HETEROCYCLES, Vol. 53, No. 1, 2000, pp. 107 - 113, Received, 9th August, 1999

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

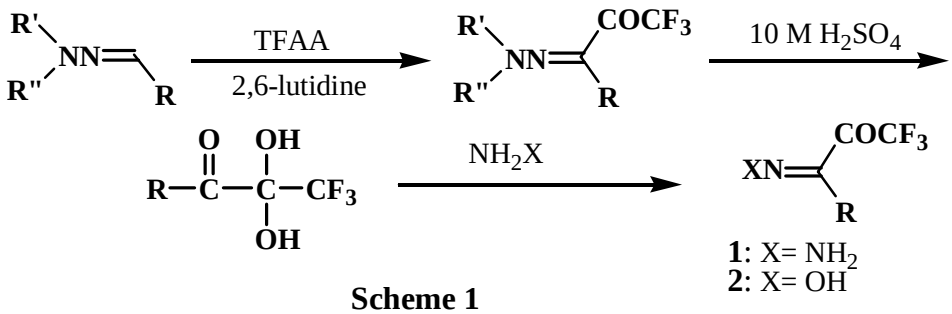
Yasuhiro Kamitori*

Department of Chemical Science and Engineering,
Faculty of Engineering, Kobe University, Kobe 657-8501, Japan

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.[1-3] 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.[4] 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**).

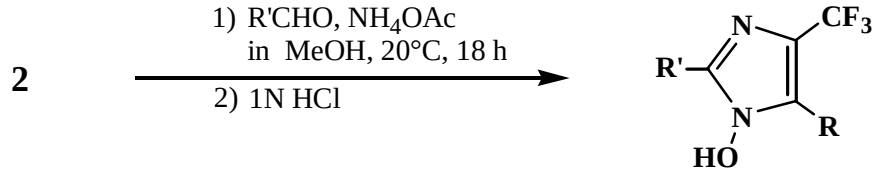
In general,[5] trifluoroacetylation of aldehyde dialkylhydrazones and subsequent hydrolysis of 3-dialkyl-



Scheme 1

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 NH_4OAc, 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).



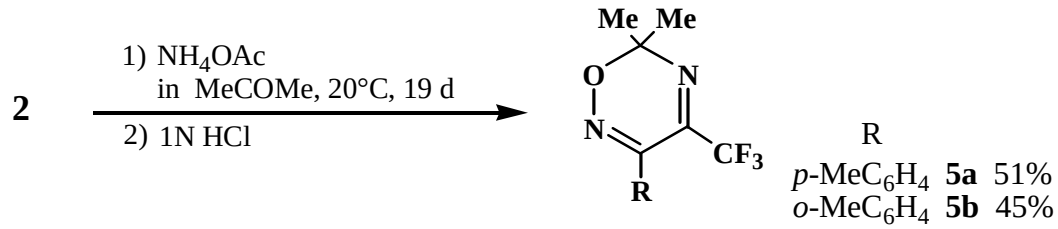
R	R'	3	Yield(%)
C_6H_5	Et	**3a**	65
p-MeC_6H_4	Et	**3b**	77
p-ClC_6H_4	Et	**3c**	66
p-MeC_6H_4	*iso*-Pr	**3d**	60
o-MeC_6H_4	*iso*-Pr	**3e**	67
p-$MeOC_6H_4$	*iso*-Pr	**3f**	61
p-$O_2NC_6H_4$	*iso*-Pr	**3g**	62
n-C_6H_{13}	*iso*-Pr	**3h**	72

