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CONVENIENT SYNTHESIS OF 4-TRIFLUOROMETHYLPYRAZOLES BY CYCLIZATION OF TRIFLUOROACETYLATED HYDRAZONES

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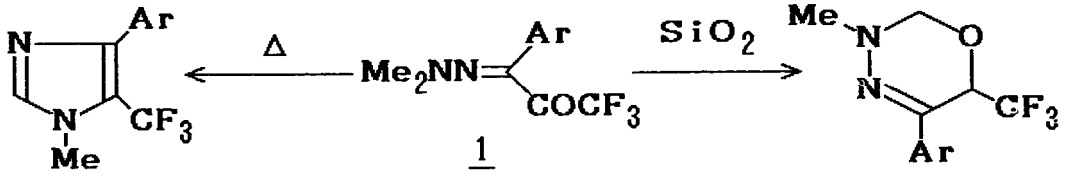
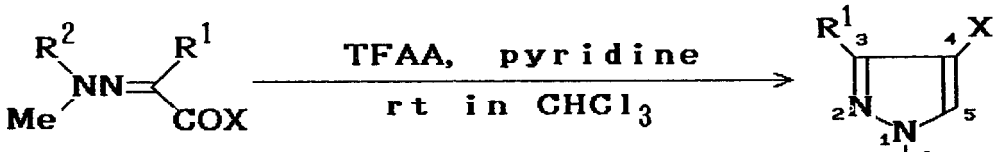
Summary: Several 4-trifluoromethyl-1-alkylpyrazoles were synthesized in good yields by trifluoroacetic anhydride-pyridine induced cyclization reaction of acylhydrazones prepared from aldehyde dialkylhydrazones and trifluoroacetic anhydride.

Recently we reported electrophilic substitution reaction undergoing quite easily at azomethine carbon atoms of aldehyde dialkylhydrazones by treating them with trifluoroacetic anhydride (TFAA).[1,2] Resulted C-trifluoroacetylated hydrazones 1 showed interesting two types of cyclization reactions affording oxadiazine derivatives and imidazoles bearing CF_3 group.[1,3] Fluorine



containing heterocycles are a class of compounds expected of potentially high physiological activities[4] and, hence, convenient synthetic methods providing these heterocycles in good yields are now highly requested. In this communication we wish to report the third type of cyclization reaction of 1 to pyrazoles bearing CF_3 group.

On treatment with an excess of ethyl chloroglyoxylate in the presence of pyridine, p-tolualdehyde dimethylhydrazone gave pyrazole 2a (R^1= p-Tol, R^2= Me, X= CO_2Et) as a main product and the expected C-acylated hydrazone 1a was rather a minor product. Obviously 2a is derived from 1a because treatment of 1a with ethyl chloroglyoxylate in the presence of pyridine gave 2a in reasonable yields. In the case of using TFAA in place of ethyl chloroglyoxylate, this transformation from 1a to 2a proceeded much faster and the yield of 2a



1a-h 2a-h

Table 1. Synthesis of Pyrazoles 2a-h from Acylhydrazones 1a-h.

1[a]	R^1	R^2	X	TFAA eq	pyridine eq	$CHCl_3$[b] ml	time	2	bp.[c](mp.) °C/torr	Yield[d] %
1a	p-Tol	Me	CO_2Et	5	3	2	3 min	2a	(61)[e]	85
1b	p-Tol	t-Bu	CO_2Et	5	3	2	5 min	2b	(92)[f]	76
1c	Et	t-Bu	CF_3	6	3	2	24 h	2c	$100/_{100}$	45
1d	i-Pr	t-Bu	CF_3	6	3	2	4 h	2d	$100/_{82}$	69
1e	$PhCH_2$	t-Bu	CF_3	6	3	6	48 h	2e	$120/_{1}$	55
1f	p-Tol	t-Bu	CF_3	8	8	5	24 h	2f	(74)[g]	61
1g	p-Tol	Me	CF_3	8	6	5	24 h	2g	$130/_{1}$	15
1h	H	t-Bu	CF_3	6	4	2	24 h	2h[h]	(37-38)[f]	64

