AN EFFICIENT SYNTHESIS OF 1,4-DIHYDRO-6-TRIFLUOROMETHYLPYRIDINES: A FACILE AND USEFUL METHOD FOR DEHYDRATION OF α-TRIFLUOROMETHYL ALCOHOLS BY USE OF PHOSPHOROUS OXYCHLORIDE / PYRIDINE ADSORBED ON SILICA GEL

Isamu Katsuyama,* Kazumasa Funabiki, Masaki Matsui, Hiroshige Muramatsu, and Katsuyoshi Shibata

Department of Chemistry, Faculty of Engineering, Gifu University, 1-1 Yanagido, Gifu 501-1193, Japan
*Present address: Hitec Co., Ltd, OAP 25F, 1-8-30 Temmabashi, Kita-ku, Osaka-shi, Osaka 530-6025, Japan E-mail: katsuyama_i@ybb.ne.jp

Abstract – The 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 facile dehydration by use of phosphorus oxychloride / pyridine adsorbed on silica gel, giving good to high yields of 1,4-dihydro-2-methyl-6-trifluoromethylpyridines (4).

INTRODUCTION
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 ability as therapeutic agents for cardiovascular ailments.¹ This class of compounds is known to indicate its biological effects by the inhibition of calcium ion influx across the cell membrane through slow calcium channels.² On the other hand, the introduction of a trifluoromethyl group into a biomolecule has sometimes resulted in an improvement in its biological activity.³ Therefore, trifluoromethyl-substituted 1,4-dihydropyridines have been worthy of remark for their potential biological properties. Furthermore, they can be utilized as intermediates for the synthesis of trifluoromethyl-substituted pyridines.⁴
This paper describes an efficient synthesis of trifluoromethyl-substituted derivatives (4) for 1,4-dihydropyridine-3,5-dicarboxylates of the nifedipine® type.

RESULTS AND DISCUSSION

No efficient methods have been reported for the synthesis of unsymmetrical fluorine-containing dihydropyridines such as 4. The previous methods such as Hantzsch conditions have the following three disadvantages: (i) unsymmetrical dihydropyridines are often more difficult to prepare than their symmetrical counterparts due to the formation of all the possible isomeric Hantzsch condensation products.\(^5\) (ii) the intermediate hydroxytetrahydropyridines (3) seem to be very stable,\(^6\) and accordingly difficult to dehydrate under the standard Hantzsch conditions.\(^7\) (iii) the intermediates (3) and desired products (4) appear to be unstable for strong agents due to the presence of esters. (Scheme 1). In order to improve the disadvantage (i), \(\alpha\)-alkoxycarbonyl-\(\alpha,\beta\)-unsaturated trifluoromethyl ketones (1) were chosen as a starting material for the synthesis of 4: the ketones 1 were prepared by the reaction of aldehydes with 4,4,4-trifluoroacetoacetates or by that of the Schiff bases for the aldehydes with the acetoacetates.\(^8\)
The reaction of the trifluoromethyl ketone (1a) with β-aminocrotonate (2a) gave a quantitative yield of the intermediate hydroxytetrahydropyridine (3a), which did not undergo dehydration in the absence of catalysts in boiling alcohol (standard Hantzsch conditions) (Table 1, Entry 1). Here, it was confirmed that a dehydration reagent is essential for the synthesis of 4. The dehydration of 3a using several agents was then attempted for the synthesis of 4a. The use of usual catalysts resulted in both a moderate consumption of 3a and formation of 4a in a low yield (Table 1, Entries 2-4). The reaction using other reagents led to the satisfactory consumption of 3a. These conditions, however, gave only a low to moderate yield of 4a (Table 1, Entries 5-6). In addition, most of the above methods require hazardous reagents and aqueous workup procedure that are detrimental to the environment. Therefore, another procedure was investigated for this reaction.

![Chemical reaction diagram]

