A Facile Synthesis of 5-Methyl-1-(phenyl/heterocyclyl)-4-trifluoroacetylpyrazoles†

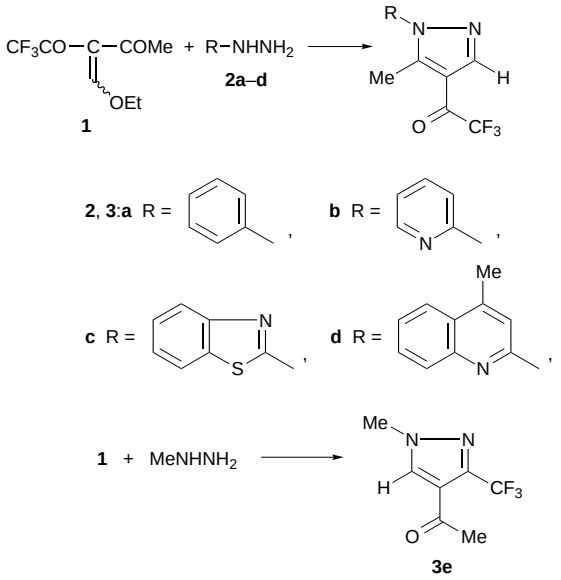
J. Chem. Research (S), 1997, 142–143†

Shiv P. Singh* and Dalip Kumar

Department of Chemistry, Kurukshetra University, Kurukshetra - 136 119, India

Treatment of substituted hydrazines (**2a–d**) with 3-acetyl-4-ethoxy-1,1,1-trifluorobut-3-en-2-one (**1**) yields the title compounds (**3a–d**) whereas methylhydrazine on similar treatment gives 4-acetyl-1-methyl-3-trifluoromethylpyrazole (**3e**).

In view of the unique biological properties displayed by many fluorinated heterocyclic compounds,[1,2] we envisaged exploring the synthesis of 4-trifluoroacetylpyrazoles. We report in this paper, a one-step synthesis of these compounds **3a–d** by utilizing the reaction of 3-acetyl-4-ethoxy-1,1,1-trifluorobut-3-en-2-one (**1**) with a variety of aryl- and heterocyclyl hydrazines (**2a–d**). Reactions of **1** with **2** at room temperature were exothermic leading to the formation of complex mixtures. After several trials it was found that slow addition of **1** to a solution of **2** in dry tetrahydrofuran (THF), while maintaining the temperature below −10 °C, provided a single compound (^{1}H NMR of the reaction mixture).



Scheme 1

Thus, reaction of **1** with phenylhydrazine (**2a**) gave an exclusive product which was formulated as 5-methyl-1-phenyl-4-trifluoroacetylpyrazole (**3a**) on the basis of its spectral characteristics. The ^{1}H NMR spectrum of **3a** exhibited two singlets at δ 2.63 and 8.12 due to the 5-Me and 3-H protons, respectively, besides signals due to aromatic protons. Its ^{13}C NMR spectrum displayed signals at δ 142.04, 122.31 and 147.39 which were assigned to the C-3, C-4 and C-5 carbons of the pyrazole moiety, respectively. A signal at δ 12.74 confirmed the location of the methyl group at the pyrazole C-5 carbon.[3] A downfield signal at δ 175.95 was assigned to the carbonyl carbon of the trifluoroacetyl group. The structure was further confirmed by its ^{19}F NMR spectrum which showed a signal at δ −75 due to the $COCF_3$ functionality.[4] Had this group been located at position 3 or 5, it would have resonated at about δ −60.[5]