[a] One mmol of substrate was used in all cases. [b] Solvent was dried over $CaCl_2$ and distilled. [c] Oven temperature on bulb-to-bulb distillation. [d] Isolated yields. [e] Purified by bulb-to-bulb distillation; oven temperature 155 °C/2.5torr [f] Recrystallized from pentane. [g] Purified by bulb-to-bulb distillation; oven temperature 140 °C/2torr. [h] R^1 of 2h is $COCF_3$.

was much improved. These facts prompted us to examine TFAA induced pyrazole formation with several trifluoroacetylated hydrazones 1c-h which can be prepared easily by the manner previously reported.[1,2] As is shown in Table 1 the reaction occurred successfully and the corresponding 4-trifluoromethyl-pyrazoles 2c-g were obtained in good yields. The reaction for t-butylmethyl-hydrazone 1f proceeded more cleanly than dimethylhydrazone 1g. Interestingly these reactions did not occur without pyridine[5] and hardly proceeded in the presence of 2,6-lutidine or 4-dimethylaminopyridine even if large excess of TFAA was used. Directly from propionaldehyde t-butylmethylhydrazone, 2c (R^1= Et) is also obtainable by treatment with TFAA (8 eq) in the presence of pyridine (3 eq), though the yield of 2c was no more than 20%. In the case of 1h (R^1= H) the product obtained was 4-trifluoromethyl-3-trifluoracetyl-pyrazole 2h in which one more trifluoroacetyl group is incorporated.[6]

The following procedure for the synthesis of 2d is illustrative. To an ice-cooled mixture of 1d (252 mg, 1 mmol) and pyridine (0.243 ml, 3 mmol) in dry $CHCl_3$ (1 ml) was added dropwise a solution of TFAA (0.847 ml, 6 mmol) in dry $CHCl_3$ (1 ml) with continuous stirring. After stirring for 4h at room temperature, the solvent was removed and the residual yellow oil was purified by bulb-to-bulb distillation to afford 161 mg (69%) of 2d as pale yellow oil.

The structure of 2a-h were confirmed by IR, and ^1H and ^{13}C NMR spectra and microcombustion analysis.[7] In particular ^{13}C NMR spectra provided us useful structural information about these compounds. ^{13}C NMR spectra of 2g

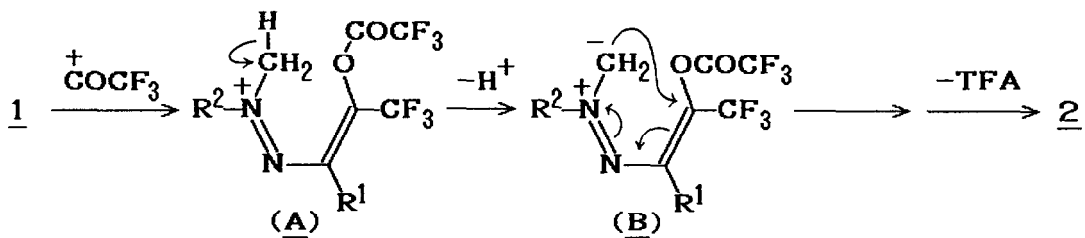
Table 2. ^{13}C Parameters[a] for Pyrazoles 2a, 2d, 2f and 2g in $CDCl_3$.

2	ppm[b] (Hz)				
	C^3 ($^3J_{CF}$)	C^4 ($^2J_{CF}$)	C^5 ($^3J_{CF}$, $^1J_{CH}$)	CF_3 ($^1J_{CF}$)	NCH_3 or N-t-Bu
2a	153.1	111.5	135.7 (- , 190)		39.1
2d	155.1	107.6 (36.3)	125.8 (4.4, 187)	123.9 (266)	58.9, 29.6
2f	148.7 (2.2)	109.5 (36.3)	127.3 (4.4, 188)	123.5 (267)	59.4, 29.6
2g	149.5 (2.2)	110.5 (37.4)	131.5 (4.4, 188)	123.1 (267)	39.2
1-methylpyrazole[c]	139.0 ($^1J_{CH}$=183Hz)	105.4 ($^1J_{CH}$=176Hz)	129.8 (- , 187)		38.2

[a] ^{13}C NMR spectra were recorded at 22.5 MHz on JEOL FX 90Q spectrometer. [b] T.M.S. was used as an internal standard. [c] See ref. 9.