Scheme 2

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

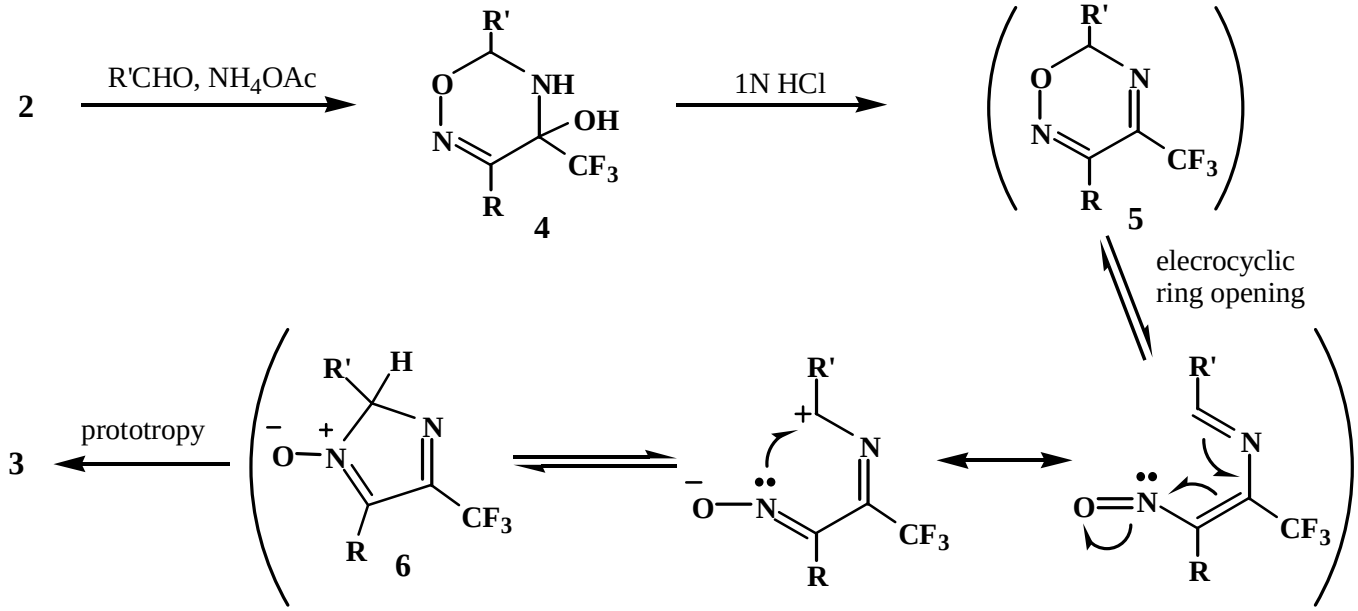
When the reaction mixture from **2** (R= *p*-MeC_6H_4) and propionaldehyde without subsequent treatment with 1 N HCl was fractionated by preparative TLC, 4-trifluoromethyl-5,6-dihydro-4*H*-[1,2,5]oxadiazin-4-ol (**4**: R= *p*- $CH_3C_6H_4$, R'= Et) was obtained in 55 % yield together with a small amount (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 NH_4OAc, 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-6*H*-[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-6*H*-[1,2,5]oxadiazines (**5**) similarly to the case of the reactions of **2** and ketones. Electrocyclic ring opening of **5** and subsequent intramoleculer nucleophilic attack of nitroso nitrogen atom toward azomethine carbon atom or electrocyclic recyclization process affords nitrone type 2*H*-imidazoles (**6**). Subsequent prototropy for aromatization on **6** gives imidazol-1-ols (**3**).