**Table 1** Synthesis of CF₃-Dihydropyridine under Various Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time* /h</th>
<th>Yield⁴/ %</th>
<th>3a</th>
<th>4a</th>
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<tbody>
<tr>
<td>1</td>
<td></td>
<td>EtOH</td>
<td>reflux</td>
<td>6</td>
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<td>98</td>
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<td>MeOH</td>
<td>reflux</td>
<td>2</td>
<td>50</td>
<td>50</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>H₃PO₄</td>
<td>EtOH</td>
<td>reflux</td>
<td>3</td>
<td>50</td>
<td>50</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>conc.H₂SO₄</td>
<td>CH₂Cl₂</td>
<td>5-10°C</td>
<td>1</td>
<td>54</td>
<td>54</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>p-TsOH</td>
<td>EtOH</td>
<td>reflux</td>
<td>3</td>
<td>31</td>
<td>31</td>
<td>trace</td>
</tr>
<tr>
<td>6</td>
<td>(CF₃CO)₂O</td>
<td>(CH₂Cl)₂</td>
<td>rt</td>
<td>3</td>
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<td>(CH₂Cl)₂</td>
<td>reflux</td>
<td>3</td>
<td>trace</td>
<td>trace</td>
<td>39</td>
</tr>
<tr>
<td>8</td>
<td>POCl₃/C₆H₅N·SiO₂</td>
<td>(CH₂Cl)₂</td>
<td>reflux</td>
<td>3</td>
<td>trace</td>
<td>trace</td>
<td>91</td>
</tr>
</tbody>
</table>

*Dehydration time. ⁴ Isolated yields referred to 1a.

Phosphorus oxychloride or thionyl chloride/ pyridine is known to be a good dehydration system and therefore is often used for the dehydration of alcohols. However, this system usually require large excess amount of phosphorus oxychloride or thionyl chloride and pyridine; this is inconvenient to manipulate and may cause severe bodily harm because of quite strong corrosion. Thus, the dehydration
of 3a using small excess amount of the reagents was attempted for the synthesis of 4a. However, at rt no reaction proceeded while at higher temperature 4a was obtained only in a low yield (Table 1, Entry 7). During the further studies, phosphorus oxychloride / pyridine adsorbed on silica gel (POCl₃/C₅H₅N-SiO₂) has been found to be an efficient reagent for the synthesis of 4a via the dehydration of 3a (Table 1, Entry 8). The high yield was due to both a satisfactory consumption of 3a and a decrease in the amount of by-products. Moreover, it was found that this reagent does not have severe stimulating smell in contrast to POCl₃/C₅H₅N; this is convenient to manipulate.

![Diagram of reaction](image)

**Table 2** One-pot Synthesis of 1,4-Dihydro-2-methyl-6-trifluoromethylpyridines (4)

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Time²/h</th>
<th>Product</th>
<th>Yield²</th>
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<tbody>
<tr>
<td>Ph</td>
<td>Et</td>
<td>Et</td>
<td>3</td>
<td>4a</td>
<td>91</td>
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<td>5</td>
<td>4b</td>
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<tr>
<td>2-ClC₅H₄</td>
<td>Me</td>
<td>Et</td>
<td>5</td>
<td>4c</td>
<td>76</td>
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<td>2-CF₃C₅H₄</td>
<td>Et</td>
<td>Et</td>
<td>6</td>
<td>4d</td>
<td>73</td>
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<tr>
<td>2-NO₂C₅H₄</td>
<td>Et</td>
<td>Et</td>
<td>3</td>
<td>4e</td>
<td>77</td>
</tr>
<tr>
<td>2-NO₂C₅H₄</td>
<td>Et</td>
<td>Me</td>
<td>5</td>
<td>4f</td>
<td>80</td>
</tr>
<tr>
<td>3-NO₂C₅H₄</td>
<td>Et</td>
<td>Et</td>
<td>6</td>
<td>4j</td>
<td>78</td>
</tr>
<tr>
<td>3-NO₂C₅H₄</td>
<td>Et</td>
<td>Me</td>
<td>6</td>
<td>4h</td>
<td>91</td>
</tr>
<tr>
<td>2-Furyl</td>
<td>Et</td>
<td>Et</td>
<td>4</td>
<td>4i</td>
<td>80</td>
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<tr>
<td>2-Thienyl</td>
<td>Et</td>
<td>Et</td>
<td>6</td>
<td>4j</td>
<td>88</td>
</tr>
</tbody>
</table>

*¹ Dehydration time. ² Isolated yields referred to 1.

Table 2 summarizes the results of the one-pot synthesis of 1,4-dihydro-2-methyl-6-trifluoromethylpyridines (4) via the dehydration of the intermediate (3) by use of POCl₃/C₅H₅N-SiO₂ starting from 1. In every case, the desired dihydropyridines (4) were obtained in good to high yields. It is worthy to notice that reactive functional groups such as esters are found to be stable under the reaction conditions.

