appropriate hydrazine (0.01 mole) in dry ethanol (50 ml) was heated at 70° for 5 minutes and then allowed to stand overnight at room temperature. The precipitate was filtered off, washed with diethyl ether and recrystallized from the solvent indicated.

*N*¹-(4-Methylbenzoyl)-2-(ethoxycarbonyl)acetamidrazone (**1h**).

This compound was obtained using (4-methylbenzoyl)hydrazine in a yield of 89%, mp 164-165° (acetone); ir: ν 3420, 3170, 1740, 1710, 1670, 1610 cm⁻¹; ¹H nmr (DMSO-*d*₆): 1.14, 1.22 (t, 3H, CH₃), 2.35 (s, 3H, CH₃), 3.24 (s, 2H, CH₂), 3.97, 4.11 (q, 2H, CH₂), 6.47 (s, 2H, NH₂), 7.25, 7.77 (m, 4H, Ar), 8.36, 9.79, 10.21 (s, 2H, NH).

Anal. Calcd. for C₁₃H₁₇N₃O₃: C, 59.29; H, 6.51; N, 15.97. Found: C, 59.34; H, 6.49; N, 16.00.

*N*¹-(4-Methoxybenzoyl)-2-(ethoxycarbonyl)acetamidrazone (**1i**).

This compound was obtained using (4-methoxybenzoyl)hydrazine in a yield of 86%, mp 174-175° (acetone); ir: ν 3420, 3180, 1725, 1670, 1640, 1610 cm⁻¹; ¹H nmr (DMSO-*d*₆): 1.05, 1.15 (t, 3H, CH₃), 3.16 (s, 2H, CH₂), 3.74 (s, 3H, CH₃), 3.84, 4.04 (q, 2H, CH₂), 6.37 (s, 2H, NH₂), 6.91, 7.76 (m, 4H, Ar), 8.26, 9.66, 10.08 (s, 2H, NH).

Anal. Calcd. for C₁₃H₁₇N₃O₄: C, 55.89; H, 6.14; N, 15.05. Found: C, 55.96; H, 6.12; N, 15.08.

*N*¹-(4-Chlorobenzoyl)-2-(ethoxycarbonyl)acetamidrazone (**1l**).

This compound was obtained using (4-chlorobenzoyl)hydrazine in a yield of 74%, mp 164-165° (acetone); ir: ν 3390, 3300, 3180, 1730, 1680, 1610 cm⁻¹; ¹H nmr (DMSO-*d*₆): δ 1.15, 1.24 (t, 3H, CH₃), 3.12 (s, 2H, CH₂), 3.91, 4.14 (q, 2H, CH₂), 6.51 (s, 2H, NH₂), 7.49, 7.96 (m, 4H, Ar), 8.45, 9.93, 10.02, 10.40 (s, 2H, NH).

Anal. Calcd. for C₁₂H₁₄ClN₃O₃: C, 50.87; H, 4.98; N, 14.84. Found: C, 50.93; H, 5.00; N, 14.87.

*N*¹-(4-Methoxyphenylacetyl)-2-cyanoacetamidrazone (**1r**).

This compound was obtained using (4-methoxyphenylacetyl)hydrazine in a yield of 73%, mp 163-164° (ethanol); ir: ν

3420, 3180, 2250, 1650, 1595 cm⁻¹; ¹H nmr (DMSO-*d*₆): δ 3.40 (s, 2H, CH₂), 3.49 (s, 2H, CH₂), 3.77 (s, 3H, CH₃), 6.58 (s, 2H, NH₂), 6.94, 7.77 (m, 4H, Ar), 9.77 (s, 1H, NH).

Anal. Calcd. for C₁₂H₁₄N₄O₂: C, 58.51; H, 5.73; N, 22.76. Found: C, 58.56; H, 5.72; N, 22.79.

*N*¹-(4-Nitrophenylacetyl)-2-cyanoacetamidrazone (**1s**).

This compound was obtained using (4-nitrophenylacetyl)hydrazine in a yield of 75%, mp 184-185° (ethanol); ir: ν 3440, 3360, 3210, 2240, 1650, 1595 cm⁻¹; ¹H nmr (DMSO-*d*₆): δ 3.43, 3.48, 3.56 (s, 5H, CH₂ and CH), 3.92 (s, 1H, CH), 6.41, 6.48 (s, 2H, NH₂), 7.48-7.54, 8.09-8.16 (m, 4H, Ar), 9.28, 9.79, 10.23 (s, 2H, NH).

Anal. Calcd. for C₁₁H₁₁N₅O₃: C, 50.56; H, 4.25; N, 26.82. Found: C, 51.02; H, 4.23; N, 26.78.

*N*¹-(4-Methylbenzoyl)-2-cyanoacetamidrazone (**1u**).

This compound was obtained using (4-methylbenzoyl)hydrazine in a yield of 90%, mp 184-185° (1-propanol); ir: ν 3420, 3350, 3180, 2210, 1650, 1600 cm⁻¹; ¹H nmr (DMSO-*d*₆): δ 2.36 (s, 3H, CH₃), 3.55 (s, 2H, CH₂), 6.65 (s, 2H, NH₂), 7.26, 7.75 (m, 4H, Ar), 9.88 (s, 1H, NH).

