# A Convenient Synthesis of Difluoromethyl-Substituted Pyridines

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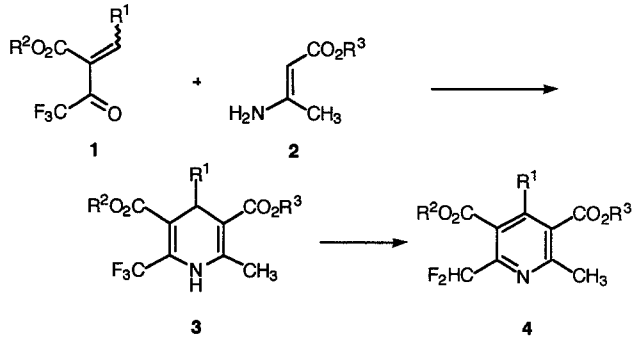
**Abstract:** The treatment of α-alkoxycarbonyl-α,β-unsaturated trifluoromethyl ketones **1** with β-aminocrotonates **2** affords 2-methyl-6-trifluoromethyl-1,4-dihydropyridines **3**, which undergo dehydrofluorination using DBU/piperazine, giving moderate to high yields of 2-difluoromethyl-6-methylpyridines **4**.

Pyridine ring systems represent an important class of compounds because they sometimes display biological activity.[1]

Fluorine-containing heterocycles have recently proved to be more bioactive than their non-fluorine analogs.[2] Thus, they are becoming increasingly important for the development of excellent biologically active compounds.[3] In recent years, it has been found that difluoromethyl-substituted pyridines possess high herbicidal activity.[4] However, no efficient method has been reported for the synthesis of 2-alkyl-6-difluoromethylpyridines such as **4**. This paper describes a convenient and effective synthesis of 2-difluoromethyl-6-methylpyridines **4** starting from α-alkoxycarbonyl-α,β-unsaturated trifluoromethyl ketones **1**.



The difluoromethyl-substituted pyridines are difficult to prepare using fluorinating agents. An alternative route to **4** involves the dehydrofluorination of 2-methyl-6-trifluoromethyl-1,4-dihydropyridines **3** readily obtained from **1**. Several methods are known for the dehydrofluorination of trifluoromethyl-substituted compounds. Bases of choice include: NaH and/or lithium amides,[5] trialkylamines,[6] or DBU.[6] However, the use of these bases resulted in the low to moderate consumption of **3a** and/or the unavoidable formation of by-products such as the corresponding trifluoromethyl-substituted pyridine, providing a poor to moderate yield of **4a** (a trace amount - 60 % yield). Therefore, we investigated another effective reagent for this reaction, and found that DBU/piperazine was useful for the synthesis of **4a** (83 % yield). The high yield was due to both the satisfactory consumption of **3a** and a decrease in the amount of by-products; the latter result could be ascribed to the efficient trapping of HF formed concomitantly by the reaction. Table 1 shows several examples of the synthesis of **4** *via* the dehydrofluorination of **3** with DBU/piperazine. The present method gave moderate to high yields of **4**. It is applicable to the synthesis of 4-aryl or 4-heteroaryl-substituted 3,5-pyridinedicarboxylates. In general, the reaction of 1,4-dihydropyridines bearing methyl ester groups with DBU affords substantial amounts of by-products, which mainly contain derivatives arising from the demethylation of the methyl ester groups, providing poor yields of the desired compounds.[6] In contrast, the treatment of the methyl esters **3b**, **d**, **f** with DBU/piperazine gave moderate to good yields of the corresponding **4b**, **d**, **f**.

**Table 1.** Synthesis of 2-difluoromethyl-6-methylpyridines **4**

| Compd. | $R^1$ | $R^2$ | $R^3$ | Yield[a] / % of **4** |
|---|---|---|---|---|
| **a** | Ph | Et | Et | 83 |
| **b** | Ph | Et | Me | 72 |
| **c** | 4-$CH_3C_6H_4$ | Et | Et | 85 |
| **d** | 4-$CH_3C_6H_4$ | Me | Et | 62 |
| **e** | 4-$CH_3OC_6H_4$ | Et | Et | 85 |
| **f** | 4-$CH_3OC_6H_4$ | Et | Me | 75 |
| **g** | 4-$ClC_6H_4$ | Et | Et | 89 |
| **h** | 2-Furyl | Et | Et | 76 |
| **i** | 2-Thienyl | Et | Et | 89 |

[a] Isolated yields referred to **1**.

A general procedure for the synthesis of **4** is as follows: a solution of α-alkoxycarbonyl-α,β-unsaturated trifluoromethyl ketones **1**[7] (1 mmol) and β-aminocrotonates **2** (1 mmol) in acetonitrile (4 mL) was refluxed for 1-2 h. To the mixture was added phosphorus oxychloride/pyridine adsorbed on silica gel[8] (0.9 g) and further refluxed while being stirred for 3-4 h. After the reaction mixture was filtered through a pad of silica gel with the aid of *n*-$C_6H_{14}$/AcOEt (3 / 1), the filtrate was concentrated. To an acetonitrile (4 mL) solution of the residue were added DBU (1.0 equiv) and piperazine (1.0 equiv), and the mixture was refluxed while being stirred for 10-13 h. After removal of the solvent, the residue was chromatographed on silica gel using $CH_2ClCH_2Cl$/AcOEt (20 / 1) as an eluent, yielding **4**.[9]

In summary, we have found a convenient and effective method of synthesizing difluoromethyl-substituted pyridines *via* the dehydrofluorination of the corresponding trifluoromethyl-substituted 1,4-dihydropyridines in the presence of DBU/piperazine.

## References and Notes

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(7) Ketones **1** were prepared by using the method described in our previous paper. See Katsuyama, I.; Funabiki, K.; Matsui, M.; Muramatsu, H; Shibata, K. *Chem. Lett.* **1996**, 179.

(8) Phosphorus oxychloride/pyridine adsorbed on silica gel was prepared by using the method described in our previous paper. See Katsuyama, I.; Funabiki, K.; Matsui, M.; Muramatsu, H; Shibata, K. *Tetrahedron Lett.*, **1996**, 37, 4177.

(9) All new compounds gave satisfactory spectroscopic and analytical data. The typical spectral data for **4a** : mp 41-42°C. $^1$H NMR ($CDCl_3$) δ 0.93 (t, *J* = 7.1Hz, 6H), 2.67 (s, 3H), 4.04 (q, *J* = 7.1Hz, 4H), 6.79 (t, *J* = 54.7Hz, 1H), 7.26-7.40 (m, 5H). $^{19}$F NMR ($CDCl_3$, TFA) δ -37.84 (d, *J* = 54.7Hz, 2F). MS (EI) m/z 363 (100, $M^+$), 318 (74), 272 (93).