A CONVENIENT SYNTHESIS OF 4-TRIFLUOROMETHYL-IMIDAZOL-1-OLS

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Abstract - 1,1,1-Trifluoroalkane-2,3-dione 3-oximes easily obtainable from aldehyde dialkylhydrazones were reacted with aldehydes in the presence of ammonium acetate followed by treatment with 1N HCl affording 4-trifluoromethylimidazol-1-ols in good yields.

Fluorine-containing heterocycles are very fascinating targets for synthetic organic chemists because of their potentially high biological activities applicable to agricultural and medicinal use. In the course of our studies on the synthesis of such fluorine-containing heterocycles, we have recently reported a successful synthesis of some trifluoromethylated heterocycles with the use of 3-hydrazono-1,1,1-trifluoroalkan-2-ones (1) as useful synthetic intermediates. 1,1,1-Trifluoroalkane-2,3-dione 3-oximes (2) which have an isoelectronic structure as hydrazones (1), are also thought to be effective intermediates to prepare several heterocycles bearing a trifluoromethyl group. Here we would like to report a convenient synthetic method to prepare 4-trifluoromethylimidazol-1-ols (3) from oximes (2).

In general, trifluoroacetylation of aldehyde dialkylhydrazones and subsequent hydrolysis of 3-dialky-
hydrazono-1,1,1-trifluoroalkan-2-ones thus obtained afforded 1,1,1-trifluoroalkane-2,3-diones as monohydrates. These diketones treated with hydroxylamine hydrochloride in the presence of NaOAc gave monooximes (2) in good yields (Scheme 1).

In the presence of NH₄OAc, oximes (2) and excess amounts of aldehydes were allowed to react for 18 h at 20°C. Treatment of the reaction mixture with 1N HCl afforded 4-trifluoromethylimidazol-1-ols (3a-h) in 60-77% yields (Scheme 2).

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R  R'   Yield(%)  3
C₆H₅  Et    3a  65
p-MeC₆H₄  Et   3b  77
p-ClC₆H₄  Et   3c  66
p-MeC₆H₄  iso-Pr  3d  60
o-MeC₆H₄  iso-Pr  3e  67
p-MeOC₆H₄  iso-Pr  3f  61
p-O₂NC₆H₄  iso-Pr  3g  62
n-C₆H₁₃  iso-Pr  3h  72
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Scheme 2

The structure of compounds (3) is confirmed by ¹H and ¹³C NMR, and IR spectra, and micro combustion analysis. In the ¹³C NMR spectra of 3d, imidazole ring carbon atoms C2, C4, and C5 appear at 149.5, 122.5 (2JCF= 37.4 Hz), and 130.6 ppm, respectively. These values are compatible with those observed for 1-methyl-5-(p-methylphenyl)-4-trifluoromethyl-1H-imidazole.⁶,⁷

When the reaction mixture from 2 (R= p-MeC₆H₄) and propionaldehyde without subsequent treatment with 1 N HCl was fractionated by preparative TLC, 4-trifluoromethyl-5,6-dihydro-4H-[1,2,5]oxadiazin-4-ol (4: R= p- CH₃C₆H₄, R’= Et) was obtained in 55 % yield together with a small amount (4 %) of imidazole (3b). After a treatment of purified 4 with 1 N HCl under the same condition described above, 4 was completely converted to 3b. The above result clearly suggests that imidazol-1-ols (3) derived from oxadiazines (4).

Contrary to the results from the reaction of oximes (2) with aldehydes, that of 2 with ketones in similar conditions afforded trifluoromethylated oxadiazine derivatives. In the presence of NH₄OAc, oximes (2) dissolved in large excess amounts of acetone were stirred for 19 d at 20°C. Treatment of the reaction
mixture with 1N HCl gave 4-trifluoromethyl-6H-[1,2,5]oxadiazines (5a - b).

