A Convenient Synthesis of 4-Trifluoromethyl-4*H*-[1,5,2]dioxazines and 4-Trifluoromethyl-6*H*-[1,2,5]oxadiazines

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1,1,1-Trifluoroalkane-2,3-dione 3-oximes **1** easily obtainable from aldehyde dimethylhydrazones were reacted with several aldehydes and ketones in the presence of acetic acid to afford 4-trifluoromethyl-4*H*-[1,5,2]dioxadines **3** in satisfactory yields. When the reaction was carried out in the presence of ammonium acetate, 4-trifluoromethyl-6*H*-[1,2,5]oxadiazines were obtained in good yields.

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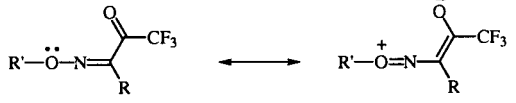
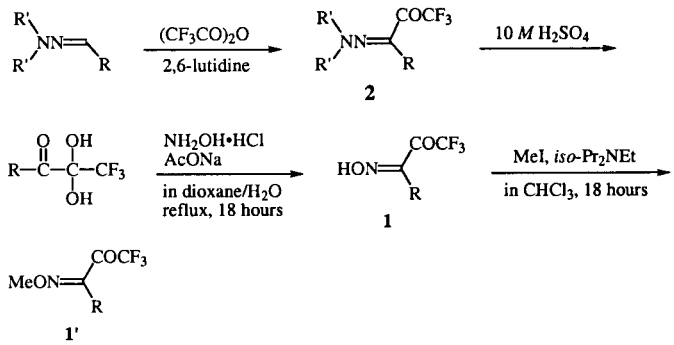
Fluorine-containing heterocycles are very attractive targets for synthetic organic chemists because of their potentially high biological activities [1-4]. So far, we reported a series of synthetic methods to prepare a variety of fluorine-containing heterocycles starting from 3-dialkylhydrazono-1,1,1-trifluoroalkan-2-ones **2** which are easily obtainable from aldehyde dialkylhydrazones and trifluoroacetic anhydride. For instance, fluorine-containing imidazoles [5], pyrazoles [6], oxadiazines [7], and so on [8,9] are conveniently obtainable by interesting cyclization reactions of **2** under a variety of conditions. Also, 3-hydrazono-1,1,1-trifluoroalkan-2-ones **2** (R = R' = H) are useful precursors for preparation of several fluorine-containing heterocycles [10]. In the course of these investigations, we were very interested in 1,1,1-trifluoroalkane-2,3-dione 3-oximes **1** and their methyl ethers **1'**, because electronic structures, and possibly chemical properties of **1** (as well as their methyl ethers **1'**) and hydrazones **2** should resemble each other; therefore, **1** and **1'** may undergo a variety of reactions to afford several fluorine-containing heterocycles similar to the cases of hydrazones **2**. These situations prompted us to try synthesis of oximes **1** and their methyl ethers **1'**.



1 R' = H
1' R' = Me

2 R' = H or Me

According to an usual manner [11], aldehyde dimethylhydrazones treated with trifluoroacetic anhydride gave 3-dimethylhydrazono-1,1,1-trifluoroalkan-2-ones **2**, (R = R' = CH_3), which were hydrolyzed with hot 10 *M* sulfuric acid to afford 1,1,1-trifluoroalkane-2,3-diones as monohydrates. Diketones thus obtained were treated with hydroxylamine hydrochloride in the presence of sodium acetate. With the use of dioxane/water (2:1) as solvent, reaction carried out under reflux conditions for 18 hours gave the corresponding monooximes **1** [12] quantitatively. In the presence of diisopropylethylamine, oximes **1**, (R = *p*-Tol) dissolved in dichloromethane was reacted with methyl iodide to afford the corresponding methyl ether **1'** in 63% yield. In order to prepare **1'** more easily, we also attempted trifluoroacetylation of oximemethyl ether of *p*-tolualdehyde, the aza analogue of methylenol ether of 2-(*p*-tolyl)acetoaldehyde, under various conditions. However all of our attempts resulted in failure, and we could not obtain oximemethyl ether **1'** in any case. Different from the case of aldehyde dimethylhydrazones [11], reactivity of an azomethyne carbon atom in aldehyde oximemethyl ethers should not be sufficient to promote such an electrophilic substitution reaction at azomethyne carbon atom by trifluoroacetic anhydride.