shows three signals assignable to pyrazole ring carbons at 149.5, 131.5 and 110.5 ppm. The last signal appearing as a quartet with the C-F coupling (37.4 Hz) indicates direct binding of this carbon with CF_3 group. The ring carbon appears at 131.5 ppm exhibits direct C-H coupling of 188 Hz.[8] Comparing these chemical shifts with those of 1-methylpyrazole,[9] the signals at 149.5, 131.5 and 110.5 ppm can be assigned as C_3, C_5 and C_4 of 2g, respectively. These values are apparently different from those reported for 1-methyl-4-(p-tolyl)-5-trifluoromethylimidazole prepared by thermal cyclization[1] of 1g. ^{13}C Parameters for representative pyrazoles are listed in Table 2.

It is worthy of note that the present cyclization reaction from 1 to 2 occurs efficiently on the N-methyl group which is not the so-called active methyl or active methylene group.[10,11] Such type of cyclization reaction has never been reported.[12] It may be speculated that the present reaction proceeds via N-methylide (B) as is shown bellow. Further works to elucidate this mechanism are now undertaken. Check for the physiological activity of 2a-h is also in progress.



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5) Even in the presence of pyridine cyclization to pyrazoles did not occur at all unless TFAA was added.

6) There are two possible reaction pathways for the formation of 2h. One involves prior formation of 1-methyl-4-trifluoromethylpyrazole same to the cases of 1a-g followed by trifluoroacetylation at C^3 of the pyrazole ring. The other contains preceding introduction of the second trifluoroacetyl group at the azomethine carbon of 1h and subsequent cyclization. However the former pathway seems improbable because trifluoroacetylation did not occur at all even on more reactive 1,4-dimethylpyrazole than 1-methyl-4-trifluoromethylpyrazole under the conditions of all 1h being converted into 2h.

7) Satisfactory microcombustion analytical data were obtained for 2a-h. ^1H NMR spectral data (in $CDCl_3$) for 2a-h are as following. 2a: δ 7.84 (s, 1H, CH), 7.73-7.03 (q, 4H, Ar), 4.19 (q, 2H, CH_2), 3.89 (s, 3H, NCH_3), 2.37 (s, 3H, CH_3), 1.27 (t, 3H, $CH_2\underline{CH_3}$). 2b: δ 7.80 (s, 1H, CH), 7.55, 6.97 (d, 4H, Ar), 4.12 (q, 2H, CH_2), 2.34 (s, 3H, CH_3), 1.60 (s, 9H, t-Bu), 1.26 (t, 3H, CH_2CH_3). 2c: δ 7.50 (s, 1H, CH), 2.70 (q, 2H, CH_2), 1.50 (s, 9H, t-Bu), 1.15 (t, 3H, CH_3). 2d: δ 7.48 (s, 1H, CH), 3.07 (hept, 1H, $C\underline{H}CH_3$), 1.52 (s, 9H, t-Bu), 1.27 (d, 6H, $CHC\underline{H}_3$). 2e: δ 7.53 (s, 1H, CH), 7.10 (s, 5H, Ar), 4.00 (s, 2H, CH_2), 1.53 (s, 9H, t-Bu). 2f: δ 7.65 (s, 1H, CH), 7.45, 7.08 (d, 4H, Ar), 2.35 (s, 3H, CH_3), 1.62 (s, 9H, t-Bu). 2g: δ 7.60 (s, 1H, CH), 7.64-7.03 (q, 4H, Ar), 3.88 (s, 3H, NCH_3), 2.34 (s, 3H, CH_3). 2h: δ 7.90 (s, 1H, CH), 1.66 (s, 9H, t-Bu).

8) ^{13}C Chemical shift and $^1J_{CH}$ for ring C^2 atom in 1-methyl-4-(p-tolyl)-5-trifluoromethylimidazole which is the product of thermal treatment of 1g, are 140.5 ppm (δ from TMS) and 209 Hz, respectively.[1]

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11) Under the present reaction conditions attempted cyclization of monodimethylhydrazone of benzil did not give corresponding pyrazole at all.

12) Russian group[13] reported the formation of 3,4-diphenyl-1-methylpyrazole by cyclization of benzil monodimethylhydrazone. Later, US. group[14] pointed out that this product is not the above pyrazole but 4,5-diphenyl-1-methylimidazole.

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