Possible reaction pathway from oximes (2) to imidazol-1-ols (3) is illustrated in Scheme 3. Acid catalyzed dehydration of oxadiazines (4) which are the initial products from 2 and aldehydes, should afford 4-trifluoromethyl-6H-[1,2,5]oxadiazines (5) similarly to the case of the reactions of 2 and ketones. Electrocyclic ring opening of 5 and subsequent intramolecular nucleophilic attack of nitroso nitrogen atom toward azomethine carbon atom or electrocyclic recyclization process affords nitrone type 2H-imidazoles (6). Subsequent prototropy for aromatization on 6 gives imidazol-1-ols (3).

On the basis of our 6-31G* level ab initio calculations, imidazol-1-ol (3: R= R’= H) is estimated 52.93 KJ/mol more stable than oxadiazine (5: R= R’= H). In contrast, 2H-imidazole (6: R= R’= H) is calculated 37.03 KJ/mol less stable than 5 (R= R’= H). Probably there are equilibriums between oxadiazines (5) and 2H-imidazoles (6) as is shown in Scheme 3. In the case of the reactions from oximes (2) and ketones instead of aldehydes, there is no hydrogen on the ring carbon atom C2 of 2H-imidazoles corresponding to 6 that is necessary for the last step in Scheme 3 and, therefore, 2H-imidazole would return to 5 even if it was formed. These should be the reason why neither 6 type 2H-imidazoles
nor any products derived from them could be detected in the reaction products from oximes (2) and ketones. Although we could not get a definite evidence for formation of oxadiazines (5) in the reaction of 2 with aldehydes, the reaction pathway in Scheme 3 is thought to be the most reasonable one for formation of imidazol-1-ols (3) from oximes (2).

In summary, we can present a convenient synthetic method accessing 4-trifluoromethylimidazol-1-ols and 4-trifluoromethyl-6H-[1,2,5]oxadiazines after few steps from various aldehydes via 1,1,1-trifluoroalkane-2,3-dione 3-oximes. These new fluorine-containing heterocycles are not easily accessible by other methods.

**EXPERIMENTAL**

Melting points were determined with a Mitamura Riken model 7-12 apparatus and uncorrected. $^1$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. Unless otherwise noted NMR spectra were measured in CDCl$_3$ containing TMS as an internal standard. IR spectra were taken with a Hitachi model G3

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

A mixture of 1,1,1-trifluoroalkane-2,3-diones (10 mmol), hydroxylamine hydrochloride (764.4 mg, 11 mmol), and NaOAc (902.3 mg, 11 mmol) in 30 mL of dioxane / H$_2$O (2 / 1) was stirred for 18 h under reflux conditions. The reaction mixture was poured into CH$_2$Cl$_2$ (150 mL), and the whole mixture was washed with 0.5 N aq. NaHCO$_3$ (100 mL) and dried over Na$_2$SO$_4$. Removal of the solvent gave the corresponding 1,1,1-trifluoroalkane-2,3-dione 3-oximes (2) quantitatively. Without further purification these monooximes (2) were used for the following reactions.

**General procedure for preparation of 4-trifluoromethylimidazol-1-ols (3a - h).**

A mixture of 2 (1 mmol), aldehyde (1.3 mmol), and NH$_4$OAc (246.1 mg, 3 mmol) in MeOH (5 mL) was stirred for 18 h at 20°C. The solvent was removed under reduced pressure, and the residue were dissolved in CH$_2$Cl$_2$ (30 mL). After filtering off insoluble materials, the mixture was washed thoroughly with 1 N HCl (50 mL) and subsequently, with 0.5 N aqueous Na$_2$CO$_3$ (50 mL), and dried over Na$_2$SO$_4$. Removal of the solvent and fractionation of the residual materials by preparative TLC (CH$_2$Cl$_2$ / EtOAc = 95/5) afforded 4-trifluoromethylimidazol-1-ols (3a - h).

