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The major products from the reaction of β -alkoxyvinyl trifluoromethyl ketones **1a-c** with methylhydrazine (**2**) in absolute ethanol are the 3-(trifluoromethyl)-substituted-1-methylpyrazoles **3a-3c** with lesser amounts of the 5-(trifluoromethyl)-substituted products **4a-4c** and **5a-5c**. Carrying out the reaction in non-polar, aprotic solvents can further enhance the regioselectivity favoring the 3- (trifluoromethyl) -substituted isomers.

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The synthesis of trifluoromethyl substituted 1*H*-pyrazoles has attracted attention because of their potential biological properties. We have recently reported that reaction of 4-ethoxy-1,1,1-trifluoro-3-buten-2-one (**1a**) with methylhydrazine (**2**) in refluxing absolute ethanol leads to the formation of a mixture of 1-methyl-3-(trifluoromethyl)pyrazole (**3a**) and 4,5-dihydro-1-methyl-5-(trifluoromethyl)pyrazol-5-ol (**5a**) in yields of 52% and 18% respectively [1]. These two compounds can be readily separated and **5a** undergoes smooth dehydration in $\text{CH}_2\text{Cl}_2/\text{HCl}$ to 1-methyl-5-(trifluoromethyl)pyrazole (**4a**). These reactions thus allow the convenient synthesis of pure samples of regioisomers **3a** and **4a**.

As a result of our interest in the chemistry of trifluoromethyl substituted pyrazoles, we have extended these studies to include the reactions of β -alkoxy vinyl trifluo-

romethyl ketones **1a - 1c** with methylhydrazine (**2**) and have examined the effects of changing the solvent on the product distributions in these reactions.

Methylhydrazine (**2**) was allowed to react with β -alkoxyvinyl trifluoromethyl ketones [2] **1a-c** in refluxing absolute ethanol and the crude product mixtures were subjected to column chromatography on silica gel. Table 1 shows the products formed and their isolated yields and reveals that in all cases the major products isolated were the 1-methyl-3-(trifluoromethyl)pyrazoles **3a**, **3b**, **3c**.

Distinction between the regioisomeric 3- and 5-(trifluoromethyl)-substituted pyrazoles was unambiguously achieved by the ^1H - and ^{13}C -NMR data shown in Tables 2 and 3. The ^{13}C -NMR spectra were particularly important since the pyrazole ring carbons generally appear in the ^{13}C -NMR spectrum in the order C_4 (furthest upfield) > C_5

Table 1

1a	2	3a (52%)	4a (0%)	5a (18%)
1b	2	3b (32%)	4b (7%)	5b (0%)
1c	2	3c (40%)	4c (7%)	5c (7%)

a: R = Et, $\text{R}_1 = \text{R}_2 = \text{H}$; **b:** R = $\text{R}_1 = \text{CH}_3$, $\text{R}_2 = \text{H}$; **c:** R = Et, $\text{R}_1 = \text{H}$, $\text{R}_2 = \text{CH}_3$

Scheme 1

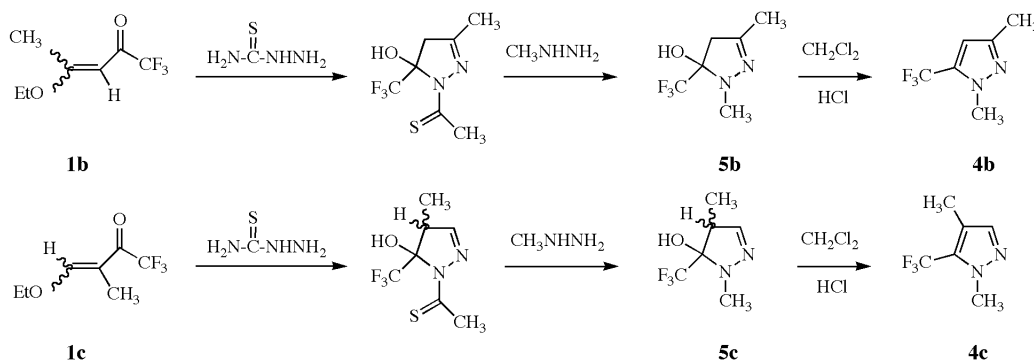


Table 2
¹H-NMR Chemical Shifts (δ ppm) of 1-Methylpyrazoles,

Compound	Ring Position			
	3	4	5	N-CH ₃
3b	-	6.27 (1H)	2.29 (3H)	3.81 (3H)
4b	2.18 (3H)	6.30 (1H)	-	3.83 (3H)
3c	-	2.04 (3H)	7.10 (1H)	3.77 (3H)
4c	7.20 (1H)	2.08 (3H)	-	3.87 (3H)

> C₃ (furthest downfield). Accordingly, observation of the long-range carbon-fluorine coupling with the trifluoromethyl group was of particular importance in identifying the regioisomers. Thus, Table 3 shows that in **3b** and **3c** the most downfield signals due to C₃ were observed as quartets indicating that these are both 3-trifluoromethyl isomers. Conversely, in the case of **4b** and **4c**, the furthest downfield signals are all sharp singlets whereas the signals due to the C₅ carbon at slightly higher field were coupled with the fluorine atoms of the trifluoromethyl group.

