A Facile Synthesis of Fluorine-containing Heterocycles - Use of 1,1,1-Trifluoro-2-alkanones as a Convenient Synthetic Intermediate

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1,1,1-Trifluoro-2,3-alkanediones **2** easily obtainable from various aldehyde dialkylhydrazones were reacted with several diamines to afford trifluoromethylquinoxalines **3** and trifluoromethylpyrazines **4** in good yields. With the use of aldehydes and aqueous ammonia instead of diamines, diketones **2** were successfully converted to the corresponding 4-trifluoromethylimidazoles **5** in satisfactory yields.

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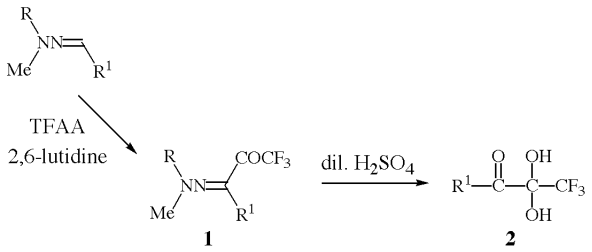
Fluorine-containing heterocycles are very fascinating targets for synthetic organic chemists because of their potentially high physiological activities [1-4]. Previously we reported successful electrophilic substitution reaction at the azomethine carbon atoms of aldehyde dialkylhydrazones with the use of trifluoroacetic anhydride (TFAA) as an acylating agent. By means of this reaction, dialkylhydrazones of a variety of aldehydes can be converted to the corresponding 3-(dialkylhydrazono)-1,1,1-trifluoro-2-alkanones (**1**) [5-8]. 1,1,1-Trifluoro-2,3-alkanediones (**2**) easily obtainable as monohydrates by hydrolysis of **1** are thought to be good synthetic intermediates for construction of several heterocycles bearing a trifluoromethyl group at their ring position. In this paper, we wish to report a facile and convenient synthetic method for a variety of trifluoromethylated heterocycles including imidazoles and pyrazine derivatives.

Scheme 1



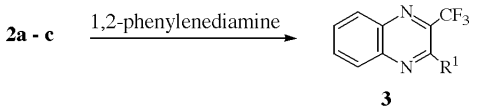
R	R^1	
Me	Ph	**1a**
Me	*p*-Tol	**1b**
t-Bu	Et	**1c**
Me	H	**1d**

R^1	
Ph	**2a**
p-Tol	**2b**
Et	**2c**
H	**2d**

According to a usual manner [5-8], aldehyde dialkylhydrazones treated with trifluoroacetic anhydride gave 3-(dialkylhydrazono)-1,1,1-trifluoro-2-alkanones (**1a-c**). These were hydrolyzed with hot 10 *M* sulfuric acid to afford 1,1,1-trifluoro-2,3-alkanedione (**2a-c**) as monohydrates.

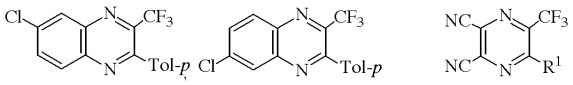
The so-obtained diketones **2a-c** reacted successfully with equimolar amounts of 1,2-phenylenediamine to afford the corresponding quinoxaline **3a-c** in high yields. When 4-chloro-1,2-phenylenediamine was used instead of 1,2-phenylenediamine, **2b** gave chloroquinoxaline (**3e**) as a mixture of two regioisomers. Quite similarly, **2b** treated with slightly excess amounts of diaminomaleonitrile afforded the corresponding 5-(*p*-tolyl)-6-trifluoromethylpyrazine-2,3-dicarbonitrile (**4b**) [5] in 76% yield. In the case of 5-trifluoromehylpyrazine-2,3-dicarbonitrile (**4d**), one pot synthesis from **1d** was successful. Hydrazone **1d** was hydrolyzed in 2.5 *M* H_2SO_4, and subsequently, treated with equimolar amounts of diaminomaleonitrile to afford **4d** in 94% yield.

