Condensation of Methylhydrazine with 4-Ethoxy-1,1,1-Trifluoro-3-buten-2-one. A Reinvestigation

James W. Pavlik [a]*, Theppawut Israsena Na Ayudhya [a] and Supawan Tantayanon [b]

[a] Department of Chemistry and Biochemistry, Worcester Polytechnic Institute, Worcester, MA 01609
[b] Department of Chemistry, Chulalongkorn University, Bangkok, 10330, Thailand

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In contrast to previous reports, 4-ethoxy-1,1,1-trifluoro-3-buten-2-one (**1**) was observed to react with methylhydrazine (**2**) in refluxing ethanol to yield 1-methyl-3-(trifluoromethyl)pyrazole (**6**) and 4,5-dihydro-1-methyl-5-(trifluoromethyl)pyrazol-5-ol (**4**). The later compound undergoes acid catalyzed dehydration to 1-methyl-5-(trifluoromethyl)pyrazole (**3**).

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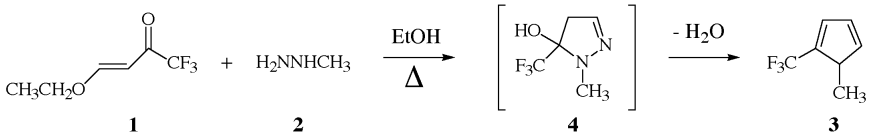
Braibante, Martins, and colleagues have reported that reaction of 4-ethoxy-1,1,1-trifluoro-3-buten-2-one (**1**) with methylhydrazine (**2**) in refluxing ethanol leads to the formation of 1-methyl-5-(trifluoromethyl)pyrazole (**3**) in 78% yield [1]. This reaction presumably occurs, as shown in Scheme 1, *via* the intermediacy of 4,5-dihydro-1-methyl-5-(trifluoromethyl)pyrazole-5-ol (**4**). Although **4** was reportedly not an isolable product in this reaction,

Scheme 1



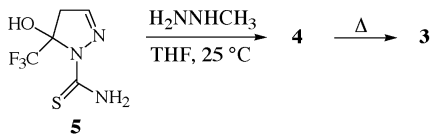
1 **2** **4** **3**

Bonacorso, Martins, and colleagues subsequently reported (Scheme 2) that **4** could be formed in 86% yield by treating the analogous 1-pyrazolethiocaboxamide (**5**) with methylhydrazine (**2**) in THF at 25 C [2]. Formed in this way, **4** was reported to undergo dehydration when heated to 100-130 C to provide **3** in unspecified yield.

We wish to report that in our laboratory reaction of **1** [3] and **2** in refluxing absolute ethanol led to different results. After refluxing a solution of **1** and **2** in absolute ethanol [4] as previously described [1], tlc examination revealed the formation of two products which could be separated by column chromatography on silica gel, or more readily, by using their greatly different volatilities.

The more volatile component of this mixture was obtained as an oil. Gas liquid partition chromatography (Glpc) of this oil showed a single volatile component. The mass spectrum of this compound exhibited a molecular ion at m/z 150 as expected for a trifluoromethyl substituted 1-methylpyrazole. The ^{1}H-NMR spectrum of the oil exhibited a 3H singlet at δ 3.86, a 1H doublet (J = 2.0 Hz) at δ 6.58, and a 1H broad singlet at δ 7.40 also consistent with a mono-substitued-1-methylpyrazole [6]. The ^{13}C-NMR spectrum of this compound exhibited a singlet at δ 39.6 and a quartet (J = 266.6 Hz) at δ 121.7 due to the *N*-methyl and trifluoromethyl carbons, respectively. In addition, the spectrum also shows signals at δ 104.9, 131.8, and 142.7 for the three carbons of the pyrazole ring. Based on the ^{13}C-NMR spectra of other 1-methylpyrazoles these signals can be assigned to the carbons at ring positions 4, 5, and 3 respectively since the C-4 carbon of the pyrazole ring absorbs furthest upfield whereas the C-3 carbon is generally observed furthest downfield. Interestingly, it

Scheme 2



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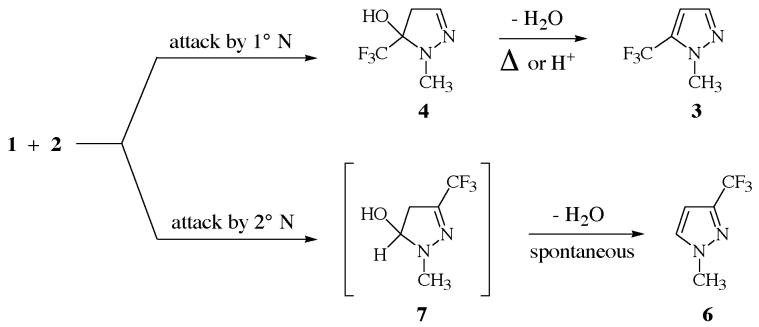
is the signal for the C-3 carbon at δ 142.7 that appeared as a quartet (J = 38 Hz) due to long-range coupling with the fluorine nuclei of the trifluoromethyl group whereas the signal due to the C-5 carbon at δ 131.8 appeared as a sharp singlet. This shows that the trifluoromethyl substituent is at ring position 3 and identifies this product as 1-methyl-3-(trifluoromethyl)pyrazole (**6**). Indeed, Bonacorso and colleagues reported that the compound they isolated from the dehydration of 4,5-dihydro-1-methyl-5-(trifluoromethyl)pyrazol-5-ol (**4**) exhibited signals in the ^{13}C-NMR spectrum at δ 107.5 (C-4), 131.9 (C-5), and 138.1 (C-3) [2]. In this case, it was the signal at δ 131.9 for C-5 which exhibited the long-range coupling (J = 39 Hz). This confirms that these workers isolated 1-methyl-5-(trifluoromethyl)pyrazole (**3**) from the dehydration of **4**.

