A CONVENIENT AND FACILE SYNTHESIS OF 3-TRIFLUOROMETHYL-1,2,5-OXADIAZOLES WITH THE USE OF SILICA GEL AS AN EFFECTIVE CATALYST

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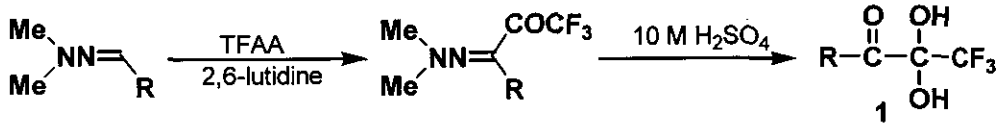
Abstract - Silica gel catalyzed intramolecular dehydration of 1,1,1-trifluoroalkane-2,3-dione dioximes (**2**) afforded 3-trifluoromethyl-1,2,5-oxadiazoles (**3**) in satisfactory yields.

Introduction of fluorine or trifluoromethyl substituents into heterocyclic ring systems is one of the attractive theme for many organic chemists because of potentially high biological activities[1] expected for fluorine-containing heterocyclic compounds. Mono- and disubstituted 1,2,5-oxadiazoles, often refered to by their trivial name furazan, have long been known and some of them show remarkable pharmaceutical activities,[2] *such as antibacterial*[3] *and anthelmintic*[4] *activities, etc.* However there has been no report for synthesis of those bearing trifluoromethyl group(s). This prompted us to try a synthesis of 3-trifluoromethyl-1,2,5-oxadiazoles (**3**) from 1,1,1-trifluoroalkane-2,3-dione monohydrates (**1**) *via* their dioximes (**2**). Now I wish to report the results.

Trifluoroacetylation of aldehyde dimethylhydrazones with the use of TFAA gave 3-dimethylhydrazono-1,1,1-trifluoroalkan-2-ones, which were hydrolyzed with hot (70℃) 10M H_2SO_4 affording **1**.[5] Thus obtained diketone monohydrates (**1**) being treated with hydroxylamine hydrochloride in the presence of pyridine afforded the corresponding dioximes (**2**), quantitatively.



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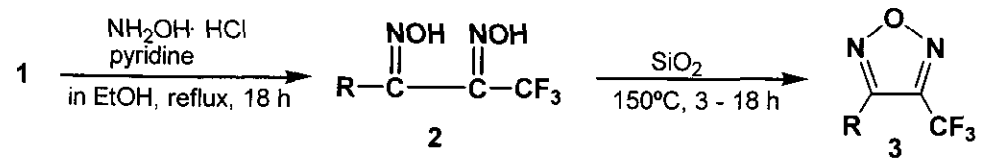
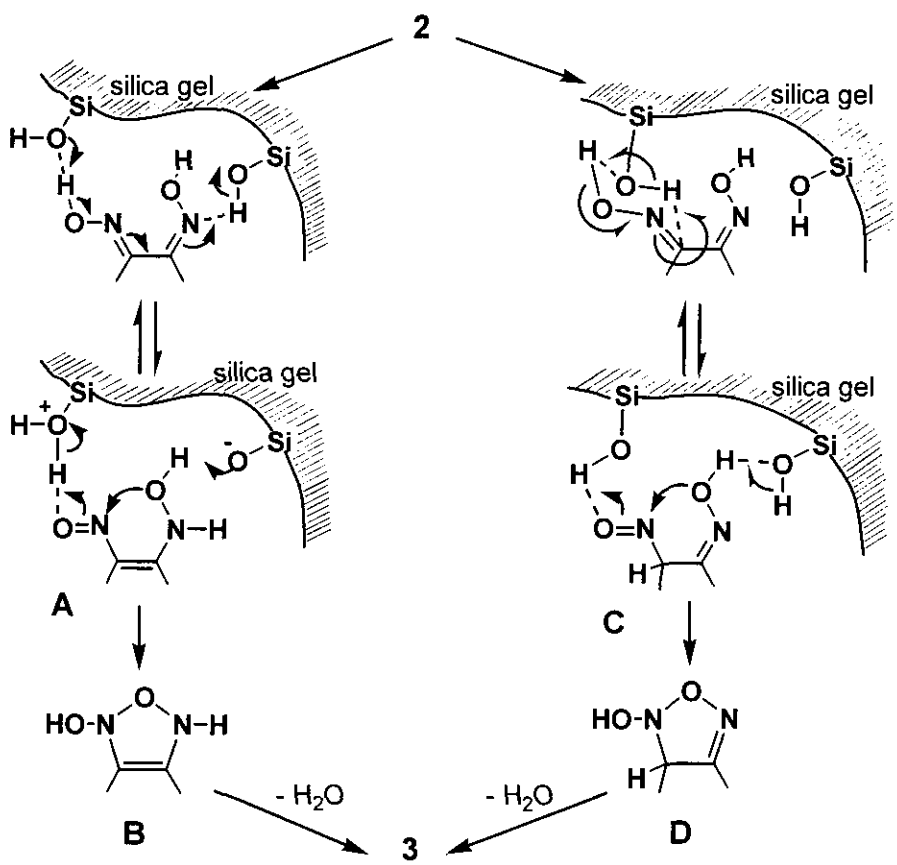
To a solution of **2** (R= *p*-Tol) in CH_2Cl_2 was added silica gel. The mixture was well stirred and evaporated to dryness under reduced pressure, and residual powder was heated at *150℃ for 18 h* under N_2. The reaction mixture was extracted with Et_2O and removal of the solvent from the extract afforded crude **3** (R= *p*-Tol). After purification by silica gel column chromatography, pure **3** was obtained in