**2-Ethyl-4-trifluoromethyl-5-phenylimidazol-1-ol (3a):** syrupy oil: $^1$H NMR $\delta$ 0.98 (t, J= 7.2 Hz, 3H, CH$_3$), 2.40 (q, J= 7.2 Hz, 2H, CH$_2$), 7.24 (s, 5H, C$_6$H$_5$), 10.50 – 11.50 (br, 1H, OH); IR (KBr): v 2200 – 3500 (OH), 1161, 1112 (CF$_3$) cm$^{-1}$. 


2-Ethyl-4-trifluoromethyl-5-(p-methylphenyl)imidazol-1-ol (3b): colorless crystals (EtOAc), mp 168-169°C, $^1$H NMR (acetone-$d_6$): $\delta$ 1.20 (t, $J= 7.2$ Hz, 3H, CH$_3$CH$_2$), 2.33 (s, 3H, p-CH$_3$C$_6$H$_4$), 2.67 (q, $J= 7.2$ Hz, 2H, CH$_3$CH$_2$), 7.27 (s, 4H, p-CH$_3$C$_6$H$_4$), 10.50-11.50 (br, 1H, OH); IR (KBr) $\nu$ 2100-3575 (OH), 1179, 1145 (CF$_3$) cm$^{-1}$. Anal. Calcd for C$_{13}$H$_{13}$N$_2$OF$_3$: C, 57.78; H, 4.85; N, 10.37. Found: C, 57.50; H, 4.77; N, 10.31.

2-Ethyl-4-trifluoromethyl-5-(p-chlorophenyl)imidazol-1-ol (3c): syrupy oil: $^1$H NMR $\delta$ 1.01 (t, $J= 7.4$ Hz, 3H, CH$_3$), 2.46 (q, $J= 7.4$ Hz, 2H, CH$_2$), 7.18 (s, 4H, p-ClC$_6$H$_4$), 10.00 - 11.00 (br, 1H, OH); IR (KBr) $\nu$ 2100-3300 (OH), 1162, 1115 (CF$_3$) cm$^{-1}$.

2-iso-Propyl-4-trifluoromethyl-5-(p-methylphenyl)imidazol-1-ol (3d): colorless crystals (EtOAc), mp 196-197°C: $^{13}$C NMR (acetone-$d_6$) $\delta$ 20.8 (C$_3$H$_3$CH), 21.3 (p-CH$_3$C$_6$H$_4$), 26.2 (CH$_3$CH), 122.5 ($^2$J$_{CF}$= 37.4 Hz, C$_4$), 123.6 ($^1$J$_{CF}$= 266.7 Hz, CF$_3$), 125.0, 129.5, 130.8, 139.4 (p-CH$_3$C$_6$H$_4$), 130.6 ($^3$J$_{CF}$= 2.7 Hz, C$_5$), 149.5 (C$_2$); $^1$H NMR (acetone-$d_6$) $\delta$ 1.24 (d, $J= 7.0$ Hz, 6H, C$_3$H$_3$CH), 2.32 (s, 3H, p-CH$_3$C$_6$H$_4$), 3.13 (hept, $J= 7.0$ Hz, CH$_3$), 7.17 (s, 4H, p-CH$_3$C$_6$H$_4$), 10.00 - 11.00 (br, 1H, OH); IR (KBr) $\nu$ 2080-3100 (OH), 1160, 1109 (CF$_3$) cm$^{-1}$. Anal. Calcd for C$_{14}$H$_{15}$N$_2$OF$_3$: C, 59.15; H, 5.32; N, 9.85. Found: C, 58.84; H, 5.22; N, 9.60.

2-iso-Propyl-4-trifluoromethyl-5-(o-methylphenyl)imidazol-1-ol (3e): colorless crystals (EtOAc), mp 198-201°C: $^1$H NMR (CD$_3$OD) $\delta$ 1.35 (d, $J= 7.0$ Hz, 6H, C$_3$H$_3$CH), 2.17 (s, 3H, o-CH$_3$C$_6$H$_4$), 3.25 (hept, $J= 7.0$ Hz, CH$_3$), 7.10 - 7.45 (m, 4H, o-CH$_3$C$_6$H$_4$); IR (KBr) $\nu$ 2000-3100 (OH), 1167, 1111 (CF$_3$) cm$^{-1}$.