Scheme 2 shows a possible mechanism for the synthesis of 1,4-dihydro-2-methyl-6-trifluoromethylpyridines (4) via the dehydration of 3 by use of POCl₃/C₅H₅N-SiO₂. In the present conditions, most of 3 and POCl₃/C₅H₅N are presumably adsorbed on the silica surface although the latter would present as the coordinated pyridine complex in a solution. The first step involves the condensation of 3 in the liquid phase with POCl₃ activated by the silanol group. The resulting
intermediates (5) undergo the addition of the chlororide and the elimination of the phosphoric moiety, yielding the chlorination derivatives (6) along with HPO$_2$Cl$_2$. The dehydrochlorination of 6 provides the dihydropyridines (4). The adsorption of POCI$_3$ and HPO$_2$Cl$_2$ on SiO$_2$ can prevent the formation of by-products arising from the addition of these phosphoric compounds to 3, 4, 5, or 6.

Scheme 2
In conclusion, 1,4-dihydro-6-trifluoromethylpyridines have successfully been synthesized by use of phosphorus oxychloride/pyridine adsorbed on silica gel (POCl$_3$/C$_5$H$_5$N-SiO$_2$), which has been developed as an efficient reagent for the dehydration of α-trifluoromethyl alcohols. The significant advantages offered by this method are: (i) the reagent can be readily handled, (ii) the procedure does not require aqueous workup and large excess amount of dehydration reagent, (iii) it is compatible with a sensitive functional group. Thus, this method is expected to provide wide application in particular when the dehydration of α-trifluoromethyl alcohols is required in complex molecules containing sensitive functional groups.

**EXPERIMENTAL**

All the commercially available reagents were used without further purification. Melting points were measured with a Yanagimoto MP-S2 micro melting point apparatus and are uncorrected. Infrared (IR) spectra were measured with a Perkin Elmer FT-IR 1640 spectrometer. $^1$H NMR spectra were recorded with a JEOL α-400 spectrometer using tetramethylsilane (TMS) as an internal standard. $^{19}$F NMR spectra were obtained on the same apparatus using trifluoroacetic acid (TFA) as an external standard. Mass (MS) spectra (EI, 70 eV) were obtained on a Shimadzu QP-1000 spectrometer. Starting materials (1) were prepared by using the method described in our previous papers. Phosphorus oxychloride/pyridine adsorbed on silica gel (POCl$_3$/C$_5$H$_5$N-SiO$_2$) was prepared by the following our procedure.

**General Procedure for the Preparation of POCl$_3$/C$_5$H$_5$N-SiO$_2$:** To a solution of phosphorus oxychloride (3mL) and pyridine (6mL) in CH$_2$Cl$_2$ (50mL) was slowly added silica gel (Merck Art. 7734, 20 g) while being cooled. The mixture was stirred for 1 h at rt. After removal of the solvent, the residue was dried in a rotary evaporator over a period of several hours.

**General Procedure for the Synthesis of 1,4-Dihydro-6-trifluoromethyl-pyridines (4):** A solution of α-alkoxycarbonyl-α,β-unsaturated trifluoromethyl ketones (1) (1 mmol) and β-aminocrotonates (2) (1 mmol) in dichloroethane (4 mL) was refluxed for 2-3 h. Phosphorus oxychloride/pyridine adsorbed on silica gel (0.9 g; ca.1mmol based on POCl$_3$/C$_5$H$_5$N) was then added, and the mixture was 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$_2$Cl$_2$/CH$_3$CO$_2$Et (20/1) as an eluent. Spectral data of 4 are shown bellow.

**Diethyl 1,4-Dihydro-2-methyl-4-phenyl-6-(trifluoromethyl)pyridine-3,5-dicarboxylate (4a):** mp 111-112 °C (hexane/Et$_2$O); IR (Nujol) ν 3356, 1707 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ 1.21 (t, $J$ = 7.2 Hz, 6H), 2.39 (s, 3H), 4.12 (m, 4H), 5.05 (s, 1H), 6.05 (br s, 1H), 7.18-7.26 (m, 5H); $^{19}$F NMR (CDCl$_3$) δ 14.25 (s,
Diethyl 4-(2-Chlorophenyl)-1,4-dihydro-2-methyl-6-(trifluoromethyl)-pyridine-3,5-dicarboxylate (4b): mp 119-120 °C (hexane/ Et₂O); IR (Nujol) ν 3311, 1708 cm⁻¹; ¹H NMR (CDCl₃) δ 1.15 (t, J = 7.1 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H), 2.39 (s, 3H), 4.04 (m, 2H), 4.13 (m, 2H), 5.05 (s, 1H), 5.89 (br s, 1H), 7.12 (td, J = 7.7, 1.6 Hz, 1H), 7.20 (td, J = 7.7, 1.6 Hz, 1H), 7.28 (dd, J = 7.7, 1.6 Hz, 1H), 7.35 (dd, J = 7.7, 1.6 Hz, 1H); ¹⁹F NMR (CDCl₃) δ 13.28 (s, 3F); MS m/z (%) 383 (M⁺, 70), 324 (33), 322 (23).