Scheme 2



3

R^1		Yield (%)
Ph	**3a**	72
p-Tol	**3b**	93
Et	**3c**	52



3e

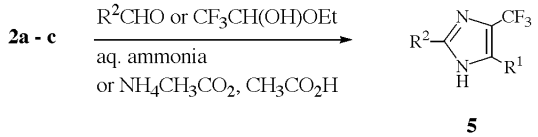
4

R^1	
p-Tol	**4b**
H	**4d**

We also tried the synthesis of **3b** directly from 3-(dialkylhydrazono)-1,1,1-trifluoro-2-alkanones (**1b**). In the presence of acetic acid, **1b** reacted with 1,2-phenylenediamine in refluxing acetonitrile to give quinoxaline **3b** in 89% yield. Similarly, quinoxaline **3c** was obtained in 34% yield directly from hydrazone **1c**. This direct method is more convenient than the above method *via* diketones **2**. However the yield of **3c** in this case was lower than the total yield (41%) of **3c** from **1c** *via* diketone **2c** using the usual method.

Diketone **2** was also found to be useful for the synthesis of 4-trifluoromethylimidazoles (**5**). In the presence of excess amounts of ammonia, **2b** and **2c** reacted with aliphatic aldehydes to afford 4-trifluoromethylimidazoles (**5a-c**) in moderate to good yields. In the case of the imidazole formation reaction from **2** and aromatic aldehydes instead of aliphatic aldehydes, the following method gave good results. In the presence of excess of ammonium acetate, **2b** was treated with *p*-tolualdehyde in hot acetic acid to afford the corresponding imidazole **5c** in 53% yield. The second method was applicable to the synthesis of 2,4-bistrifluoromethylimidazoles. With the use of 1-ethoxy-2,2,2- trifluoroethanol instead of aldehyde, diketones **2b** and **2c** were successfully converted to the corresponding 2,4-bistrifluoromethylimidazoles (**5e** and **5f**, respectively).

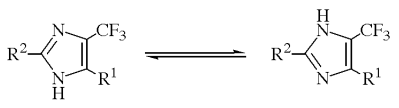
Scheme 3



5

R^1	R^2		Yield (%)
p-Tol	Et	**5a**	42
p-Tol	*iso*-Pr	**5b**	85
Et	*iso*-Pr	**5c**	47
p-Tol	*p*-Tol	**5d**	53
p-Tol	CF_3	**5e**	56
Et	CF_3	**5f**	41

The structures of compounds **3-5** were confirmed by ^1H and ^{13}C nmr, and ir spectra, and micro combustion analysis. A tautomeric equilibrium between A and B is possible for imidazoles **5**. In the ^{13}C nmr spectra of **5b**, the imidazole ring carbon atoms C2, C4, and C5 appear at 158.8, 123.8 ($^2J_{CF}$ = 36.0 Hz), and 131.0 ppm, respectivery. These values are more compatible with those observed for 1-methyl-5-(*p*-tolyl)-4-trifluoromethyl-1*H*-imidazole than those for 1-methyl-4-(*p*-tolyl)-5-trifluoromethyl-1*H*-imidazole [9,10]. This indicates that imidazole **5b** is predominantly present as tautomer A (4-trifluoromethylimidazole).



In conclusion, we present here convenient synthetic methods applicable to quinoxalines, pyrazines, and imidazoles bearing a trifluoromethyl group at their ring position. 1,1,1-Trifluoro-2,3- alkanediones **2** were the common intermediate used for the synthesis of these heterocycles. Also, 3-(dialkylhydrazono)-1,1,1-trifluoro-2-alkanones **1**, the precursor of **2**, can be used for the convenient synthesis of quinoxalines **3** and pyrazines **4**. These diketones **2** and hydrazones **1** should be powerful intermediates for construction of a variety of other trifluoromethylated heterocycles, such as furanes, pyroles, thiophenes, pyridazinones, triazinones, and so on. Syntheses of these heterocycles are now under investigation.

EXPERIMENTAL

Melting points were determined with a Mitamura Riken model 7-12 apparatus and are 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 AC 250, 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-(Dialkylhydrazono)-1,1,1-trifluoro-2-alkanones **1** and 1,1,1-trifluoro-2,3-alkanediones **2** were prepared according to a literature method [5-8].

3-Trifluoromethylquinoxalines **3a-e**.

General Procedure.