47% yield. When R is electron withdrawing p-$O_2NC_6H_4$, conversion of **2** to **3** proceeded more smoothly. The reaction completed within 3 h and the corresponding **3** (R= p-$O_2NC_6H_4$) was obtained in 77% yield. In the absence of silica gel, no **3** was obtained in both cases.

In general, 1,2,5-oxadiazoles can be prepared by heating the corresponding dioximes in aqueous neutral or basic solvent, or in the presence of carboxylic acid anhydrides as a dehydrating agent.[2,6] Cyclization from the corresponding dioxime diacetates is also an useful method to prepare them.[2,7] However these procedures resulted in formation of none or trace amounts of **3** from **2** together with many tarry materials in any cases. After several trials, we found that silica gel acts as a effective catalyst for this cyclization reaction.

The structure of **3** was confirmed on the basis of ^1H and ^{13}C NMR, and IR spectra and micro combustion analysis. In ^{13}C NMR spectra, oxadiazole ring carbon atoms of **3** (R= p-Tol) appear at 145.7 and 152.7



Scheme 1

ppm as a qualtet ($^2J_{CF}$=39.3Hz) and a singlet, respectively.

As a mechanism for the present cyclization reaction from **2** to **3**, two routes as illustrated in Scheme 1 should be possible. In both cases, cooparative interaction between **2** and silanol groups on silica gel surface is thought to assist the cyclization reaction from **2** to intermediate (**B**) or (**D**) effectively. Unfortunately such intermediates could not be detected throughout our controlled experiments even at lower temperatures in spite of our careful inspection of the reaction mixtures. Dehydration process from **B** or **D** to aromatic **3** could be catalyzed by silica gel.[8] These may be easier processes than those from **A** to **B** and **C** to **D**. In other words, the process from **A** to **B** or **C** to **D** is probably the rate-determining step for the series of processes in Scheme 1. Electron withdrawing *p*-nitrophenyl group instead of *p*-tolyl group on **2** should affect advantageously for the nucleophilic attack of hydroxy group toward nitroso group in this step and, consequently, accelerate the overall reaction.

Mechanistic studies and physiological activity tests for the synthesized oxadiazoles, **3** are now in progress.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded at 60 MHz on a JEOL PMX 60SI and at 59.5 MHz on a Bruker AC250, respectively. IR spectra were taken with a Hitachi model G3.

General procedure for preparation of 1,1,1-trifluoroalkane-2,3-dione dioximes (2).

