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NEW METHOD FOR THE SYNTHESIS OF 4-HYDROXY-2-TRIFLUOROMETHYLPYRIDINE

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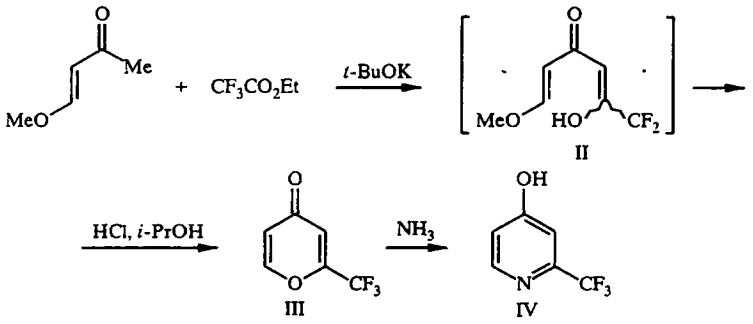
4(1H)-Pyridinones and their condensed analogs containing perfluoroalkyl groups have recently found wide use as herbicides and plant growth regulators [1, 2] and also in the synthesis of medical materials [3]. The precursor of this series of compounds, 4-hydroxy-2-trifluoromethylpyridine (IV), was recently prepared by a three-stage synthesis based on 4-amino-5,5,5-trifluoro-3-penten-2-one [4]. We report a two-stage synthesis of the hydroxypyridine (IV) based on commercially available *trans*-4-methoxy-3-buten-2-one (I):



Product II from the condensation of the ether of enol I with ethyl trifluoroacetate was subjected to acid catalyzed cyclization to the pyranone III without separation from the reaction mixture. The latter can be used as a suitable starting material for the synthesis not only of the hydroxypyridine IV but also various N-substituted 4(1H)-pyridinones by reaction with ammonia or primary amines.

2-Trifluoromethyl-4H-pyran-4-one (III, $C_6H_3F_3O_2$). A mixture of freshly distilled I (10.0 cm^3, 0.1 mol) and ethyl trifluoroacetate (14.2 cm^3, 0.12 mol) was added dropwise with cooling to −15°C over 30 min to *tert*-butyl potassium (14.6 g, 0.13 mol) in absolute ether (100 cm^3). After stirring for 3 h, the reaction mixture was neutralized with glacial acetic acid (7.8 cm^3, 0.13 mol), diluted with water (50 cm^3), and the water layer was extracted with ether (5 × 15 cm^3). The combined ether extracts were carefully washed with sodium hydrogen carbonate. The residue after evaporation of the ether was dissolved in isopropanol (150 cm^3), hydrochloric acid (2.5 cm^3 of 35%) was added, and the mixture refluxed for 45 min. The residue after removal of the alcohol was fractionated at low pressure to give the pyranone III: yield 6.6 g (40%), b.p. 71-73°C (17 hPa), n_D^{20} 1.4402. M.p. 21-22°C (pentane−Et_2O). IR spectrum (CCl_4): 1680, 1645, 1635 cm^{-1}. ^1H NMR spectrum (60 MHz, CCl_4): 7.90 (1 H, d, J = 5.8 Hz, 6-H), 6.67 (1 H, d, J = 2.5 Hz, 3-H), 6.35 ppm (1 H, dd, J = 5.8 Hz, J = 2.5 Hz, 5H). Mass spectrum, *m/z* (I_{rel}, %): 164 (M^+, 10), 163 (100), 144 (16), 136 (4), 135 (7), 115 (5), 94 (76), 75 (7), 69 (22), 53 (10). Found, %: C 44.08, H 1.96. Calculated %: C 43.92, H 1.84.

4-Hydroxy-2-trifluoromethylpyridine (IV, $C_6H_4F_3NO$). Aqueous ammonia (0.7 cm^3 25%, 9 mmol) was added to a solution of the pyrone III (1 g, 6 mmol) in methanol (5 cm^3). The mixture was boiled for 6 h, the methanol removed and the residue crystallized from benzene to give IV (0.7 g, 70%), m.p. 123-124°C (chloroform). IR spectrum (CCl_4): 3565, 1615, 1588 cm^{-1}. ^1H NMR spectrum (60 Hz, $CDCl_3$): 10.76 (1 H, s, OH), 8.11 (1 H, d, J = 5.8 Hz, 6-H), 7.09 (1 H, d, J = 2.3 Hz, 3-H), 6.85 ppm (1 H, dd, J = 5.8, J = 2.3 Hz, 5-H). Mass spectrum, *m/z*: 164 (M^+ + 1, 100), 163 (M^+, 73).

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