One-pot Preparation of 2,6-Disubstituted 4-(Trifluoromethyl)pyrimidines *via* the Tandem Cyclization, Dehydration, and Oxidation Reaction of α,β-Unsaturated Trifluoromethyl Ketones Using $POCl_3$-Pyridine-Silica Gel and MnO_2 Systems

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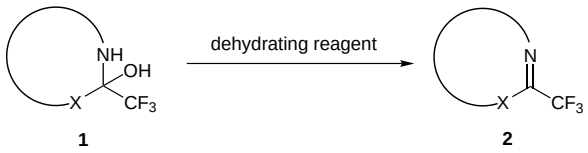
Abstract: The treatment of *α,β*-unsaturated trifluoromethyl ketones with amidines in acetonitrile gave the corresponding 4-hydroxy-4-(trifluoromethyl)-3,5,6-trihydropyrimidines, followed by successive dehydration with phosphorus oxychloride-pyridine-silica gel and oxidation with manganese(IV) oxide, producing 2,6-disubstituted 4-(trifluoromethyl)pyrimidines in good to excellent yields.

Key words: 4-(trifluoromethyl)pyrimidine, $POCl_3$-pyridine, silica gel, dehydration, oxidation

Trifluoromethylated nitrogen-containing heterocycles, such as pyridines, pyrimidines, pyrazoles, pyrroles, and related compounds, have gained much attention due to their versatile utility in agricultural and medicinal chemistries. In close connection with these circumstances, remarkable progress has been made in the development of a facile access to the trifluoromethylated aza-heterocycles using trifluoromethylated building blocks. However, few successful examples are known of the efficient dehydration from the α-trifluoromethylated α-hydroxy intermediate **1** under neutral or weakly basic conditions, which has formed by the reaction of α-trifluoromethylated ketones with various reagents, because of the potent electron withdrawing properties of the trifluoromethyl group (Scheme 1).

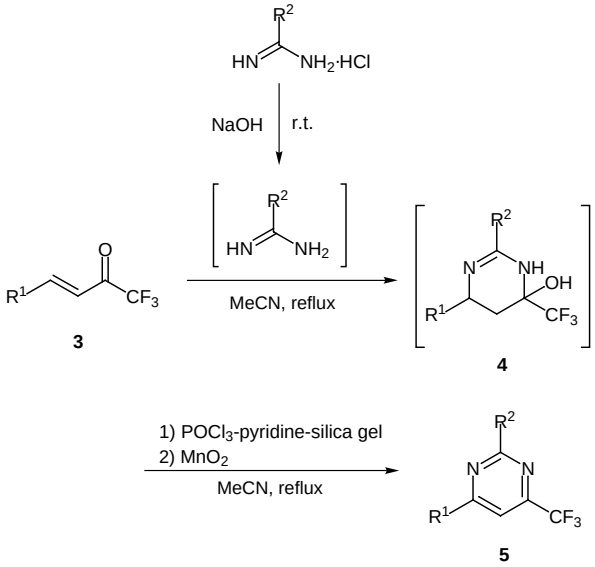


1 2

Scheme 1

During the course of our current studies on the synthesis of trifluoromethylated nitrogen-containing heterocycles, we have recently reported a facile route to the 2-(trifluoromethyl)-1,4-dihydro-, 2-(difluoromethyl)-, and 6-(trifluoromethyl)-pyridines *via* effective dehydration from **1** using phosphorus oxychloride (POCl)-pyridine-silica gel (SiO).

This communication discloses the one-pot preparation of 2,6-disubstituted 4-(trifluoromethyl)pyrimidines **5** by the reaction of β-substituted α,β-unsaturated trifluoromethyl ketones **3** with amidines, including the tandem efficient dehydration–oxidation reaction from the adducts **4** using this system (Scheme 2).