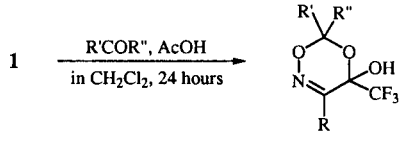


To elucidate the chemical properties of oximemethyl ether **1'**, we examined several reactions of **1'** under a variety of conditions which were employed for conversions of the corresponding dimethylhydrazone **2** (R' = R" = CH_3, R = *p*-Tol) into a series of fluorine-containing heterocycles [5-9]. In any case, however, no heterocycles could be obtained and these reactions gave complicated mixtures of unidentified materials or unchanged **1'** in some cases.

Thus the chemical properties of oximemethyl ether **1'** were found to be significantly different from those of dimethylhydrazone **2**.

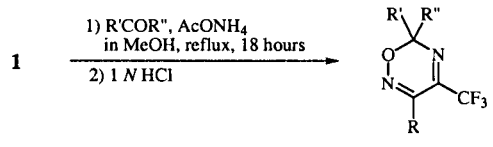
In contrast, oximes **1** were found to react successfully with various aldehydes and ketones in the presence of acetic acid to afford the corresponding 4-trifluoromethyl-4*H*-[1,5,2]dioxazine in sufficient yields (Scheme 1). For instance, the reaction of **1** (R = *p*-Tol) and isobutylaldehyde completed within 24 hours to afford 6-(*iso*-propyl)-3-(*p*-tolyl)-4-trifluoromethyl-4*H*-[1,5,2]dioxazin-4-ol (**3b**) in 69% yield. On the other hand, oximes **1** reacted with ketones more sluggishly. Thus both 3 molar amounts of acetone and acetic acid in addition to longer reaction time (20 days) were necessary for complete conversion of **1** (R = *p*-Tol) to the corresponding dioxazine **3e**. Alternatively **3e** could be obtained (62%) when **1** dissolved in large exess of acetone was reacted at 50° for 5 days in the presence of trifluoroacetic acid.

Scheme 1



R	R'	R"	3	Yield (%)
p-Tol	Et	H	**3a**	65
p-Tol	*iso*-Pr	H	**3b**	69
p-Tol	*p*-Tol	H	**3c**	47
n-C_6H_{13}	Et	H	**3d**	64
p-Tol	Me	Me	**3e**	61

We also examined a synthesis of oxadiazine derivatives from oximes **1**. In the presence of ammonium acetate, **1** (R = *p*-Tol) reacted with 3 molar amounts of cyclohexanone in refluxing methanol. This reaction proceeded more smoothly compared to above reaction of **1** (R = *p*-Tol) to dioxazine. After treatment with 1 *N* hydrochloric acid 4-trifluoromethyl-6*H*-[1,2,5]oxadiazine (**4**) was obtained in 92% yield. On the contrary, attempted reactions of oximes **1** with the use of aldehydes instead of ketones afforded no oxadiazines.



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R = *p*-Tol
R', R" = -$(CH_2)_5$-

In conclusion, we can present a convenient synthetic method to prepare 4-trifluoromethyl-4*H*-[1,5,2]dioxazines **3** and 4-trifluoromethyl-6*H*-[1,2,5]oxadiazines **4** starting from aldehyde dimethylhydrazones. Continuous examinations in order to synthesize fluorine-containing heterocycles starting from oximemethyl ether **1'**, and biological activity tests for those newly synthesized dioxazines **3** and oxadiazines **4** are now in progress.

EXPERIMENTAL

Melting points were determined with a Mitamura Riken model 7-12 apparatus and uncorrected. The ^1H 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. Unless otherwise noted nmr spectra were measured in deuteriochloroform containing tetramethylsilane as an internal standard. The ir spectra were taken with a Hitachi model G3. 3-Dimethylhydrazono-1,1,1-trifluoroalkan-2-ones **2** (R = R' = Me) and 1,1,1-trifluoroalkane-2,3-diones were prepared according to a literature method [11].

1,1,1-Trifluoroalkane-2,3-dione 3-Oximes **1**.

General Procedure.