Scheme 3



The less volatile component of the mixture was obtained as a white crystalline compound, which melted at 69-70 C. Glpc-mass spectroscopic analysis with an oven temperature of 70 C showed a single volatile compound with a retention time of 14 minutes. The mass spectrum exhibited a molecular ion at m/z 168, consistent with a hydrated product, and a base peak at m/z 150, which indicates that the major fragmentation pathway involves dehydration. Interestingly, when the analysis was carried out at an oven temperature of 100 C, Glpc showed that the compound with a retention time of 14 minutes was replaced by a single peak with a retention time of 7 minutes. The mass spectrum of this compound exhibited a molecular ion at m/z 150 with no sign of the signal at m/z 168. This indicates that at the higher oven temperature dehydration occurs in the column and that the hydrated compound never reaches the detector.

This data indicates that this product is 4,5-dihydro-1-methyl-5-(trifluoromethyl)pyrazol-5-ol (**4**) [2]. The NMR spectra are consistent with this assignment. Thus, as demanded by the structure, the ^{1}H-NMR spectrum exhibited a 3H singlet at δ 2.95 for the protons of the *N*-methyl group, a pair of 1H doublets (J = 18.7 Hz) at δ 2.89 and 3.20 for the two non-equivalent protons at C-4, and a 1H singlet at δ 6.67 due to the imine proton at C-3. The ^{13}C-NMR spectrum was also consistent with the assigned structure and showed singlets at δ 34.5 due to the *N*-methyl carbon, at δ 45.0 due to the C-4 ring carbon, and at δ 139.1 due to the C-3 imine carbon. As expected by these assignments only the signal at 45.0 was negative in the DEPT-135 spectrum confirming that this signal is due to a methylene carbon. In addition to these singlets, the ^{13}C-NMR spectrum also exhibited one quartet (J = 282.7 Hz) at δ 124.0 and a second quartet (J = 31.4 Hz) at δ 92.0 due to the trifluoromethyl and C-5 ring carbons respectively.

4,5-Dihydro-1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-5-ol (**4**) was found to undergo smooth dehydration upon treatment with methylene chloride – conc. hydrochloric acid at room temperature [7]. The ^{1}H-NMR spectrum of the resulting oil [8] exhibited a 3H singlet at δ 3.91 and a 1H doublet (J = 1.2 Hz) at δ 6.52 and a broad 1H singlet at δ 7.39, almost indistinguishable from the ^{1}H-NMR spectrum of 1-methyl-3-(trifluoromethyl)pyrazole (**6**). The ^{13}C-NMR spectrum, however, clearly shows that this compound is 1-methyl-5-(trifluoromethyl)pyrazole (**3**). Thus, in addition to singlets at δ 38.8 (*N*-methyl) and δ 107.9 (C-4 ring carbon) and a quartet (J = 268.3 Hz) at δ 120.6 (trifluoromethyl carbon), the ^{13}C spectrum also showed that the most downfield carbon due to the C-3 ring carbon appeared as a sharp singlet at δ 138.5 while the signal due to the C-5 ring carbon appeared upfield at δ 132.2 as a quartet (J = 39.2 Hz). This confirms that in this product the trifluoromethyl substituent is bonded to the C-5 ring carbon.

These results indicate that reaction of vinyl ketone **1** with methylhydrazine (**2**) involves a competition of Michael attack by both the primary and secondary nitrogen atoms of **2** and subsequent cyclization, as shown in Scheme 3, to 4,5-dihydro-1-methyl-5-(trifluoromethyl)-pyrazol-5-ol (**4**) and 4,5-dihydro-1-methyl-3-(trifluoromethyl)pyrazol-5-ol (**7**). Dehydration of either **4** or **7** would be accompanied by development of a positive charge at C-5 of the dihydropyrazole ring. In both **4** and **7** this positive charge would be stabilized by resonance interaction with the adjacent non-bonded electrons on nitrogen. In the case of **4**, however, the charge would be significantly destabilized by the trifluoromethyl group at C-5. This destabilization would increase the energy barrier to dehydration. As a result, **4** is sufficiently stable to allow its isolation. In contrast, the trifluoromethyl group at position 3 is expected to have little effect on the developing positive charge at C-5 in **7**, which therefore is not isolated but undergoes spontaneous dehydration to pyrazole **6**.