2-iso-Propyl-4-trifluoromethyl-5-(p-methoxyphenyl)imidazol-1-ol (3f): colorless crystals (EtOAc), mp 194-196°C: $^1$H NMR (CD$_3$OD) $\delta$ 1.34 (d, $J= 7.0$ Hz, 6H, C$_3$H$_3$CH), 3.25 (hept, $J= 7.0$ Hz, CH$_3$), 6.73 - 7.48 (q, $J= 9.0$ Hz, 4H, p-CH$_3$OC$_6$H$_4$); IR (KBr) $\nu$ 2100-3100 (OH), 1138, 1120, 1105 (CF$_3$) cm$^{-1}$.

2-iso-Propyl-4-trifluoromethyl-5-(p-nitrophenyl)imidazol-1-ol (3g): yellow crystals (EtOAc), mp 193-194°C, $^1$H NMR: $\delta$ 1.29 (d, $J= 7.0$ Hz, 6H, CH$_3$), 3.14 (hept, $J= 7.0$ Hz, 1H, CH), 7.53, 8.15 (d, $J= 8.4$ Hz, 4H, p-O$_2$NC$_6$H$_4$), 10.80 - 11.80 (br, 1H, OH); IR (KBr): $\nu$ 2100-3100 (OH), 1150, 1102 (CF$_3$) cm$^{-1}$.

2-iso-Propyl-4-trifluoromethyl-5-(n-hexyl)imidazol-1-ol (3h): syrupy oil: $^1$H NMR $\delta$ 0.60-1.90 (m, 17H, n-C$_5$H$_{11}$CH$_2$), 2.40 - 2.76 (m, n-C$_5$H$_{11}$CH$_2$), 3.15 (hept, $J= 7.0$ Hz, 1H, CH$_3$CH), 10.60 - 10.95 (br, 1H, OH); IR (KBr) $\nu$ 2100-3100 (OH), 1153, 1112 (CF$_3$) cm$^{-1}$.

4-Trifluoromethyl-5,6-dihydro-4H-[1,2,5]oxadiazin-4-ol (4).

A mixture of 2 (R= p-MeC$_6$H$_4$, 115.6 mg, 1 mmol), propionaldehyde (75.5 mg, 1.3 mmol), and NH$_4$OAc
(246.1 mg, 3 mmol) in MeOH (5 mL) was stirred for 18 h at 20°C. The reaction mixture was poured into CH₂Cl₂ (50 mL), and the whole mixture was washed with water (100 mL) and dried over Na₂SO₄. Removal of the solvent and fractionation of the residual materials by preparative TLC (CH₂Cl₂/EtOAc = 9/1) gave 158.5 mg (55%) of 3-(p-methylphenyl)-4-trifluoromethyl-6-ethyl-5,6-dihydro-4H-[1,2,5]-oxadiazin-4-ol (4: 5/2 mixture of diastereomers) as colorless crystals, mp 117-119°C (cyclohexane): ¹³C NMR (acetone-d₆) δ 7.2 (CH₂CH₂), 21.5 (p-C₆H₃C₆H₄), 27.2, 27.7 (CH₂), 84.8, 85.8 (CH), 92.5, 92.9 (²JCF=32.9 Hz and 33.1 Hz, respectively CCF₃), 123.9, 125.1 (¹JCF=284.5 Hz and 288.5Hz, respectively, CF₃), 124.3 125.3 (C1' of p-CH₃C₆H₄), 128.5, 129.0, 129.2, (C2', C3', C5', and C6' of p-CH₃C₆H₄), 134.0, 135.2 (N=C-), 141.2 (C4' of p-CH₃C₆H₄); ¹H NMR (acetone-d₆) δ 0.90 (t, ²J = 7.4 Hz, 3H, CH₃CH₂), 1.20-2.15 (m, 2H, CH₃CH₂), 2.33 (s, 3H, p-C₆H₃C₆H₄), 3.90, 4.23 (br d, ²J = 5.5 Hz, 1H, NH), 4.80 - 5.10 (m, 1H, CH), 6.42 - 7.42 (br, 1H, OH), 7.16 (d, ²J = 8.0 Hz, 2H, p-CH₃C₆H₄), 8.08, 8.43 (d, 1H, ²J = 8.0 Hz, 2H, p-CH₃C₆H₄); IR (KBr) ν 2050-3625 (OH), 1182, 1131 (CF₃) cm⁻¹. Anal. Calcd for C₁₃H₁₅N₂O₂F₃: C, 54.17; H, 5.24; N, 9.72.  Found: C, 54.37; H, 5.22; N, 9.69.