3-Ethyl 5-Methyl 4-(2-Chlorophenyl)-1,4-dihydro-2-methyl-6-(trifluoromethyl)pyridine-3,5-dicarboxylate (4c): mp 116-117 °C (hexane/ Et₂O); IR (Nujol) ν 3381, 1703 cm⁻¹; ¹H NMR (CDCl₃) δ 1.15 (t, J = 7.1 Hz, 3H), 2.40 (s, 3H), 3.67 (s, 3H), 4.05 (m, 2H), 5.49 (s, 1H), 5.91 (br s, 1H), 7.12 (td, J = 7.7, 1.6 Hz, 1H), 7.20 (td, J = 7.7, 1.6 Hz, 1H), 7.29 (dd, J = 7.7, 1.6 Hz, 1H), 7.34 (dd, J = 7.7, 1.6 Hz, 1H); ¹⁹F NMR (CDCl₃) δ 13.28 (s, 3F); MS m/z (%) 403 (M⁺, 7), 374 (23), 292 (100), 244 (22). Anal. Calcd for C₁₉H₁₇NO₄ClF₃: C, 53.54; H, 4.24; N, 3.47. Found: C, 53.39; H, 4.14; N, 3.60.

Diethyl 1,4-Dihydro-2-methyl-6-[(2-trifluoromethyl)-phenyl]pyridine-3,5-dicarboxylate (4d): mp 95-96 °C (hexane/ Et₂O); IR (Nujol) ν 3315, 1703 cm⁻¹; ¹H NMR (CDCl₃) δ 1.08 (t, J = 7.2 Hz, 3H), 1.16 (t, J = 7.2 Hz, 3H), 2.42 (s, 3H), 3.96-4.13 (m, 4H), 5.41 (s, 1H), 5.78 (br s, 1H), 7.32-7.57 (m, 4H); ¹⁹F NMR (CDCl₃) δ 12.73 (s, 3F), 21.11 (s, 3F); MS m/z (%) 451 (M⁺, 9), 306 (100), 278 (20). Anal. Calcd for C₂₀H₁₉NO₄F₆: C, 52.22; H, 4.24; N, 3.10. Found: C, 52.85; H, 4.14; N, 3.15.

Diethyl 1,4-Dihydro-2-methyl-4-(2-nitrophenyl)-6-(trifluoromethyl)-pyridine-3,5-dicarboxylate (4e): mp 113-115 °C (hexane/ Et₂O); IR (Nujol) ν 3359, 1707 cm⁻¹; ¹H NMR (CDCl₃) δ 1.09 (t, J = 7.1 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H), 2.40 (s, 3H), 3.92-4.20 (m, 4H), 5.75 (s, 1H), 5.92 (br s, 1H), 7.32-7.78 (m, 4H); ¹⁹F NMR (CDCl₃) δ 12.87 (s, 3F); MS m/z (%) 428 (M⁺, 6), 411 (100), 352 (35), 338 (70), 322 (28). Anal. Calcd for C₁₉H₁₉N₂O₆F₃: C, 53.27; H, 4.47; N, 6.54. Found: C, 53.18; H, 4.37; N, 6.56.

5-Ethyl 3-Methyl 1,4-Dihydro-2-methyl-4-(2-nitrophenyl)-6-(trifluoromethyl)pyridine-3,5-dicarboxylate (4f): mp 127-128 °C (hexane/ i-Pr₂O); IR (Nujol) ν 3312, 1736 cm⁻¹; ¹H NMR (CDCl₃) δ 1.20 (t, J = 7.2 Hz, 3H), 2.39 (s, 3H), 3.53 (s, 3H), 3.53 (s, 3H), 4.10-4.22 (m, 2H), 5.68 (s, 1H), 5.90 (br s, 1H), 7.32-7.74 (m, 4H); ¹⁹F NMR (CDCl₃) δ 13.03 (s, 3F); MS m/z (%) 414 (M⁺, 5), 397 (100), 352 (28), 338 (70), 324 (33), 322 (23). Anal. Calcd for C₁₉H₁₇N₂O₆F₃: C, 52.18; H, 4.14; N, 6.76. Found: C, 51.89; H, 4.03; N, 6.71.
Diethyl 1,4-Dihydro-2-methyl-4-(3-nitrophenyl)-6-(trifluoromethyl)pyridine-3,5-dicarboxylate (4g): mp 103-104 °C (hexane/Et₂O); IR (Nujol) ν 3341, 1709 cm⁻¹; ¹H NMR (CDCl₃) δ 1.23 (t, J = 7.2 Hz, 6H), 2.44 (s, 3H), 4.07-4.20 (m, 4H), 5.17 (s, 1H), 6.23 (br s, 1H), 7.44 (t, J = 7.9 Hz, 1H), 7.63 (d, J = 7.9 Hz, 1H), 8.06-8.13 (m, 2H); ¹⁹F NMR (CDCl₃) δ 14.30 (s, 3F); MS m/z (%) 373 (M⁺, 4), 306 (100), 278 (21). Anal. Calcd for C₁₉H₁₉N₂O₆F₃: C, 53.27; H, 4.47; N, 6.54. Found: C, 53.07; H, 4.36; N, 6.54.