The ratio of the yields of **6**:**4** was observed to vary over the range from 2.9:1 to 2.1:1. The factors controlling the regioselectivity of this and the reactions of methylhydrazine (**2**) with other related trifluoro-substituted vinyl ketones is currently under investigation and will be reported at a later time.

EXPERIMENTAL

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

1-Methyl-3-(trifluoromethyl)pyrazole (**6**) and 4,5-Dihydro-1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-5-ol (**4**).

Methylhydrazine (**2**) (1.5 g, 33.0 mmol) was added dropwise to a stirred solution of 4-ethoxy-1,1,1-trifluoro-3-buten-2-one (**1**) (4.12 g, 24.5 mmol) in absolute ethanol (16 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 (5x5 ml). The aqueous phase was saturated with sodium chloride and extracted with dichloromethane (3x15 ml). The combined organic phase was dried (sodium sulfate) and concentrated by distillation through a vigreux column. The residue (3.2 g) was connected to a vacuum line and pumped down to 0.1-1.0 Torr [9]. The effluent from the flask containing the residue was passed through a glass trap submerged in a dry ice-acetone bath. After 3 hours the trap contained 1-methyl-3-(trifluoromethyl)pyrazole (**6**) as an oil (1.9 g, 12.7 mmol, 52%); ^{1}H-NMR (deuteriochloroform): δ 3.86 (s, 3H), 6.58(d, 1H, J = 2.0 Hz), 7.32 (br. s, 1H), lit [4]; ^{13}C-NMR (deuteriochloroform): δ 39.8, 104.9, 121.7 (q, J = 267 Hz), 131.8, 142.7 (q, J = 37.9 Hz); ms: m/z 150 (M^+). The non-volatile residue (1.07 g) was crystallized from dichloromethane to give 4,5-dihydro-1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-5-ol (**4**) as white crystals (739 mg, 4.4 mmol, 18%) mp 69-70 C, lit [2], mp 75-76 C; ^{1}H-NMR (deuteriochloroform): δ 2.95 (s, 3H), 2.89 (d, 1H, J = 18.8 Hz), 3.20 (d, 1H, J = 18.8 Hz), 6.67 (s, 1H); ^{13}C-NMR (deuteriochloroform): δ 34.5, 45.0, 92.0 (q, J = 31.4 Hz), 124.0 (q, J = 283 Hz), 139.1; ms (70 C): m/z 168 (M^+); ms (100 C): m/z 150 (M^+).

1-Methyl-5-(trifluoromethyl)pyrazole (**3**).

Concentrated hydrochloric acid (6 drops) was added to a stirred solution of 4,5-dihydro-1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-5-ol (**4**) (1.03 g, 6.1 mmol) in dichloromethane (30 ml) at room temperature. After stirring for 30 minutes saturated aqueous sodium bicarbonate (25 ml) was added. The organic layer was separated, dried (sodium sulfate) and concentrated by distillation. The residue (823 mg) was connected to a vacuum line and pumped down to 0.1-1.0 Torr. The effluent from the flask containing the residue was passed through a glass trap submerged in a dry ice-acetone bath. After 30 minutes the trap contained 1-methyl-5-(trifluoromethyl)pyrazol (**3**) as an oil (732 mg, 4.9 mmol, 80%): ^{1}H-NMR (deuteriochloroform): δ 3.91 (s, 3H), 6.52 (d, 1H, J = 1.2 Hz), 7.39 (br. s, 1H); ^{13}C-NMR (deuteriochloroform): δ 38.8, 107.9, 120.6 (q, J = 268 Hz), 132.2 (q, J = 39 Hz), 138.5.

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REFERENCES AND NOTES

[1] M. E. F. Braibante, G. Clar, and M. A. P. Martins, *J. Heterocyclic Chem.*, **30**, 1159 (1993).

[2] H. G. Bonacorso, A. D. Wastowski, N. Zanatta, and M. A. P. Martins, *Synth. Commun.*, **30**, 1457 (2000).

[3] A. Colla, M. A. P. Martins, G. Clar, S. Krimner, and P. Fischer, *Synthesis*, 483 (1991).

[4] Commercially available absolute ethanol was further purified by refluxing over magnesium ethoxide followed by fractional distillation [5].

[5] A. Lund and J. Bejerrum, *Ber*., **64B**, 210 (1931).

[6] Y. Kamitori, M. Hojo, R. Masuda, M. Fujishiro, and M. Wada, *Heterocycles*, **38**, 21 (1994), See reference 3.

[7] J. W. Lyga and R. M. Patera, *J. Heterocyclic Chem.*, **27**, 919 (1990).

[8] This compound was inexplicably reported in reference 1 to have a melting range of 68-70 C.

[9] 1-Methyl-3-(trifluoromethyl)pyrazole (**6**) and 4,5-dihydro-1-methyl-5-(trifluoromethyl)pyrazol-5-ol (**4**) could also be separated by column chromatography on silica gel. Elution with ethyl acetate (10%)-hexane (90%) gave **6** (first fraction) and **4** (second fraction) in yields of 6% and 23% respectively.