General procedure for preparation of 4-trifluoromethyl-6H-[1,2,5]oxadiazines (5a - b).
A mixture of 2 (1 mmol), acetone (5 mL, 68.1 mmol), and NH₄OAc (246.1 mg, 3 mmol) was stirred for 19 d at 20°C. The subsequent workup procedures were quite similar to those described in the section for 3a - h. Fractionation of the products by preparative TLC (CH₂Cl₂) afforded 4-trifluoromethyl-6H-[1,2,5]oxadiazines (5a - b).

6,6-Dimethyl-3-(p-methylphenyl)-4-trifluoromethyl-6H-[1,2,5]oxadiazine (5a): pale yellow crystals (n-hexane), mp 76-77°C: ¹H NMR δ 1.66 (s, 6H, 6-CH₃), 2.35 (s, 3H, p-CH₃C₆H₄), 7.20, 7.57 (d, ²J = 8.0 Hz, 4H, p-CH₃C₆H₄); IR (KBr) ν 1208, 1138 (CF₃) cm⁻¹. Anal. Calcd for C₁₃H₁₃N₂O₂F₃: C, 57.78; H, 4.85; N, 10.37; F, 21.09.  Found: C, 58.01; H, 4.72; N, 10.60; F, 20.87.

6,6-Dimethyl-3-(o-methylphenyl)-4-trifluoromethyl-6H-[1,2,5]oxadiazine (5b): pale yellow crystals (n-hexane), mp 91-92°C: ¹H NMR δ 1.67 (s, 6H, 6-CH₃), 2.14 (s, 3H, o-CH₃C₆H₄), 7.07 - 7.40 (m, 4H, o-CH₃C₆H₄); IR (KBr) ν 1205, 1138 (CF₃) cm⁻¹.

REFERENCES AND NOTES


8. Calculations were accomplished using the computer program package PC SPARTAN plus (Wavefunction, Inc). Calculations including geometry optimizations were performed with the 6-31G* basis set at Hartree-Fock levels.

9. For instance, **2** (R= p-MeC₆H₄, syn / anti= 1 / 1): mp 89-101°C: ¹³C NMR (CDCl₃ / TMS) δ 21.4 (p-CH₃C₆H₄), 114.8 (¹JC=291.2 Hz, CF₃), 116.7 (¹JC=291.2 Hz, CF₃), 126.4, 129.2, 129.4, 130.2 (C2’, C3’, C5’, and C6’ of p-CH₃C₆H₄), 123.6, 125.7 (C1’ of p-CH₃C₆H₄), 141.0, 142.3 (C4’ of p-CH₃C₆H₄), 152.7, 153.5 (C=N), 179.1 (²JC=35.3 Hz, C=O), 186.6 (²JC=40.6 Hz, C=O); ¹H NMR (CDCl₃ / TMS) δ 2.32 (s, 3H, p-CH₃C₆H₄), 7.13, 6.80 - 7.40 (s and br, 5H, p-CH₃C₆H₄ and OH); IR (KBr) ν 2000 - 3700 (OH), 1188, 1152 (CF₃) cm⁻¹.