5-Ethyl 3-Methyl 1,4-Dihydro-2-methyl-4-(3-nitrophenyl)-6-(trifluoromethyl)pyridine-3,5-dicarboxylate (4h): mp 105-107 °C (hexane/Et₂O); IR (Nujol) ν 3365, 1709 cm⁻¹; ¹H NMR (CDCl₃) δ 1.24 (t, J = 7.1 Hz, 3H), 2.45 (s, 3H), 3.67 (s, 3H), 4.13-4.22 (m, 2H), 5.17 (s, 1H), 6.23 (br s, 1H), 7.45 (t, J = 7.9 Hz, 1H), 7.63 (d, J = 7.9 Hz, 1H), 8.06-8.12 (m, 2H); ¹⁹F NMR (CDCl₃) δ 14.35 (s, 3F); MS m/z (%) 414 (M⁺, 4), 292 (100), 264 (17), 196 (19). Anal. Calcd for C₁₈H₁₇N₂O₆F₃: C, 52.18; H, 4.14; N, 6.76. Found: C, 51.92; H, 4.01; N, 6.80.

Diethyl 1,4-Dihydro-2-methyl-4-(2-furyl)-6-(trifluoromethyl)pyridine-3,5-dicarboxylate (4i): mp 68-70 °C (hexane/Et₂O); IR (Nujol) ν 3339, 1703 cm⁻¹; ¹H NMR (CDCl₃) δ 1.26 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 2.39 (s, 3H), 4.12-4.25 (m, 4H), 5.23 (s, 1H), 6.03 (d, J = 2.8 Hz, 1H), 6.25 (br s, 1H), 6.25 (s, 1H), 7.26 (d, J = 2.8 Hz, 1H); ¹⁹F NMR (CDCl₃) δ 14.34 (s, 3F); MS m/z (%) 373 (M⁺, 21), 344 (20), 328 (22), 300 (100), 272 (20). Anal. Calcd for C₁₈H₁₇NO₅F₃: C, 54.69; H, 4.86; N, 3.75. Found: C, 54.44; H, 4.83; N, 3.76.

Diethyl 1,4-Dihydro-2-methyl-4-(2-thienyl)-6-(trifluoromethyl)pyridine-3,5-dicarboxylate (4j): mp 81-82 °C (hexane/Et₂O); IR (Nujol) ν 3344, 1690 cm⁻¹; ¹H NMR (CDCl₃) δ 1.28 (t, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H), 2.40 (s, 3H), 4.14-4.26 (m, 4H), 5.38 (s, 1H), 6.27 (br s, 1H), 6.83-6.84 (m, 1H), 6.88 (dd, J = 5.1, 3.7 Hz, 1H), 7.12 (dd, J = 5.1, 1.2 Hz, 1H); ¹⁹F NMR (CDCl₃) δ 14.38 (s, 3F); MS m/z (%) 389 (M⁺, 21), 360 (60), 343 (31), 320 (30), 316 (100), 306 (34), 288 (30), 204 (51), 111 (35). Anal. Calcd for C₁₈H₁₇NO₅F₃S: C, 52.44; H, 4.66; N, 3.60. Found: C, 52.29; H, 4.61; N, 3.66.

ACKNOWLEDGEMENTS

We are grateful to Osaka University for elemental analyses.

REFERENCES AND NOTES


9. A similar behavior is reported: strong acids are essential for the Biginelli synthesis of CF₃-containing dihydropyrimidine, see C. O. Kappe and S. F. Falsone, *Synlett*, 1998, 718.


