



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

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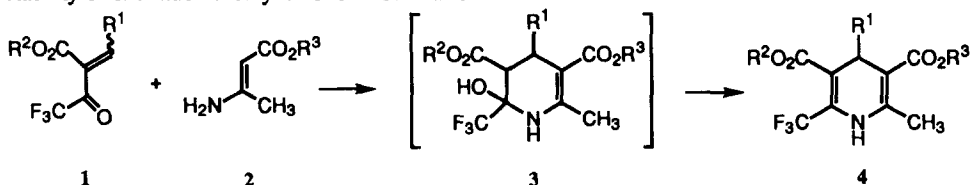
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**Abstract:** Treatment of  $\alpha$ -alkoxycarbonyl- $\alpha,\beta$ -unsaturated trifluoromethyl ketones **1** with  $\beta$ -aminocrotonates **2** affords 2-hydroxy-6-methyl-2-trifluoromethyl-1,2,3,4-tetrahydropyridines **3**, which undergo dehydration 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.<sup>1</sup>

The introduction of a trifluoromethyl group into a biomolecule has sometimes resulted in improvement of its biological activity.<sup>2</sup> 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  $\alpha$ -alkoxycarbonyl- $\alpha,\beta$ -unsaturated trifluoromethyl ketones **1**.

In general, treatment of  $\alpha$ -alkoxycarbonyl- $\alpha,\beta$ -unsaturated methyl ketones with  $\beta$ -aminocrotonates readily affords 2,6-dimethyl-1,4-dihydropyridines in the absence of catalyst under boiling alcohol.<sup>3</sup> However, under the same conditions, reaction of **1** with  $\beta$ -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  $\alpha$ -trifluoromethyl alcohols<sup>4</sup> such as **3**.



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<sup>5</sup>, concentrated sulfuric acid<sup>6</sup>, or phosphorus oxychloride / pyridine.<sup>7</sup> 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 <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Time <sup>a</sup> /h	Yield <sup>b</sup> / % of <b>4</b>
<b>a</b>	Ph	Et	Et	3	91
<b>b</b>	2-ClC <sub>6</sub> H <sub>4</sub>	Et	Et	5	77
<b>c</b>	2-ClC <sub>6</sub> H <sub>4</sub>	Me	Et	5	76
<b>d</b>	2-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	Me	Me	5	78
<b>e</b>	2-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	Et	Me	6	80
<b>f</b>	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	Et	Me	6	91
<b>g</b>	2-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	Et	Et	6	73
<b>h</b>	2-Furyl	Et	Et	4	80
<b>i</b>	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  $\alpha$ -alkoxycarbonyl- $\alpha,\beta$ -unsaturated trifluoromethyl ketones **1**<sup>8</sup> (1 mmol) and  $\beta$ -aminocrotonates **2** (1 mmol) in CH<sub>2</sub>ClCH<sub>2</sub>Cl (4 ml) was refluxed for 2-3 h. To the mixture was added phosphorus oxychloride / pyridine adsorbed on silica gel<sup>9</sup> (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<sub>2</sub>Cl<sub>2</sub>/AcOEt (20/1) as an eluent, yielding **4**.<sup>10</sup>

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.

## REFERENCES AND NOTES

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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<sub>2</sub>Cl<sub>2</sub> (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. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  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). <sup>19</sup>F NMR (DMSO-d<sub>6</sub>, TFA)  $\delta$  14.21 (s, 3F). MS (EI) m/z 400 (M<sup>+</sup>, 5 %).

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