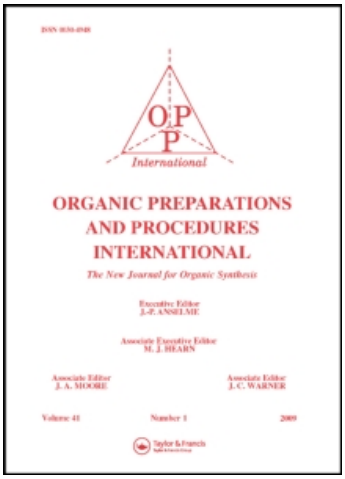

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A Practical Synthesis of 2'-Fluoro- 4'-hydroxyacetophenone

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A Practical Synthesis of 2′-Fluoro-4′-hydroxyacetophenone

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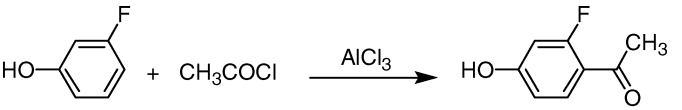
2′-Fluoro-4′-hydroxyacetophenone (**2**) is an important building block for many pharmaceutically active agents,[1] used to treat bacterial and parasitic infections.[2] A review of the literature indicated that its synthesis has rarely been reported.[3]

Kees and Musser *et al*. developed the only method to obtain 2′-fluoro-4′-hydroxyacetophenone (**2**) from 3-fluorophenol (**1**) through Friedel-Crafts reaction (*Scheme 1*), but the yield was not reported.[3] Numerous repetitions of the procedure showed that the yield never exceeded 40% and at least 18% of 4′-fluoro-2′-hydroxyacetophenone accompanied the desired product. Furthermore, the starting compound, 3-fluorophenol (**1**) is expensive to purchase and tedious to prepare.[4,5]



1 **2**

Scheme 1

Based on the report of Gryko *et al*.[6] and as a continuation of our interest in the study of medicinal compounds,[7] we have developed a practical pilot-scale method for the preparation of 2′-fluoro-4′-hydroxyacetophenone (**2**) from 2′,4′-difluoroacetophenone (**3**) (*Scheme 2*); the latter was easily prepared by acetylation of 1,3-difluorobenzene.[8]

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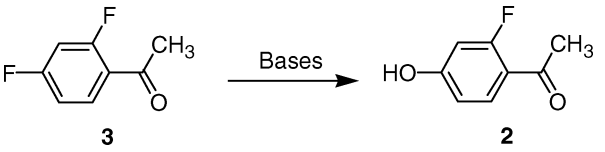

3 2

Scheme 2

It is noteworthy that the use of a mixture of sodium hydroxide and calcium hydroxide is necessary in this reaction in order to ensure an adequate reaction rate and an acceptable yield of the product.

Experimental Section

Mps and bps are uncorrected. The purity of products was established on an Agilent 1100 HPLC. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker 400 (400 MHz) instrument with TMS as internal standard. All chemicals were reagent grade and available commercially. The elemental analysis was performed on a Flash EA1112 instrument.

2′-Fluoro-4′-hydroxyacetophenone

In a 1 L round-bottomed flask fitted with a mechanical stirrer was placed 60.0 g (0.38 mol) of 2′,4′-difluoroacetophenone (**3**), 14.1 g calcium hydroxide, 16.0 g sodium hydroxide and 500 mL water. The mixture was stirred under reflux for 18 h. Then the mixture was cooled to room temperature and filtered. The filtrate was extracted with 150 mL CH_2Cl_2 to recover 11.2 g 2′,4′-difluoroacetophenone (HPLC > 96%), and acidified with 100 mL of 4M hydrochloric acid followed by steam distillation to remove a small quantity of 4′-fluoro-2′-hydroxyacetophenone (about 1.1 g). The water phase was cooled to 5°C, and the precipitated crystals collected and dried *in vacuo* to afford 38.1 g (79%) of the crude product (**2**) as a white solid (HPLC > 98.5%). ^{1}H NMR (DMSO- d_6): δ 2.46 (3 H, d, J = 4.8 Hz), 6.65 (1 H, d, J = 8.8 Hz), 6.74 (1 H, d, J = 8.8 Hz), 7.75 (1 H, t, J = 8.8 Hz), 10.85 (1 H, b). ^{13}C NMR (DMSO-d_6): δ 193.7, 164.1 (J = 12.1 Hz), 163.6 (J = 252.5 Hz), 132.4 (J = 4.7 Hz), 117.1 (J = 12.0 Hz), 112.5 (J = 7.8 Hz), 103.3 (J = 25.4 Hz), 31.0 (J = 7.0 Hz). An analytical sample was prepared by recrystallization from methanol and water (v/v = 30/70), mp.120–121°C.[9]

Anal. Calcd. for $C_8H_7FO_2$: C, 62.34; H, 4.58. Found: C, 62.44; H, 4.66.

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