A mixture of **2a-c** (0.5 mmoles), and 1,2-phenylenediamine or 4-chloro-1,2-phenylenediamine (0.5 mmol) in acetonitrile (3 ml) was stirred at room temperature for 24 hours. Removal of the solvent afforded 3-trifluoromethylquinoxalines **3a-e**.

3-Trifluoromethyl-2-phenylquinoxaline (**3a**).

This compound was obtained as pale yellow crystals (cyclohexane): mp 117°, ^1H nmr: δ 7.37 (s, 5H, Ph), 7.57-7.88 (m, 2H, C6-*H* and C7-*H*), 7.93-8.18 (m, 2H, C5-*H* and C8-*H*); ir (potassium bromide): ν 1075, 1131, 1192 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{15}H_9F_3N_2$: C, 65.69; H, 3.31; N, 10.21. Found: C, 65.77; H, 3.24; N, 10.03.

3-Trifluoromethyl-2-(*p*-tolyl)quinoxaline (**3b**).

This compound was obtained as pale yellow crystals (cyclohexane): mp 141-142° (lit 115°) [5].

2-Ethyl-3-trifluoromethylquinoxaline (**3c**).

This compound was obtained as yellow oil: bp 120°/80 Torr (oven temperature of Kugelrohr distillation), ^1H nmr: δ 1.45 (t, *J* = 7.2 Hz, 3H, CH_3), 3.20 (q, *J* = 7.2 Hz, 2H, CH_2), 7.68-8.30 (m, 4H, aryl); ir (potassium bromide): ν 1120, 1185 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{11}H_9F_3N_2$: C, 58.41; H, 4.01; N, 12.38. Found: C, 58.63; H, 4.29; N, 12.11.

6-Chloro-3-trifluoromethyl-2-(*p*-tolyl)quinoxaline and 6-Chloro-2- trifluoromethyl-3-(*p*-tolyl)quinoxaline (**3e**).

These compounds were obtained as 13:5 mixture. Fractionation of the mixture by preparative tlc (benzene/ethyl acetate = 9:1) afforded each regioisomer. One (Rf = 0.85) was obtained as pale yellow crystals (83 mg, 52%): mp 126.3° (cyclohexane), ^1H nmr: δ 2.44 (s, 3H, CH_3), 7.10–7.58 (dd, *J* = 8.0 Hz, 4H, $C_6H_4CH_3$), 7.69 (dd, *J* = 8.8 Hz and 2.0 Hz, 1H, C7-*H*), 8.08 (d, *J* = 2.0 Hz, 1H, C5-*H*), 8.09 (d, *J* = 8.8 Hz, 1H, C8-*H*); ir (potassium bromide): ν 1077, 1135, 1182 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{16}H_{10}ClF_3N_2$: C, 59.55; H, 3.12; N, 8.68. Found: C, 59.36; H, 3.29; N, 8.52.

The other (Rf = 0.79) was obtained as pale yellow crystals (29 mg, 20%): mp 112.5° (cyclohexane), ^{1}H nmr: δ 2.43 (s, 3H, CH_3), 7.10–7.54 (dd, *J* = 8.0 Hz, 4H, $C_6H_4CH_3$), 7.70 (dd, *J* = 9.0 Hz and 2.0 Hz, 1H, C7-*H*), 8.03 (d, *J* = 9.0 Hz, 1H, C8-*H*), 8.12 (d, *J* = 2.0 Hz, 1H, C5-*H*).

Direct Synthesis of 3-Trifluoromethylquinoxalines **3b-c** from **1b-c**.

To a mixture of **1b-c** (0.5 mmoles) and 1,2-phenylenediamine (60 mg, 0.55 mmol) in acetonitrile (2.5 ml) was added acetic acid (0.035 ml, 0.6 mmoles). The whole mixture was stirred for 24 hours under reflux conditions. The solvent was removed under *vacuum* and the residue was dissolved in dichloromethane (50 ml). The mixture was washed with 0.5 *M* aqueous sodium carbonate (100 ml) and dried over sodium sulfate. Removal of the solvent afforded 3-trifluoromethylquinoxalines **3b-c**.

One Pot Synthesis of 5-Trifluoromethylpyrazine-2,3-dicarbonitrile (**4d**) from 1,1,1-Trifluoro-3-(dimethylhydrazono)-2-propanone (**1d**).