Table 3
¹³C-NMR Chemical Shifts (δ ppm) of 1-Methylpyrazoles,

Compound	C ₃	C ₄	C ₅	N-CH ₃	C-CH ₃	CF ₃
3b	141.2,q (J=38Hz)	104.1	104.5	39.9	11.4	121.8,q (J=268Hz)
4b	147.8	107.2	132.7,q (J=38Hz)	37.5	13.5	120.5,q (J=268Hz)
3c	140.0,q (J=36Hz)	116.0	131.4	39.5	8.3	122.3,q (J=269Hz)
4c	138.3	117.7	127.3,q (J=38Hz)	37.5	7.9	120.1,q (J=269Hz)

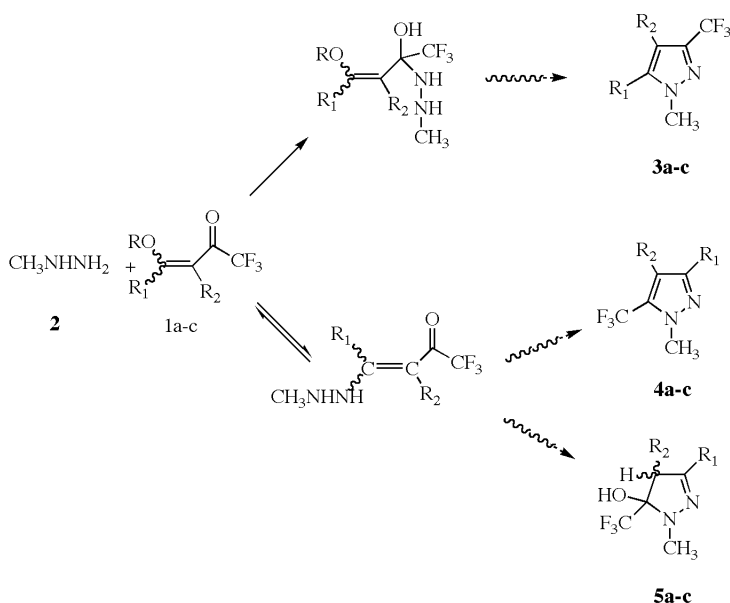
Table 4
 Product Distributions in Various Solvents.

Reactant	Products	Yields (%)		
		EtOH,abs	THF	CH ₂ Cl ₂
1a + 2	3-CF ₃ Pyrazole 3a	56	66	73
	5-CF ₃ Pyrazole 4a	21	19	14
	5-CF ₃ Pyrazol-5-ol 5a	9	8	7
1b + 2	3-CF ₃ Pyrazole 3b	32	60	65
	5-CF ₃ Pyrazole 4b	7	12	11
1c + 2	3-CF ₃ Pyrazole 3c	40	62	68
	5-CF ₃ Pyrazole 4c	7	0	0
	5-CF ₃ Pyrazol-5-ol 5c	4	3	3

These, accordingly, are the 5-trifluoromethyl isomers. Furthermore, in the case of **3b** and **4b**, the only signals observed in the DEPT-90 spectrum were those due to the C4 carbons confirming that in these compounds the C4 carbon is unsubstituted. In the case of **3c** and **4c**, however, the signals due to C5 and C3 respectively were observed in the DEPT-90 spectrum indicating that these ring positions were unsubstituted in these isomers.

The structures of **4b** and **4c** were further confirmed by showing that these products were chromatographically and spectroscopically identical to 1,3-dimethyl-5-(trifluoromethyl)pyrazole (**4b**) and 1,4-dimethyl-5-(trifluoromethyl)pyrazole (**4c**) respectively that were regiospecifically synthesized by the procedure shown in Scheme 1 [3]. Although the originally published procedure [3] employed a thermal dehydration of the 5-trifluoromethyl-1-methylpyrazol-5-ols, we observed that treatment of a dichloromethane solution of **5b** or **5c** with conc. hydrochloric acid gives superior results [1].

