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An Effective Synthesis of Trifluoromethyl-Substituted 1,4-Dihydropyridines with Phosphorus Oxychloride / Pyridine Adsorbed on Silica Gel

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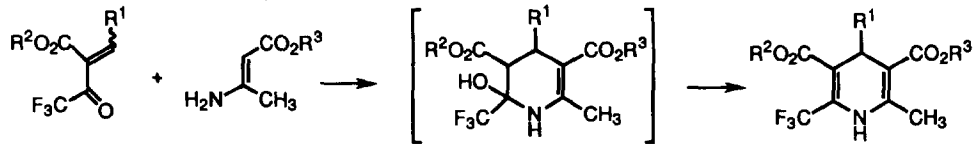
Abstract: Treatment of α-alkoxycarbonyl-α,β-unsaturated trifluoromethyl ketones **1** with β-aminocrotonates **2** affords 2-hydroxy-6-methyl-2-trifluoromethyl-1,2,3,4-tetrahydropyridines **3**, which undergo dehydration by using phosphorus oxychloride / pyridine adsorbed on silica gel, giving good to high yields of 2-methyl-6-trifluoromethyl-1,4-dihydropyridines **4**. Copyright © 1996 Elsevier Science Ltd

Since the discovery of nifedipine®, which is a clinically important antihypertensive and antiangina drug, much interest has been led to the synthesis of substituted 1,4-dihydropyridines and their biological activity.[1]

The introduction of a trifluoromethyl group into a biomolecule has sometimes resulted in improvement of its biological activity.[2] This led us to prepare 2-methyl-6-trifluoromethyl-1,4-dihydropyridines **4** and study their properties. No efficient method has been reported for the synthesis of unsymmetrical fluorine-containing dihydropyridines such as **4**. This paper describes an effective synthesis of trifluoromethyl-substituted 1,4-dihydropyridines starting from α-alkoxycarbonyl-α,β-unsaturated trifluoromethyl ketones **1**.

In general, treatment of α-alkoxycarbonyl-α,β-unsaturated methyl ketones with β-aminocrotonates readily affords 2,6-dimethyl-1,4-dihydropyridines in the absence of catalyst under boiling alcohol.[3] However, under the same conditions, reaction of **1** with β-aminocrotonates **2** afforded the intermediate hydroxypyridines **3** instead of the desired 2-methyl-6-trifluoromethyl-1,4-dihydropyridines **4**. This result could be ascribed to the high stability of α-trifluoromethyl alcohols[4] such as **3**.



1 **2** **3** **4**

Several methods have been known for the synthesis of 1,4-dihydropyridines *via* dehydration of the intermediate hydroxypyridines. Reagents of choice include: concentrated hydrochloric acid[5], concentrated sulfuric acid[6], or phosphorus oxychloride / pyridine.[7] However, the use of the above reagents resulted in moderate consumption of **3a** and / or further conversion of **4a** into several kinds of compounds, providing low yield of **4a** (14-39 % yield). Therefore, we investigated another effective reagent for this reaction, finding that phosphorus oxychloride / pyridine adsorbed on silica gel was useful for the synthesis of **4a** (91 % yield). The high yield was ascribed to both satisfactory consumption of **3a** and decrease in the amount of by-products. Table 1 shows several examples for one-pot synthesis of **4** *via* dehydration of **3** with phosphorus oxychloride / pyridine adsorbed on silica gel. In every cases, the method gave good to high yields of **4**.

Table 1. Synthesis of 2-methyl-6-trifluoromethyl-1, 4-dihydropyridines **4**

Compd.	R^1	R^2	R^3	Time[a]/h	Yield[b]/% of **4**
a	Ph	Et	Et	3	91
b	2-ClC_6H_4	Et	Et	5	77
c	2-ClC_6H_4	Me	Et	5	76
d	2-$NO_2C_6H_4$	Me	Me	5	78
e	2-$NO_2C_6H_4$	Et	Me	6	80
f	3-$NO_2C_6H_4$	Et	Me	6	91
g	2-$CF_3C_6H_4$	Et	Et	6	73
h	2-Furyl	Et	Et	4	80
i	2-Thienyl	Et	Et	6	88

a) Dehydration time. b) Isolated yields referred to **1**.

General procedure for the synthesis of **4** is as follows: a solution of α-alkoxycarbonyl-α,β-unsaturated trifluoromethyl ketones **1**[8] (1 mmol) and β-aminocrotonates **2** (1 mmol) in CH_2ClCH_2Cl (4 ml) was refluxed for 2-3 h. To the mixture was added phosphorus oxychloride / pyridine adsorbed on silica gel[9] (0.9 g) and further refluxed while being stirred until **3** was consumed as monitored by GLC analysis. After removal of the solvent, the residue was chromatographed on silica gel using CH_2Cl_2/AcOEt (20/1) as an eluent, yielding **4**.[10]

In summary, phosphorus oxychloride / pyridine adsorbed on silica gel is a new and effective reagent for the synthesis of trifluoromethyl-substituted 1,4-dihydropyridines *via* dehydration of the intermediate hydroxypyridines.

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8. 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.
9. Phosphorus oxychloride / pyridine adsorbed on silica gel was prepared by the following procedure. To a solution of phosphorus oxychloride (3 ml) and pyridine (6 ml) in CH_2Cl_2 (50 ml) was slowly added silica gel (Merck Art. 7734, 20 g) while being cooled. The mixture was stirred for 1 h at room temperature. After removal of the solvent, the residue was dried in a rotary evaporator over a period of several hours.
10. All new compounds gave satisfactory spectroscopic and analytical data. The typical spectral data for **4d** : mp 185-187°C. ^1H NMR (DMSO-d_6) δ 2.34 (s, 3H), 3.40 (s, 3H), 3.60 (s, 3H), 5.29 (s, 1H), 7.44-7.81 (m, 4H), 9.41 (s, 1H). ^{19}F NMR (DMSO-d_6, TFA) δ 14.21 (s, 3F). MS (EI) m/z 400 (M^+, 5 %).

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