To 2.5 *M* sulfuric acid (125.3 ml) was added **1d** (10.533 g, 62.7 mmoles), and the mixture was stirred at room temperature for 24 hours. After cooling the mixture to 0° diaminomaleonitrile (6.911 g, 62.7 mmoles) was added, and the whole mixture was stirred for additional 1 hour. The reaction mixture was poured into 1 *M* aqueous sodium hydroxide (626.5 ml), and the organic layer was extracted three times with dichloromethane (100 ml x 3). Combined extracts was dried over sodium sulfate and dichloromethane was removed under vacuum. The residue was chromatographed on to silica gel using benzene/ethyl acetate (95:5) as the eluent to yield 11.669 g (94%) of 5-trifluoromethylpyrazine-2,3-dicarbonitrile (**4d**) as pale yellow crystals: mp 74° (cyclohexane), ^{1}H nmr: δ 9.13 (s, 1H, CH); ir (potassium bromide): ν 1140, 1166, 1178 (CF_3) cm^{-1}.

Anal. Calcd. for $C_7HF_3N_4$: C, 42.44; H, 0.51; N, 28.28. Found: C, 42.51; H, 0.73; N, 28.09.

2-Alkyl-4-trifluoromethylimidazoles **5a-c**.

General Procedure.

To a mixture of **2b-c** (1 mmole) and aliphatic aldehyde (1.2 mmoles) in methanol (5 ml) was added 28% aqueous ammonia (2 ml, 106 mmoles). The whole mixture was stirred at room temperature for 24 hours, and then poured into dichloromethane (100 ml). The mixture was washed with saturated aqueous sodium chloride and the organic layer was dried over magnesium sulfate. Removal of the solvent afforded 2-alkyl-4-trifluoromethylimidazoles **5a-c**.

2-Ethyl-4-trifluoromethyl-5-(*p*-tolyl)-1*H*-imidazole (**5a**).

This compound was obtained as pale brown crystals: mp 229-230° (cyclohexane-benzene), ^{1}H nmr: δ 1.20 (t, *J* = 7.4 Hz, 3H,CH_2CH_3), 2.26 (s, 3H, ArCH_3), 2.73 (q, *J* = 7.4 Hz, 2H, CH_2CH_3), 7.00-7.45 (dd, *J* = 8.0 Hz, 4H, aryl), 8.03-8.17 (br, 1H, NH); ir (potassium bromide): ν 1104, 1115, 1161 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{13}H_{13}F_3N_2$: C, 61.41; H, 5.15; N, 11.02. Found: C, 60.81; H, 5.08; N, 10.88.

4-Trifluoromethyl-2-isopropyl-5-(*p*-tolyl)-1*H*-imidazole (**5b**).

This compound was obtained as colorless crystals: mp 172.5-173.5° (benzene), ^{13}C nmr (d_6-dimethylsulfoxide): δ 20.8 (ArCH_3), 21.2 (CHCH_3), 27.6 ($CHCH_3$), 123.0 ($^1J_{CF}$ = 266.9 Hz, CF_3), 123.8 ($^2J_{CF}$ = 36.0 Hz, C4), 125.9 (C1' of *p*-Tol), 128.3, 129.1 (C2', C3', C5', and C6' of *p*-Tol), 131.0 ($^3J_{CF}$ = 3.1 Hz, C5), 138.1 (C4' of *p*-Tol), 158.8 (C2); ^{1}H nmr (d_3-acetonitrile): δ 1.30 (t, *J* = 6.8 Hz, 6H, CHCH_3), 2.35 (s, 3H, ArCH_3), 3.08 (hept, *J* = 6.8 Hz, 1H, C*H*CH_3), 7.01-7.45 (dd, J = 8.0 Hz, 4H, aryl), 8.03-8.17 (br, 1H, NH); ir (potassium bromide): ν 1100, 1115, 1150 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{14}H_{15}F_3N_2$: C, 62.68; H, 5.64; N, 10.44. Found: C, 62.77; H, 5.62; N, 10.27.

5-Ethyl-4-trifluoromethyl-2-isopropyl-1*H*-imidazole (**5c**).