Scheme 2



The product distributions resulting from the reactions of trifluoromethyl ketones **1a-1c** with methylhydrazine were found to be sensitive to the solvent employed. Table 4 thus shows that the regiochemistry favors formation of the 3-trifluoromethyl substituted pyrazoles **3a**, **3b**, and **3c** as the solvent is changed from absolute ethanol to tetrahydrofuran, to dichloromethane. These results suggest that these reactions involve competition (Scheme 2) between 1,2-addition, which leads ultimately to the 3-trifluoromethyl isomers, and 1,4-addition, which places the trifluoromethyl group in position 5 of the product. The kinetically controlled 1,2-addition leading to the 3-trifluoromethylisomers **3a-c** would be expected to be favored in the less polar, aprotic solvents while the thermodynamically controlled 1,4 addition leading to the 5-trifluoromethyl substituted products would be enhanced in the more polar, protic ethanol solvent.

EXPERIMENTAL

¹H and ¹³C spectra were recorded at 400.1 and 100.6 MHz in deuteriochloroform on a Bruker FT-NMR system. ¹H and ¹³C chemical shifts were measured relative to internal tetramethyl silane and chloroform respectively. Mass spectra were recorded with an HP 5970 B mass selective detector interfaced to an HP 588 capillary column gas chromatograph.

General Procedure for the Reaction of Methylhydrazine **2** with β -Alkoxyvinyl-1,1,1-trifluoro-3-buten-2-ones **1a**, **1b**, and **1c**.

Methylhydrazine **2** (0.42 g, 9.2 mmol) was added dropwise to a stirred solution of **1a**, **1b**, or **1c** (6.8 mmol) in the appropriate solvent (Table 4) (4.5 ml) at room temperature. The resulting solution was stirred and refluxed for 2 hours and then diluted with dichloromethane (20 ml). The solution was extracted with water (5 x 5 ml). The combined aqueous phase was saturated with sodium chloride and extracted with dichloromethane (3x15 ml). In the reaction when dichloromethane was used as the solvent, no extraction was needed. The combined organic phase was dried (sodium sulfate) and concentrated by distillation through a Vigreux column. The residue was purified by column chromatography on silica gel (20 g, 20 cm long x 1.2 cm diameter). The column was eluted with ethyl acetate (10%)-hexane (90%).

1-Methyl-3-(trifluoromethyl)pyrazole (**3a**) and 4,5-Dihydro-1-methyl-5-(trifluoromethyl)-1H-pyrazol-5-ol (**5a**).

The crude product from the reaction of methylhydrazine (**2**) and 4-ethoxy-1,1,1-trifluoro-3-buten-2-one (**1a**) could be separated as previously described [1]. Since these techniques invariably resulted in some loss of the volatile **3a**, the yields in Table 4 for **3a** and **5a** were determined by gas-liquid chromatography. Under these conditions some **5a** is dehydrated to **4a**, which is not an observed product by preparative separation techniques [1].

1,5-Dimethyl-3-(trifluoromethyl)pyrazole (**3b**) and 1,3-Dimethyl-5-(trifluoromethyl)pyrazole (**4b**).

Column Chromatography of the crude product from the reaction of methylhydrazine (**2**) and 4-methoxy-4-methyl-1,1,1-trifluoro-3-buten-2-one (**1b**) gave 1,3-dimethyl-5-(trifluoromethyl)pyrazole (**4b**) (first fraction) as an oil: MS: m/z 164 (M⁺); see Tables 2 and 3 for NMR data and 1,5-dimethyl-3-(trifluoromethyl)pyrazole (**3b**) (second fraction) as an oil: MS: m/z 164 (M⁺); see Tables 2 and 3 for NMR data.

1,4-Dimethyl-3-(trifluoromethyl)pyrazole (**3c**), 1,4-Dimethyl-5-(trifluoromethyl)pyrazole (**4c**), and 4,5-Dihydro-1,4-dimethyl-5-(trifluoromethyl)-pyrazol-5-ol (**5c**).

Column chromatography of the crude product from the reaction of methylhydrazine (**2**) and 4-ethoxy-3-methyl-1,1,1-trifluoro-3-buten-2-one (**1c**) gave 1,4-dimethyl-5-(trifluoromethyl)pyrazole (**4c**) (first fraction) as an oil: MS: m/z 164 (M⁺), see Tables 2 and 3 for NMR data; 1,4-dimethyl-3-(trifluoromethyl)pyrazole (**3c**) (second fraction) as an oil: MS: m/z 164 (M⁺); see Tables 2 and 3 for NMR data; and 4,5-dihydro-1,4-dimethyl-5-(trifluoromethyl)pyrazol-5-ol (**5c**) (third fraction) as a white solid, mp 72-73 °C, lit [3], mp 71-73 °C; ¹H-NMR (deuteriochloroform): δ 1.17 (d, 3H, J= 7.5 Hz), 2.87 (s, 3H), 3.27 (q, 1H, J=7.5 Hz), 6.5 (s, 1H); ¹³C-NMR (deuteriochloroform): δ 9.6, 35.0, 47.6, 98.0 (q, J=29,8 Hz), 124.4(q, J=283 Hz), 145.0.

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