3 4 5

Scheme 2

The following procedure is representative of the one-pot condensation of trifluoromethyl ketone **3** with amidines. A suspension of benzamidine hydrochloride (1.0 mmol) and sodium hydroxide (NaOH) (1.1 mmol) in acetonitrile (MeCN) (3 ml) was stirred at room temperature for 1 h, then, to the mixture was slowly added ketone **3a** (1 mmol) at that temperature. After the mixture was refluxed for 3 h, POCl (4.0 mmol), pyridine (8.0 mmol), and SiO(Merck Art. 7734) (1.2 g) were sequentially introduced into the mixture at room temperature, then the resulting suspension was stirred at reflux temperature for 24 h. Manganese(IV) oxide (MnO) (1.4 g) was added to the suspension, and the mixture was refluxed for an additional 2.5 h. The entire mixture was concentrated under vacuum to give the residue, which was chromatographed on silica gel using hexane:benzene (1:2), producing the 2,6-diphenyl-4-(trifluoromethyl)pyrimidine (**5a**) (0.258 g) in 86% yield.

The results for the one-pot synthesis of 2,6-disubstituted 4-(trifluoromethyl)pyrimidines are summarized in Table 1.

Table 1. One-pot preparation of 4-trifluoromethylated pyrimidines **5**

Entry	R^1	R^2	Pyrimidine **5**	Yield[a](%) of **5**
1	Ph	Ph	**5a**	86
2	4-$MeOC_6H_4$	Ph	**5b**	75
3	4-MeC_6H_4	Ph	**5c**	63
4	4-ClC_6H_4	Ph	**5d**	71
5	4-$CF_3C_6H_4$	Ph	**5e**	79
6	4-$NO_2C_6H_4$	Ph	**5f**	40 (70)[b]
7	2-Thienyl	Ph	**5g**	67
8	2-Furyl	Ph	**5h**	69
9	*c*-Hex	Ph	**5i**	75
10	Ph	4-$MeOC_6H_4$	**5j**	63
11	Ph	4-MeC_6H_4	**5k**	65
12	Ph	4-ClC_6H_4	**5l**	50
13	Ph	4-$CF_3C_6H_4$	**5m**	61
14	Ph	Me	**5n**	9[c]

[a] Isolated yields. [b] Carried out at room temparture only in the preparation of **4**. [c] Determined by ^{19}F NMR.

Various aromatic (Entries 1-5 and 10-13), heteroaromatic (Entries 7 and 8), and aliphatic (Entry 9) ketones **3** react well with benzamidine hydrochloride to give the corresponding **5** in moderate to good yields. Unexpectedly, the reaction of **3f** did not proceed readily to give fair yields of **5f** under the usual conditions, being accompanied by unidentified products, which could be improved by lowering the reaction temperature in the preparation of **4** from **3** (Entry 6). Other aromatic amidines smoothly underwent the condensation reaction affording good yields of **5** (Entries 10-13). The reaction of acetamidine hydrochloride, unfortunately, provided an unsatisfactory result, probably due to its high basicity or low stability, and the yield was not increased at all in spite of the reaction conditions being varied (Entry 14).

In summary, we demonstrated an effective dehydration of the 4-hydroxy-4-(trifluoromethyl)-3,5,6-trihydropyrimidines, which were formed by the reaction of α,β-unsaturated trifluoromethyl ketones with amidines, by the POCl-pyridine-SiO system, and the successive oxidation of the formed dehydrated products in the presence of MnO leading to the corresponding 2,6-disubstituted 4-(trifluoromethyl)pyrimidines in good yields. The present one-pot reaction can serve as a convenient and alternative method for the synthesis of 2,6-disubstituted 4-(trifluoromethyl)pyrimidines.

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(8) For the preparation of 4-hydroxy-2,6-diphenyl-4-(trifluoromethyl)-3,5,6-trihydropyrimidines **4a** from the *α,β*-unsaturated trifluoromethyl ketone **3a**, potassium *t*-butoxide (*t*-BuOK), Na_2CO_3, and triethylamine were not suitable, and the yield of **4a** became low (4-18%).