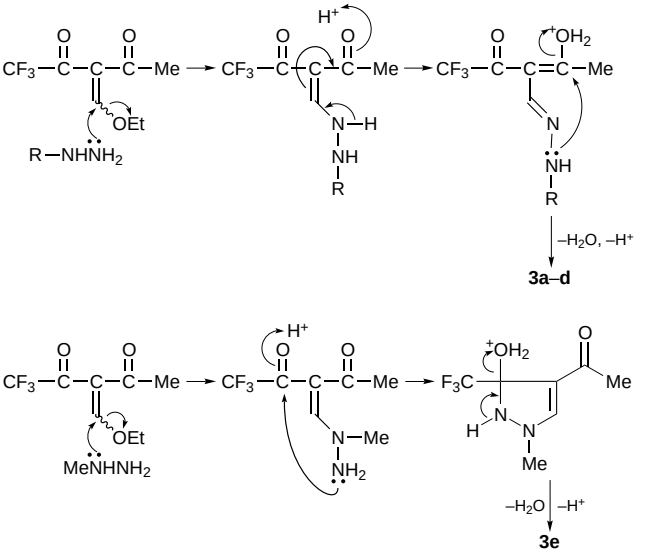
Treatment of **1** with heterocyclylhydrazines (**2b–d**) under similar conditions provided exclusive products **3b–d**. Characterization of these compounds using ^{1}H NMR spectroscopy was relatively easy, as the spectra of all the compounds displayed a sharp singlet at *ca*. 3.0 assigned to the 5-CH_3 of the pyrazole moiety. The planarity of these molecules and the concomitant deshielding of 5-CH_3 neatly explains the difference in chemical shift between **3a** and **3b–d**.[6]

The ^{13}C NMR spectrum of **3b** exhibits signals at δ 142.10, 123.36 and 149.05 for C-3, C-4 and C-5, respectively, values which are close to those observed earlier in the case of **3a**. The ^{19}F NMR spectrum displayed a signal at δ −75.3. Compounds **3c** and **3d** displayed similar NMR (^{1}H, ^{13}C and ^{19}F) spectral characteristics (see Experimental section), thus establishing the identity of all these compounds as **3a–d**.

However, reaction of methylhydrazine (**2e**) with **1** under similar conditions, afforded a single crystalline compound, mp 87 °C, whose structure was established as 4-acetyl-1-methyl-3-trifluoromethylpyrazole (**3**) on the basis of elemental analysis and NMR (^{1}H, ^{13}C and ^{19}F) spectral data. The ^{1}H NMR spectrum of **3e** showed singlets at δ 2.46, 3.98 and 7.94 due to $COCH_3$, N-CH_3 and 5-H, respectively. The ^{13}C NMR spectrum displayed signals at δ 140.29, 121.57 and 135.89 assigned to C-3, C-4 and C-5 of the pyrazole moiety, in addition to a downfield signal at δ 189.80 ($COCH_3$). A further signal at δ 28.78 confirmed the $COCH_3$ functionality. These values are in complete agreement with those reported for similarly constituted molecules.[3,4] Finally, the location of the trifluoromethyl substituent at the pyrazole 3-position was established by a signal at δ −62.0 in the ^{19}F spectrum.[5]

The formation of two types of products (**3a–d** and **3e**) can be explained when one considers that the products arise by the nucleophilic attack of a nitrogen on the carbonyl carbon of either the $COCH_3$ (**3a–d**) or $COCF_3$ moiety (**3e**). Obviously, different mechanisms are operating in the two cases.

It looks attractive to speculate that the reaction proceeds through the initial attack of NH_2 in the case of **2a–d** but of NH in the case of **2e** on **1**, causing expulsion of an ethoxide



Scheme 2

*To receive any correspondence.

†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1997, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

ion (Scheme 2). The resultant intermediate then undergoes cyclization by nucleophilic attack of nitrogen on the carbonyl carbon of either $COCH_3$ or $COCF_3$. Although, $COCF_3$ is a better electrophilic site, the attack takes place at $COCH_3$ leading to the formation of **3a–d**, whereas the intermediate obtained from **3e** undergoes cyclization at the expected position, *i.e.* $COCF_3$.

Experimental

Mps were determined in open capillaries and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker-300 (300 MHz) spectrometer. ^{19}F NMR spectra were recorded on a Varian EM 60NMR spectrometer. 2-Hydrazinopyridine was obtained from Aldrich and other hydrazines (**2c** and **2d**) were prepared using a literature procedure.[7]

3-*Acetyl*-4-*ethoxy*-1,1,1-*trifluorobut*-3-*en*-2-*one* (**1**).—A mixture of 1,1,1-trifluoropentane-2,4-dione (6.35 g, 41.2 mmol), triethyl orthoformate (13.70 ml, 82.4 mmol) and acetic anhydride (3.88 ml, 41.2 mmol) was heated at reflux for 18 h and then the volatile component was distilled at 127 °C and 4 mmHg. 3-Acetyl-4-ethoxy-1,1,1-trifluoromethylbut-3-en-2-one (**1**) (a mixture of *E* and *Z* isomers as evident by its ^1H NMR spectrum which showed two singlets at δ 7.63 and 7.83 due to olefinic protons) thus obtained was used without further purification.