A mixture of 1,1,1-trifluoroalkane-2,3-diones (10 mmoles), hydroxylamine hydrochloride (764.4 mg, 11 mmoles), and sodium acetate (902.3 mg, 11 mmoles) in 30 ml of dioxane/water (2:1) was stirred for 18 hours under reflux conditions. The reaction mixture was poured into dichloromethane (150 ml), and the whole mixture was washed with 0.5 *N* aqueous sodium bicarbonate (100 ml) and dried over sodium sulfate. Removal of the solvent gave the corresponding 1,1,1-trifluoroalkane-2,3-dione 3-oximes **1** quantitatively. Without further purification these monooximes **1** were used for the following reactions.

3-(*p*-Tolyl)-1,1,1-trifluoropropane-2,3-dione 3-Oximemethyl Ether (**1'**).

A mixture of **1** (R = *p*-Tol, 462.3 mg, 2 mmoles), diisopropylethylamine (775.5 mg, 6 mmoles), and methyl iodide (567.8 mg, 4 mmoles) dissolved in chloroform (2 ml) was stirred for 18 hours. The reaction mixture was poured into dichloromethane (100 ml) and the whole mixture was washed with 1*N* hydrochloric acid (100 ml), subsequently with water, and finally with saturated aqueous sodium carbonate (50 ml). After removal of the solvent the residue was column chromatographed on to silica gel using *n*-hexane/benzene (1:1) as the eluent to yield 309.7 mg (63%) of 3-(*p*-tolyl)-1,1,1-trifluoropropane-2,3-dione 3-oximemethyl ether (**1'**) as pale yellow oil, bp 100°C/4 Torr (oven temperature of Kugelrohr distillation), ^{13}C nmr: δ 21.4 (CH_3), 64.8 (OCH_3) 116.5 ($^1J_{CF}$ = 290.7 Hz, CF_3), 123.9 (C1' of *p*-Tol), 128.9, 129.3 (C2', C3', C5', and C6' of *p*-Tol), 140.6 (C4' of *p*-Tol), 150.9 (C=N), 178.4 ($^2J_{CF}$ = 35.3 Hz, C=O); ^1H nmr (carbon tetrachloride): δ 2.23 (s, 3H, CH_3), 4.07 (OCH_3), 7.10 (s, 4H, aryl).

Anal. Calcd. for $C_{11}H_{10}NO_2F_3$: C, 53.88; H, 4.11; N, 5.71. Found: C, 54.27; H, 4.01; N, 6.10.

4-Trifluoromethyl-4*H*-[1,5,2]dioxazines **3a-d**.

General Procedure.

A mixture of **1** (1 mmole), aldehyde (1.3 mmoles), and acetic acid (60.1 mg, 1 mmole) dissolved in dichloromethane (5 ml) was stirred for 24 hours. The reaction mixture was washed with

0.5 *N* aqueous sodium bicarbonate (100 ml) and dried over sodium sulfate. Removal of the solvent afforded 4-trifluoromethyl-4*H*-[1,5,2]dioxazines **3a-d**.

6-Ethyl-3-(*p*-tolyl)-4-trifluoromethyl-4*H*-[1,5,2]dioxazin-4-ol (**3a**).

This compound was obtained as colorless crystals (carbon tetrachloride), mp 118-119°, ^{13}C nmr: δ 7.5, 7.6 (CH_3CH_2), 21.7 ($ArCH_3$) 25.8, 26.0 (CH_3CH_2), 99.6, 100.5 (C6), 103.9 ($^2J_{CF}$ = 36.1 Hz, C4), 120.9, 121.9 ($^1J_{CF}$ = 286.0 Hz and 289.0 Hz, respectively, CF_3), 120.9, 121.7 (C1' of *p*-Tol), 128.1, 128.7, 129.1, 129.3 (C2', C3', C5', and C6' of *p*-Tol), 135.4, 133.5 (C3), 142.5, 143.1 (C4' of *p*-Tol); ^1H nmr: δ 0.80, 0.87 (t, *J* = 7.0 Hz, 3H, CH_3CH_2), 1.42-2.28 (m, 2H, CH_3CH_2), 2.31, 2.35 (s, 3H, $ArCH_3$), 4.70, 5.33 (t, *J* = 4.0 Hz, 1H, CH), 6.40-6.60 (br, 1H, OH), 7.07, 7.15 (d, *J* = 8.0 Hz, 2H, aryl), 8.05, 8.18 (d, *J* = 8.0 Hz, 2H, aryl); ir (potassium bromide): ν 2275-3550 (OH), 1185, 1153 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{13}H_{14}NO_3F_3$: C, 53.98; H, 4.88; N, 4.84. Found: C, 53.90; H, 5.13; N, 4.84.