(9) After quenching, extraction, drying, concentration, column chromatography (hexane:EtOAc=1:1), and recrystallization, the major isomer of 4-hydroxy-2,6-diphenyl-4-(trifluoromethyl)-3,5,6-trihydropyrimidine (**4a**) was obtained in 86% yield. The data for the major isomer of **4a** are as follows: Mp 204-206 °C; IR (KBr) 3392 (NH), 3062 (OH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 1.84 (dd, *J* = 13.0, 12.7 Hz, 1H), 2.30 (dd, *J* = 13.0, 3.9 Hz, 1H), 3.76 (br s, 1H), 4.57 (dd, *J* = 12.7, 3.9 Hz, 1H), 5.59 (br s, 1H), 7.35-7.52 (m, 8H), 7.74-7.76 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$, ext. CF_3COOH) δ -7.68 (s, 3F); MS (EI) *m/z* (rel intensity) 320 (M^+; 12), 251 (58), 121 (17), 104 (100).

(10) In the absence of SiO_2, the reaction did not cleanly proceed to give the product **3a** in less than 70% yield, together with some unidentified products in the TLC monitoring. At present, although the exact role of SiO_2 is not clear, the absorption of reagents onto the surface of SiO_2 may be crucial for the efficiency of the reaction. Further studies on the mechanistic aspects for the part of SiO_2 are now in progress. For recent reviews of organic reactions in the presence of SiO_2, see: Nishiguchi, T. *J. Synth. Org. Chem. Jpn.* **1993**, *51*, 308, and references cited therein. For recent reports, see: Ogawa, H.; Amano, M.; Chihara, T. *Chem. Commun.* **1998**, 495. Chisem. I. C.; Rafelt, J.; Shieh, M. T.; Chisem, J.; Clark, J. H.; Jachuck, R.; Macqarrie, D.; Ramshaw, C.; Scott, K. *Chem. Commun.* **1998**, 1949. Braga, A. L.; Rodrigues, O. E. D.; Avila, E. D.; Silveira, C. C. *Tetrahedron Lett.* **1998**, *39*, 3395. Chandrasekhar, S.; Ramachander, T.; Takhi, M. *Tetrahedron Lett.* **1998**, *39*, 3263. Macquarrie, D. J. *Tetrahedron Lett.* **1998**, *39*, 4125. Kotsuki, H.; Shimanouchi, T.; Ohshima, R.; Fujiwara, S. *Tetrahedron* **1998**, *54*, 2709. Li, T.; Wang, J. –X.; Zheng, X. –J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3975. Ranu, B. C.; Sakar, A.; Majee, A. *J. Org. Chem.* **1997**, *62*, 1841. Kotsuki, H.; Arimura, K. *Tetrahedron Lett.* **1997**, *38*, 7583. Varma, R. S.; Dahiya, R.; Saini, R. K. *Tetrahedron Lett.* **1997**, *38*, 8819.

(11) MnO_2 was purchased from Nacarai Tesque, Inc. *N*-Bromosuccinimide (NBS) (1 equiv.) was also effective for the oxidation.

(12) All compounds gave satisfactorily analytical data. Selected data for **5**: **2,6-Diphenyl-4-(trifluoromethyl)pyrimidine *(5a)***: Mp 83-84 °C; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 7.52-7.60 (m, 6H), 7.90 (s, 1H), 8.26-8.29 (m, 2H), 8.63-8.65 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$, ext. CF_3COOH) δ 7.76 (s, 3F); MS (EI) *m/z* (rel intensity) 300 (M^+; 100), 128 (79), 103 (48).
6-(4-Methoxyphenyl)-2-phenyl-4-(trifluoromethyl)-pyrimidine *(5b)*: Mp 120-121 °C; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 3.91 (s, 3H), 7.07 and 8.26 (AB quartet, *J* = 9.0 Hz, 4H), 7.52-7.55 (m, 3H), 7.82 (s, 1H), 8.61-8.63 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$, ext. CF_3COOH) δ 7.62 (s, 3F); MS (EI) *m/z* (rel intensity) 330 (M^+; 100), 128 (24), 102 (18), 90 (15).
2-(4-Methoxyphenyl)-6-phenyl-4-(trifluoromethyl)-pyrimidine *(5j)*: Mp 85-86 °C; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 3.91 (s, 3H), 7.04 and 8.60 (AB quartet, *J* = 8.8 Hz, 4H), 7.55-7.58 (m, 3H), 7.82 (s, 1H), 8.24-8.27 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$, ext. CF_3COOH) δ 7.68 (s, 3F); MS (EI) *m/z* (rel intensity) 330 (M^+; 100), 128 (36), 103 (29).

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