5-*Methyl*-1-(*phenyl*/*heterocyclyl*)-4-*trifluoroacetylpyrazoles and* 4-*acetyl*-3-*trifluoromethylpyrazole* (**3a–d** *and* **3e**).—To a solution of an appropriate hydrazine (**2a–e**) (2 mmol) and dry THF (40 ml) at −10 °C was added dropwise **1** (2 mmol) over 1 h. The mixture was stirred for 30 min and then at room temperature for a further 1 h. The solvent was removed under reduced pressure and the residue was extracted with chloroform (2 × 30 ml). The extract was dried over Na_2SO_4 and the excess of chloroform was distilled off. The residue so obtained was purified by column chromatography using light petroleum (bp 65–70 °C)–ethyl acetate (19:1) as eluent which afforded after evaporation the solids **3a–e**.

5-*Methyl*-1-*phenyl*-4-*trifluoroacetylpyrazole* (**3a**) had mp 85 °C, yield 58%; ν_{max}/cm^{-1} 1709 (C=O); δ_H ($CDCl_3$) 2.63 (s, 3 H, 5-CH_3), 7.42 (m, 2 H, 2′-H and 6′-H), 7.53 (m, 3 H, 3′-H, 4′-H and 5′-H), 8.12 (q, 1 H, 3-H, *J* 1.92 and 1.76 Hz); δ_C ($CDCl_3$) 12.74 (5-CH_3), 116.54 (CF_3, *J* 290.8 Hz), 122.31 (C-4), 125.58 (C-2′ and C-6′), 129.52 (C-3′, C-4′ and C-5′), 137.84 (C-1′), 142.04 (C-3), 147.39 (C-5) and 175.95 (*C*OCF_3); δ_F ($CDCl_3$) −75.0 (Found: C, 56.81; H, 3.52; N, 10.70. $C_{12}H_9F_3N_2O$ requires C, 56.69; H, 3.54; N, 11.02%).

5-*Methyl*-1-(2-*pyridyl*)-4-*trifluoroacetylpyrazole* (**3b**) had mp 95 °C, yield 60%; ν_{max}/cm^{-1} 1708 (C=O); δ_H ($CDCl_3$) 2.99 (s, 3 H, 5-CH_3), 7.33 (m, 1 H, 2′-H), 7.90 (m, 2 H, 3′-H and 4′-H), 8.11 (s, 1 H, 3-H) and 8.55 (s, 1 H, 6′-H); δ_C ($CDCl_3$) 13.58 (5-CH_3), 113.40 (CF_3), 118.23 C−3′), 123.36 (C-5′ and C-4), 138.87 (C-4′), 142.10 (C-3), 147.98 (C-6′), 149.05 (C-5), 152.03 (C-2′) and 175.55 (*C*OCF_3); δ_F ($CDCl_3$) −75.30 (Found: C, 51.74; H, 3.10; N, 15.95. $C_{11}H_8F_3N_3O$ requires C, 51.76; H, 3.13; N, 16.47%).

1-(1,3-*Benzothiazol*-2-*yl*)-5-*methyl*-4-*trifluoroacetylpyrazole* (**3c**) had mp 170–172 °C, yield 68%; ν_{max}/cm^{-1} 1706 (C=O) δ_H ($CDCl_3$) 3.23 (, 3 H, 5-CH_3), 7.39–7.44 (ddd, 1 H, 6′-H, *J* 1.22 and 7.81 Hz), 7.48–7.53 (ddd, 1 H, 5′-H, *J* 1.28 and 7.28 Hz), 7.86 (dd, 1 H, 7′-H, *J* 1.00 and 7.48 Hz), 7.96 (dd, 1 H, 7′-H, *J* 0.61 and 7.48 Hz) and 8.11 (q, 1 H, 3-H, *J* 1.61 and 1.92 Hz); δ_C ($CDCl_3$) 13.58 (5-CH_3), 120.57 (CF_3, *J* 269.65 and 268.74 Hz), 121.43 (C-6′), 121.57 (C-4), 123.41 (C-7′), 125.82 (C-4′), 126.80 (C-5′), 133.32 (C-7′a), 142.99 (C-3), 149.89 (C-5), 150.99 (C-3′a), 159.86 (C-2′) and 175.92 (*C*OCF_3); δ_F ($CDCl_3$) −76.0 (Found: C, 52.30; H, 2.60; N, 13.77. $C_{13}H_8F_3N_3S$ requires C, 52.88; H, 2.71; N, 14.23%).