To a solution of 1,1,1-trifluoroalkane-2,3-diones (**1**, 5 mmol) and hydroxylamine hydrochloride (1.390 g, 20 mmol) in EtOH (20 mL) was added pyridine (5.933 g, 75 mmol), and the mixture was stirred for 18 h under reflux. The reaction mixture was pored onto CH_2Cl_2 (100 mL), and the whole mixture was washed with 1 N HCl (100 mL) and subsequently with 1 N aq. Na_2CO_3 (100 mL). After drying the mixture over $MgSO_4$, the solvent was removed under reduced pressure affording 1,1,1-trifluoroalkane-2,3-dione dioximes (**2**), which were used for the next reaction without farther purification. Purification by preparative TLC (*n*-hexane / CCl_4 = 4 / 1) gave pure **2** in 71 % (R= *p*-Tol) and 88 % (R= *p*-$O_2NC_6H_4$) yields.

2 (R= *p*-Tol): syrupy oil: ^{13}C NMR ($CDCl_3$ / TMS) δ 21.3 (Me), 119.1 ($^1J_{CF}$=281.8 Hz, CF_3), 129.0, 129.7, 130.4, 140.7 (Ar), 144.2 ($^2J_{CF}$=29.8 Hz, N=**C**-CF_3), 148.6 (N=**C**-Ar); ^{1}H NMR ($CDCl_3$ / TMS) δ 2.32 (s, 3H, Me), 4.47 (s, 2H, OH), 6.95 - 7.56 (AA'BB'q, *J*=8 Hz, 4H, ArH); IR (KBr) 2500 - 3675 (br), 1600 (m), 1395 (m), 1340 (m), 1250 (m), 1170 (s), 1135 (s), 985 (s), 870 (m) cm^{-1}.

2 (R= *p*-$O_2NC_6H_4$): syrupy oil: ^{1}H NMR ($CDCl_3$ / TMS) δ 7.45 -8.20 (br and AA'BB'q, *J*=8 Hz, 6H, OH and ArH).

General procedure for preparation of 3-trifluoromethyl-1,2,5-oxadiazoles (3) from 2.

To a solution of **2** (0.5 mmol) in CH_2Cl_2 (10 mL) was added silica gel (1.23 g, commercial grade silica

gel: Wakogel C-300 was dried at 150 - 170℃/ 0.1 mmHg for 3 h before use). The mixture was well stirred and evaporated to dryness under reduced pressure, and residual powder was heated at 150℃ for 18 h under N_2. The reaction mixture was extracted with Et_2O (100 mL) and removal of the solvent from the extract afforded crude **3**. After purification by silica gel column chromatography (*n*-hexane / benzene = 3 / 2), pure **3** was obtained in 47% (R= *p*-Tol) and 77 % (R= *p*-$O_2NC_6H_4$) yields.

3-Trifluoromethyl-4-(*p*-tolyl)-1,2,5-oxadiazoles, (**3**, R= *p*-Tol): colorless oil, bp 80℃/10 torr (oven temperature of Kugelrohr): ^{13}C NMR ($CDCl_3$ / TMS) δ 21.5 (Me), 119.4 ($^1J_{CF}$=271.4 Hz, CF_3), 120.4, 128.6, 130.0, 142.1 (Ar), 145.7 ($^2J_{CF}$=39.3 Hz, N=**C**-CF_3), 152.7 (N=**C**-Ar); ^1H NMR ($CDCl_3$ / TMS) δ 2.42 (s, 3H, Me), 7.16 - 7.72 (AA'BB'q, *J*=8 Hz, 4H, ArH); IR (KBr) 1470 (m), 1325 (m), 1200 (m), 1155 (s), 1140 (s), 1015 (m) cm^{-1}. Anal. Calcd for $C_{10}H_7N_2OF_3$: C, 52.64; H, 3.09; N, 12.28. Found: C, 53.09; H, 3.08; N, 12.12.

3-Trifluoromethyl-4-(*p*-nitrophenyl)-1,2,5-oxadiazoles, (**3**, R= *p*-$O_2NC_6H_4$): pale yellow oil, bp 80℃/ 5 torr (oven temperature of Kugelrohr): ^1H NMR ($CDCl_3$ / TMS) δ 8.37, 8.85 (d, d, *J*=9 Hz, 4H, ArH); IR (KBr) 1560 (m), 1525 (s), 1340 (s), 1315 (m), 1190 (s), 1160 (s), 1135 (s), 1010 (m), 990 (m), 900 (m), 850 (m) cm^{-1}. Anal. Calcd for $C_9H_4N_3O_3F_3$: C, 41.71; H, 1.56; N, 16.21. Found: C, 41.97; H, 1.47; N, 16.41.

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