Anal. Calcd. for C₁₁H₁₂N₄O: C, 61.08; H, 5.60; N, 25.92. Found: C, 61.02; H, 5.62; N, 25.88.

*N*¹-(4-Methoxybenzoyl)-2-cyanoacetamidrazone (**1v**).

This compound was obtained using (4-methoxybenzoyl)hydrazine in a yield of 90%, mp 172-173° (ethanol); ir: ν 3420, 3230, 2280, 1680, 1655, 1635, 1615 cm⁻¹; ¹H nmr (DMSO-*d*₆): δ 3.57 (s, 2H, CH₂), 3.84 (s, 3H, CH₃), 6.68 (s, 2H, NH₂), 7.02, 7.86 (m, 4H, Ar), 9.88 (s, 1H, NH).

Anal. Calcd. for C₁₁H₁₂N₄O₂: C, 56.87; H, 5.21; N, 24.13. Found: C, 56.84; H, 5.22; N, 24.17.

*N*¹-(4-Nitrobenzoyl)-2-cyanoacetamidrazone (**1w**).

This compound was obtained using (4-nitrobenzoyl)hydrazine in a yield of 93%, mp 180-181° (1-propanol); ir: ν 3420, 3210, 3180, 2250, 1670, 1630, 1595 cm⁻¹; ¹H nmr (DMSO-*d*₆): δ 3.60 (s, 2H, CH₂), 5.03 (s, 1H, CH), 6.66, 6.79 (s, 2H, NH₂), 6.92 (s, 1H, NH), 8.10, 8.31 (m, 4H, Ar), 10.30 (s, 1H, NH).

Anal. Calcd. for C₁₀H₉N₅O₃: C, 48.57; H, 3.67; N, 28.34. Found: C, 48.63; H, 3.66; N, 28.37.

*N*¹-(4-Pyridyl)-2-cyanoacetamidrazone (**1x**).

This compound was obtained using (isonicotinoyl)hydrazine in a yield of 73%, mp 186-187° (ethanol); ir: ν 3410, 3220, 2280, 1680, 1660, 1640, 1620 cm⁻¹; ¹H nmr (DMSO-*d*₆): δ 3.40 (s, 2H, CH₂), 6.72 (s, 2H, NH₂), 7.72, 8.65 (m, 4H, Ar), 10.19 (s, 1H, NH).

Anal. Calcd. for C₉H₉N₅O: C, 53.18; H, 4.47; N, 34.48. Found: C, 53.24; H, 4.44; N, 34.52.

Reactions Between *N*¹-Acylacetamidrazones **1** and 4-Methoxy-1,1,1-trifluoro-3-penten-2-one **2**.

Method A.

A solution of *N*¹-acylacetamidrazones **1** (0.005 mole) and trifluoroacetylvinyl ether **2** (0.84 g, 0.005 mole) in anhydrous ethanol (30 ml) was heated under reflux. In the case of **1a-m** the mixture was refluxed for 2 hours while in the case of **1n-x** for 6 hours. After removal of the solvent the residue was collected and recrystallized to give **3** and/or **4** (Tables 1 and 3). In the relevant cases compounds **3** and **4** were separated by column chromatography (eluent ethyl ether).

Method B.

Trifluoroacetylvinyl ether **2** (0.84 g, 0.005 mole) was added to a stirred mixture of the appropriate *N*¹-acylacetamidrazone **1** (0.005 mole) and potassium carbonate (0.7 g, 0.005 mole) in dimethyl sulfoxide (5 ml). The mixture was stirred at room temperature for one hour and then diluted with ice-water. The formed precipitate was collected by filtration and recrystallized to give the 6-trifluoromethylpyridine derivatives **3**.

Method C.

A mixture of *N*¹-acylacetamidrazone **1** (0.005 mole) and trifluoroacetylvinyl ether **2** (0.84 g, 0.005 mole) in acetic acid (10 ml) was stirred at room temperature for six days. After concentration the residue was poured in 50 ml of water and neutralized with sodium bicarbonate. After extraction with chloroform, organic layers were dried (sodium sulfate) and evaporated. The crude product was recrystallized to give the 4-trifluoromethylpyridine derivatives **4**.

4-Methyl-6-trifluoromethyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-ol.

Trifluoroacetylvinyl ether **2** (0.84 g, 0.005 mole) was added to a stirred mixture *N*¹-acylacetamidrazones **1a-e** (0.005 mole) and potassium carbonate (1.4 g, 0.01 mole) in dimethyl sulfoxide (5 ml). The mixture was stirred at room temperature for one hour and then diluted with ice-water. The precipitate was collected by

filtration and recrystallized from ethanol to give the title compound in 50-62% yield, mp 314-315°; ir: ν 3175, 3110, 1610, 1555 cm⁻¹; ¹H nmr (DMSO-*d*₆): δ 2.58 (s, 3H, CH₃), 7.26 (s, 1H, H-5), 11.07 (s, 1H, NH), 12.54 (s, 1H, NH).

Anal. Calcd. for C₈H₆F₃N₃O: C, 44.23; H, 2.79; N, 19.35. Found: C, 44.27; H, 2.80; N, 19.31.

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