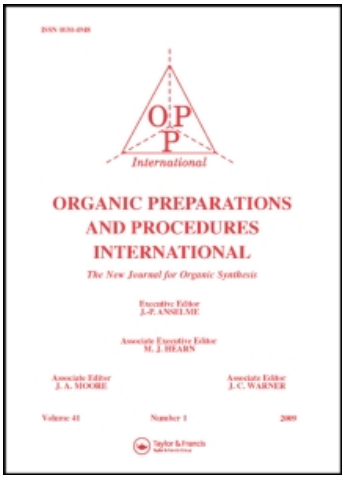

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AN IMPROVED SYNTHETIC ROUTE TO TRIFLUOROMETHYL-6-SUBSTITUTED-2(1H)-PYRIDONES

B. Narsaiah[a]; A. Sivaprasad[a]; R. V. Venkataratnam[a]
[a] Indian Institute of Chemical Technology, Hyderabad, India

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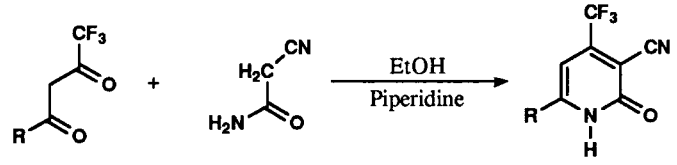
AN IMPROVED SYNTHETIC ROUTE TO TRIFLUOROMETHYL-6-SUBSTITUTED-2(1H)-PYRIDONES†

Submitted by B. Narsaiah, A. Sivaprasad and R. V. Venkataratnam*
(07/08/92)

Indian Institute of Chemical Technology, Hyderabad 500 007, INDIA

Fluorinated-1,3-dicarbonyl compounds[1] have considerable importance in the synthesis of many biologically active heterocycles. The preparation of fluorinated nitrogen heterocycles *via* cyclization of fluorinated intermediates has been reported in the literature.[2-4] In connection with a program of synthesis of biologically active compounds, we required 4-trifluoromethyl-6-substituted-2(1H)-pyridones (**3**).

The first reported synthesis[5] of **3** involves, for example, treatment of 1,1,1-trifluoro-2,4-pentanedione (**1a**) with cyanoacetamide in the presence of sodium ethoxide, followed by several recrystallizations to obtain 17% pure 3-cyano-6-methyl-4-trifluoromethyl-2(1H)-pyridone. For other pyridones in the series,[5] the yield ranged from 12-36%. We attempted to improve the yield and purity of the pyridones and found that piperidine acts as a better catalyst in giving 72% in the above preparation



1 2 3

a) R = CH_3 b) R = C $_2H_5$ c) R = C $_6H_5$ d) R = *p*-$CH_3C_6H_4$ e) R = *p*-$OCH_3C_6H_4$ f) R = *p*-ClC_6H_4

and better than 70% yield in the preparation of other similar pyridones obtained in this work. The reaction times are shorter, the workup procedures are simpler, and the purity of the products obtained after washing the reaction product with cold ethanol is sufficiently high for further steps. The regioselectivity of the formation of 4CF_3-substituted-2(1H)-pyridones is not affected.

Products **3b**, **3d**, **3e** and **3f** are being reported for the first time. The structure of **3a** was established by comparison with the work of Lang and Wenk[6] and the structures of the others follow by analogy. The most electrophilic site is the carbonyl adjacent to the CF_3 group in the diketones and hence the formation of 4-CF_3 substituted regioisomers.

EXPERIMENTAL SECTION

Melting points are uncorrected. Infrared spectra were recorded using a Perkin-Elmer 810 model. ^1H NMR spectra were measured with a Varian (80 MHz) spectrometer in DMSO-d_6. Chemical shifts are reported in ppm, internal standard was tetramethylsilane (δ scale). Mass spectra were recorded on a VG micromass-7070H. Microanalysis were performed by Indian Institute of Chemical Technology, Hyderabad.

General Procedure for the Preparation of 3a-f.- To a solution of cyanoacetamide (1.78 g, 0.02 mol) in 95% ethanol (10 mL) was added 1,1,1-trifluoromethyl-2,4-pentanedione (3.08 g, 0.02 mol) with stirring. To the homogenous mixture obtained, piperidine (0.20 mL, 0.002 mol) was then added dropwise, the reaction mixture was refluxed for 2 hrs and cooled to room temperature. The resulting solid was collected, washed with small portions of cold ethanol and dried at 85°.

3a: Yield 72%, white powdery crystals, mp 234°, lit.[6] mp. 232-234°. ^{1}H NMR: δ 2.37 (s, 3H, CH_3-C(6)), 6.62 (s, 1H, H-C(5)); IR (Nujol): 3320, 2225, 1655 cm^{-1}. MS: m/z 202.

3b: Yield 71%, white crystals, mp. 215°. ^{1}H NMR: δ 1.18 (d, 3H, CH_3), 2.62 (q, 2H, CH_2), 6.56 (s, 1H, H-C(5)); IR (Nujol): 3300, 2218, 1650 cm^{-1}. MS: m/z 216.

Anal. Calcd. for $C_9H_7F_3N_2O$: C, 50.00; H, 3.26; F, 26.36; N, 12.95
Found: C, 50.01; H, 3.26; F, 26.35; N, 12.95

3c: Yield 73%, yellow needles, mp. 301°. ^{1}H NMR: δ 7.22 (s, 1H, H-C(5)), 7.56 (m, 3H, ArH), 7.93 (m, 2H, ArH); ν IR(Nujol): 3350, 2225, 1648cm^{-1}. MS: m/z 264.

3d: Yield 73%, yellow needles, mp. > 305°. ^{1}H NMR: δ 2.43 (s, 3H, CH_3), 7.21 (s, 1H, H-C(5)), 7.41 (d, 2H, ArH), 7.91 (d, 2H, ArH); IR (Nujol): 3150, 2200, 1648 cm^{-1}. MS: m/z 278.

Anal. Calcd. for $C_{14}H_9F_3N_2O$: C, 60.43; H, 3.26; F, 20.48; N, 10.06
Found: C, 60.42; H, 3.25; F, 20.48; N, 10.06

3e: Yield 72%, yellow needles, mp. 285°. ^{1}H NMR: δ 3.87 (s, 3H, OCH_3), 7.21 (s, 1H, H-C(5)) 7.11 (d, 2H, ArH) 7.97 (d, 2H, ArH); IR (Nujol): 3150, 2210, 1645 cm^{-1}. MS: m/z 294.

Anal. Calcd. for $C_{14}H_9F_3N_2O_2$: C, 57.15; H, 3.08; F, 19.37; N, 9.52
Found: C, 57.14; H, 3.08; F, 19.36; N, 9.51

3f: Yield 71%, yellow needles, mp. 287°. ^{1}H NMR: δ 7.37 (s, 1H, H-C(5)), 7.37 (d, 2H, ArH), 8.03 (d, 2H, ArH); IR (Nujol): 3375, 2200, 1645 cm^{-1}. MS: m/z 298.

Anal. Calcd. for $C_{13}H_6ClF_3N_2O$: C, 52.28; H, 2.02; Cl, 11.87; F, 19.08; N, 9.38
Found: C, 52.28; H, 2.02; Cl, 11.86; F, 19.08; N, 9.37

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