5-*Methyl*-1-(4-*methylquinolin*-2-*yl*)-4-*trifluoroacetylpyrazole* (**3d**) had mp 127 °C, yield 65%; ν_{max}/cm^{-1} 1706 (C=O); δ_H ($CDCl_3$) 2.80 (s, 3 H, 4′-CH_3), 3.13 (s, 3 H, 5-CH_3), 7.60–7.65 (m, 1 H, 7′-H), 7.74–7.79 (m, 1 H, 6′-H), 7.86 (s, 1 H, 3′-H), 8.02–8.14 (m, 2 H, 5′-H and 8′-H) and 8.14 (s, 1 H, 3-H); δ_C ($CDCl_3$) 14.06 (5-CH_3), 19.04 (4′-CH_3), 114.72 (CF_3, *J* 290.36 and 249.0 Hz), 116.31 (C-3′), 122.29 (C-4′a and C-4), 123.87 (C-6′), 127.16 (C-5′), 129.67 (C-7′), 130.30 (C-8′), 142.10 (C-3), 145.90 (C-8′a), 148.12 (C-5), 150.49 (C-4′), 154.71 (C-2′) and 175.39 (*C*OCF_3); δ_F ($CDCl_3$) −75.30 (Found: C, 59.90; H, 3.56; N, 12.67. $C_{16}H_{12}F_3N_3O$ requires C, 60.19; H, 3.76; N, 13.17%).

4-*Acetyl*-1-*methyl*-3-*trifluoromethylpyrazole* (**3e**) had mp 87 °C, yield 55%; ν_{max}/cm^{-1} 1692 (C=O); δ_H ($CDCl_3$) 2.46 (s, 3 H, $COCH_3$), 3.98 (s, 3 H, NCH_3) and 7.94 (s, 1 H, 5-H); δ_C ($CDCl_3$) 28.78 CO*C*H_3), 39.77 (NCH_3), 120.58 (q, CF_3, *J* 269.0 and 271.89 Hz), 121.57 (C-4), 135.89 (C-5), 140.29 (C-3) and 189.80 (*C*OCH_3); δ_F ($CDCl_3$) −62.0 (Found: C, 43.20; H, 3.57; N, 14.35. $C_7H_7F_3N_2O$ requires C, 43.75; H, 3.64; N, 14.58%).

We are grateful to the CSIR, New Delhi, for financial assistance, and Professor J. Elguero, CSIC, Madrid, Spain, for helpful suggestions.

Received, 18th September 1996; Accepted, 23rd December 1996
Paper E/6/06444B

References

1 J. Elguero, in *Comprehensive Heterocyclic Chemistry*, ed. A. R. Katritzky and C. W. Rees, Pergamon, Oxford, 1984, vol. 5, pp. 167–303; M. R. Grimmett, in *Comprehensive Organic Chemistry*, ed. P. G. Sammes, Pergamon, Oxford, 1979, vol. 4, pp. 357–410.
2 H. Zimmer and A. Amer, *Heterocycles*, 1987, **26**, 1177.
3 M. Begtrup, G. Boyer, P. Cabildo, C. Cativiela, R. M. Claramunt, J. Elguero, J. I. Garcia, C. Toiron and P. Vedro, *Magn. Reson. Chem*., 1993, **31**, 107.
4 P. Bravo, D. Diliddo and G. Resnati, *Tetrahedron*, 1994, **50**, 8827.
5 S. P. Singh, D. Kumar and J. K. Kapoor, *J. Chem. Res*., 1993, (*S*) 163; (*M*) 1168.
6 S. P. Singh, S. Sehgal and L. S. Tarar, *Indian J. Chem*., 1989, **28B**, 27.
7 L. Katz, *J. Am. Chem. Soc*., 1951, **73**, 4007; V. K. Rao and V. R. Srinivasan, *Experientia*, 1964, **20**, 200; K. T. Potts, J. Bhattacharyya, S. L. Smith, A. M. Ihrig and C. A. Girard, *J. Org. Chem*., 1972, **37**, 4410.