This compound was obtained as brown oil: bp 135°/15 Torr (oven temperature of Kugelrohr distillation), ^{1}H nmr: δ 1.20, 1.29 (t and d, *J* = 7.2 and 7.0 Hz, 9H, CH_2CH_3 and CHCH_3), 2.75 and 3.04 (q and hept, 3H, CH_2 and CH), 7.58-7.76 (br, 1H, NH); ir (potassium bromide): ν 1110, 1157 (CF_3) cm^{-1}.

Anal. Calcd. for $C_9H_{13}F_3N_2$: C, 52.42; H, 6.35; N, 13.59. Found: C, 52.66; H, 6.70; N, 13.43.

4-Trifluoromethyl-2-(*p*-tolyl)imidazoles **5d** and 2,4-Bis(trifluoromethyl)imidazoles **5e-f**.

General Procedure.

To a mixture of **2b-c** (1 mmole), ammonium acetate (555 mg, 7.2 mmoles), and *p*-tolualdehyde (144 mg, 1.2 mmoles) or 1-ethoxy-2,2,2-trifluoroethanol (432 mg, 3 mmoles) was added acetic acid (7 ml). The mixture was stirred at room temperature for 15 minutes, and then, heated to 100°, and stirring was continued for 5 hours. The reaction mixture was poured into water (100 ml) and neutralized (pH 7) with 28% aqueous ammonia. The organic layer was extracted twice with dichloromethane (50 ml x 2). Combined extracts were dried over sodium sulfate and the solvent was removed to afford **5d-f**.

4-Trifluoromethyl-2,5-di-(*p*-tolyl)imidazole (**5d**).

This compound was obtained as pale brown crystals: mp 270.5° (benzene), ^{1}H nmr (d_3-acetonitrile): δ 2.37 (s, 6H, ArCH_3), 7.13-7.55, 7.23 (dd and d, *J* = 8.2 and 8.0 Hz, 6H, aryl), 7.78 (d, *J* = 8.0 Hz, 2H, aryl), 10.03-11.0 (br, 1H, NH); ir (potassium bromide): ν 1115, 1163 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{18}H_{15}F_3N_2$: C, 68.35; H, 4.78; N, 8.86; F, 18.01. Found: C, 68.61; H, 4.78; N, 8.80; F, 17.81.

2,4-Bis(trifluoromethyl)-5-(*p*-tolyl)imidazole (**5e**).

This compound was obtained as colorless crystals: mp 148.5-149.5° (chloroform), ^{1}H nmr (d_3-acetonitrile): δ 2.38 (s, 3H, CH_3), 7.11-7.50 (dd, *J* = 8.2 Hz, 4H, aryl), 11.5-12.2 (br, 1H, NH); ir (potassium bromide): ν 1125, 1144, 1184 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{12}H_8F_6N_2$: C, 48.99; H, 2.74; N, 9.52. Found: C, 48.76; H, 2.81; N, 9.33.

5-Ethyl-2,4-bis(trifluoromethyl)imidazole (**5f**).

This compound was obtained as brown oil: bp 140°/80 Torr (oven temperature of Kugelrohr distillation), ^{1}H nmr: δ 1.24 (t, *J* = 7.4 Hz, 3H, CH_2CH_3), 2.81 (q, 2H, CH_2CH_3), 7.00-7.45 (br, 1H, NH); ir (potassium bromide): ν 1130, 1178 (CF_3) cm^{-1}.

Anal. Calcd. for $C_7H_6F_6N_2$: C, 36.22; H, 2.61; N, 12.07. Found: C, 36.51; H, 2.68; N, 11.84.

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[10] Imidazole ring carbon atoms of 1-methyl-5-(*p*-tolyl)-4-trifluoromethyl-1*H*-imidazole appear at 137.6 (C2), 128.8 ($^2J_{CF}$ = 37.4 Hz, C4), and 133.0 (C5) ppm. Those of 1-methyl-4-(*p*-tolyl)-5-trifluoromethyl-1*H*-imidazole (as a reference compound of 2-ethyl-4-(*p*-tolyl)-5-trifluoromethylimidazol) are observed at 140.5 (C2), 145.1 (C4), and 116.5 ($^2J_{CF}$= 39.1 Hz, C5) ppm.