6-(*iso*-Propyl)-3-(*p*-tolyl)-4-trifluoromethyl-4*H*-[1,5,2]dioxazin-4-ol (**3b**).

This compound was obtained as colorless crystals (cyclohexane): mp 177-179°, ^{13}C nmr: δ 13.0, 13.2, 16.8, 17.2 (CH_3CH), 21.8, 21.7 ($ArCH_3$), 29.6, 29.7 (CH_3CH), 100.9, 103.3 (C6), 103.3, 103.6 ($^2J_{CF}$ = 35.7 Hz, C4), 120.8, 121.9 ($^1J_{CF}$ = 285.4 Hz CF_3), 120.6, 121.7 (C1' of *p*-Tol), 127.8, 128.7, 129.1, 129.4 (C2', C3', C5', and C6' of *p*-Tol), 132.3, 136.6 (C3), 142.2, 143.2 (C4' of *p*-Tol); ^1H nmr: δ 0.73 (d, *J* = 7.0 Hz, 6H, CH_3CH), 1.74-2.64 (br, 1H, CH_3CH), 2.40 (s, 3H, $ArCH_3$), 4.13-4.34 (br, 1H, CH), 6.77-7.54 (br, 1H, OH), 7.22 (d, *J* = 8.0 Hz, 2H, aryl), 8.06 (d, *J* = 8.0 Hz, 2H, aryl); ir (potassium bromide): ν 2600-3600 (OH), 1192, 1161 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{14}H_{16}NO_3F_3$: C, 55.45; H, 5.32; N, 4.62. Found: C, 55.19; H, 5.16; N, 4.76.

3,6-Di-(*p*-tolyl)-4-trifluoromethyl-4*H*-[1,5,2]dioxazin-4-ol (**3c**).

This compound was obtained as colorless crystals (carbon tetrachloride), mp 177-179°, ^1H nmr (d_4-methanol): δ 2.30 (s, 6H, $ArCH_3$), 6.10, 6.23 (s, 1H, CH), 6.80-7.43 (AA'BB'q and d, 6H aryl), 7.93, 8.23 (d, *J* = 8.0 Hz, 2H, aryl); ir (potassium bromide): ν 2275-3675 (OH), 1191, 1142 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{18}H_{16}NO_3F_3$: C, 61.54; H, 4.59; N, 3.99. Found: C, 60.88; H, 4.77; N, 4.07.

6-Ethyl-3-(*n*-hexyl)-4-trifluoromethyl-4*H*-[1,5,2]dioxazin-4-ol (**3d**).

This compound was obtained as pale yellow syrupy oil; ^1H nmr: δ 0.57-2.71, 0.93, and 1.95 (m, t, and q, *J* = 5.5 Hz, 18H, n-C_6H_{13}, CH_3CH_2 and CH_3CH_2), 5.30 (t, *J* = 4.0 Hz, 1H, CH), 6.50-7.10 (br, 1H, OH); ir (potassium bromide): ν 2280-3490 (OH), 1181, 1119 (CF_3) cm^{-1}.

6,6-Dimethyl-3-(*p*-tolyl)-4-trifluoromethyl-4*H*-[1,5,2]dioxazin-4-ol (**3e**).

A mixture of **1** (R = *p*-Tol, 231.2 mg, 1 mmole), acetone (174.2 mg, 3 mmoles), and acetic acid (180.2 mg, 3 mmoles) dissolved in dichloromethane (5 ml) was stirred for 20 days. The reaction mixture was poured into dichloromethane (50 ml), and the mixture was washed with 0.5 *N* aqueous sodium bicarbonate (100 ml) and dried over sodium sulfate. Removal of the solvent and fractionation of the residual materials by preparative tlc (dichloromethane) gave 176.4 mg (61%) of 6,6-dimethyl-3-(*p*-tolyl)-4-trifluoromethyl-4*H*-[1,5,2]dioxazin-4-ol (**3e**).

Alternative Procedure.

To a solution of **1** (R = *p*-Tol, 231.2 mg, 1 mmole) in acetone (5 ml) was added trifluoroacetic acid (342.1 mg, 3 mmoles), and the mixture was stirred at 50° for 5 days. The reaction mixture was poured into dichloromethane (100 ml), and the whole mixture was washed with 0.5 *N* aqueous sodium bicarbonate (100 ml) and dried over sodium sulfate. Removal of the solvent and fractionation of the residual materials by preparative tlc (dichloromethane) gave 179.3 mg (62%) of **3e** as colorless crystals, mp 134-135° (benzene): ^{13}C nmr: δ 21.6 ($ArCH_3$), 25.7, 27.1 ($C6CH_3$), 103.5 ($^2J_{CF}$ = 35.2 Hz, C4), 105.5 (C6), 122.7 ($^1J_{CF}$ = 286.8 Hz, CF_3), 123.9 (C1' of *p*-Tol), 128.9 (C3), 128.2, 129.5 (C2', C3', C5', and C6' of *p*-Tol), 141.8 (C4' of *p*-Tol); ^1H nmr: δ 1.64 (s, 6H, $C6CH_3$) 2.30 (s, 3H, $ArCH_3$), 6.97 and 6.50-7.20 (d and br, 3H, aryl and OH), 7.95 (d, *J* = 8.0 Hz, 2H, aryl); ir (potassium bromide): ν 2200-3570 (OH), 1170, 1135 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{13}H_{14}NO_3F_3$: C, 53.98; H, 4.88; N, 4.84. Found: C, 53.93; H, 4.93; N, 4.82.

4-Trifluoromethyl-6*H*-[1,2,5]oxadiazine (4-Trifluoromethyl-1-oxa-2,5-diazaspiro[5.5]undeca-2,4-diene, **4**).

To a mixture of **1** (R = *p*-Tol, 462.3 mg, 2 mmoles) and $AcONH_4$ (462.5 mg, 6 mmoles) dissolved in methanol (10 ml) was added cyclohexanone (588.8 mg, 6 mmoles). The mixture was stirred for 18 hours under reflux conditions and then, the reaction mixture was poured into dichloromethane (100 ml). The whole mixture was washed with 1 *N* hydrochloric acid (100 ml) and subsequently with 0.5 *N* aqueous sodium carbonate (100 ml), and dried over sodium sulfate. After removal of the solvent the residue was submitted to silica gel column chromatography using benzene/dichloromethane (4:1) as eluent to yield 571.0 mg (92%) of 4-trifluoromethyl-1-oxa-2,5-diazaspiro[5.5]undeca-2,4-diene (**4**) as colorless crystals, mp 110-111° (*n*-hexane): ^1H nmr: δ 1.10-2.35 (m, 10H, C_5H_{10}), 2.35 (s, 3H, $ArCH_3$), 7.18, 7.55 (d, *J* = 8.0 Hz, 4H, aryl); ir (potassium bromide): ν 1185, 1125, 1115 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{16}H_{17}N_2OF_3$: C, 61.93; H, 5.52; N, 9.03. Found: C, 62.01; H, 5.44; N, 9.04.

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[12] For instance, **1** (R = *p*-Tol, syn:anti = 1:1); ^{13}C nmr: δ 21.4 (CH_3), 114.8 ($^1J_{CF}$ = 291.2 Hz, CF_3), 116.7 ($^1J_{CF}$ = 291.2 Hz, CF_3), 126.4, 129.2, 129.4, 130.2 (C2', C3', C5', and C6' of *p*-Tol), 123.6, 125.7 (C1' of *p*-Tol), 141.0, 142.3 (C4' of *p*-Tol), 152.7, 153.5 (*C*=N), 179.1 ($^2J_{CF}$ = 35.3 Hz, *C*=O), 186.6 ($^2J_{CF}$ = 40.6 Hz, *C*=O); ^1H nmr: δ 2.32 (s, 3H, CH_3), 7.13, 6.80-7.40 (s and br, 5H, aryl and OH); ir (potassium bromide): ν 2000-3700 (OH), 1188, 1152 (CF_3) cm^{-1}.