Scheme 3

On the basis of our 6-31G* level *ab initio* calculations,[8] imidazol-1-ol (**3**: R= R'= H) is estimated 52.93 KJ/mol more stable than oxadiazine (**5**: R= R'= H). In contrast, 2*H*-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 2*H*-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 2*H*-imidazoles corresponding to **6** that is necessary for the last step in Scheme 3 and, therefore, 2*H*-imidazole would return to **5** even if it was formed. These should be the reason why neither **6** type 2*H*-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-6*H*-[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_2O (2 / 1) was stirred for 18 h under reflux conditions. The reaction mixture was poured into CH_2Cl_2 (150 mL), and the whole mixture was washed with 0.5 N aq. $NaHCO_3$ (100 mL) and dried over Na_2SO_4. Removal of the solvent gave the corresponding 1,1,1-trifluoroalkane-2,3-dione 3-oximes (**2**)[9] quantitatively. Without farther 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_4OAc (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_2Cl_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_2CO_3 (50 mL), and dried over Na_2SO_4. Removal of the solvent and fractionation of the residual materials by preparative TLC (CH_2Cl_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 δ 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_6H_5), 10.50 – 11.50 (br, 1H, OH); IR (KBr): ν 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): δ 1.20 (t, *J*= 7.2 Hz, 3H, C**H**$_3$CH$_2$), 2.33 (s, 3H, *p*-C**H**$_3$C$_6$H$_4$), 2.67 (q, *J*= 7.2 Hz, 2H, CH$_3$C**H**$_2$), 7.27 (s, 4H, *p*-CH$_3$C$_6$**H**$_4$), 10.50-11.50 (br, 1H, OH); IR (KBr) ν 2100-3575 (OH), 1179, 1145 (CF$_3$) cm^{-1}. *Anal*. Calcd for $C_{13}H_{13}N_2OF_3$: 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 δ 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) ν 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) δ 20.8 (**C**H$_3$CH), 21.3 (*p*-**C**H$_3$C$_6$H$_4$), 26.2 (CH$_3$**C**H), 122.5 ($^2J_{CF}$= 37.4 Hz, C4), 123.6 ($^1J_{CF}$= 266.7 Hz, CF$_3$), 125.0, 129.5, 130.8, 139.4 (*p*-CH$_3$**C**$_6$H$_4$), 130.6 ($^3J_{CF}$= 2.7 Hz, C5), 149.5 (C2); ^{1}H NMR (acetone-d_6) δ 1.24 (d, *J*= 7.0 Hz, 6H, C**H**$_3$CH), 2.32 (s, 3H, *p*-C**H**$_3$C$_6$H$_4$), 3.13 (hept, *J*= 7.0 Hz, 1H, CH$_3$C**H**), 7.17 (s, 4H, *p*-CH$_3$C$_6$**H**$_4$), 10.00 - 11.00 (br, 1H, OH); IR (KBr) ν 2080-3100 (OH), 1160, 1109 (CF$_3$) cm^{-1}. *Anal*. Calcd for $C_{14}H_{15}N_2OF_3$: 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) δ 1.35 (d, *J*= 7.0 Hz, 6H, C**H**$_3$CH), 2.17 (s, 3H, *o*-C**H**$_3$C$_6$H$_4$), 3.25 (hept, *J*= 7.0 Hz, CH$_3$C**H**), 7.10 - 7.45 (m, 4H, *o*-CH$_3$C$_6$**H**$_4$); IR (KBr) ν 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) δ 1.34 (d, *J*= 7.0 Hz, 6H, C**H**$_3$CH), 3.25 (hept, *J*= 7.0 Hz, CH$_3$C**H**), 3.81 (s, 3H, OCH$_3$), 6.73 - 7.48 (q, *J*= 9.0 Hz, 4H, *p*-CH$_3$OC$_6$**H**$_4$); IR (KBr) ν 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: δ 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): ν 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 δ 0.60-1.90 (m, 17H, *n*-C$_5$**H**$_{11}$CH$_2$, C**H**$_3$CH), 2.40 - 2.76 (m, *n*-C$_5$H$_{11}$C**H**$_2$), 3.15 (hept, *J*= 7.0 Hz, 1H, CH$_3$C**H**), 10.60 - 10.95 (br, 1H, OH); IR (KBr) ν 2100-3100 (OH), 1153, 1112 (CF$_3$) cm^{-1}.

4-Trifluoromethyl-5,6-dihydro-4*H*-[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 CH_2Cl_2 (50 mL), and the whole mixture was washed water (100 mL) and dried over Na_2SO_4. Removal of the solvent and fractionation of the residual materials by preparative TLC (CH_2Cl_2 / EtOAc = 9/1) gave 158.5 mg (55%) of 3-(*p*-methylphenyl)-4-trifluoromethyl-6-ethyl-5,6-dihydro-4*H*-[1,2,5]-oxadiazin-4-ol (**4**: 5/2 mixture of diastereomers) as colorless crystals, mp 117-119°C (cyclohexane): ^{13}C NMR (acetone-d_6) δ 7.2 (**C**H_3CH_2), 21.5 (*p*-**C**$H_3C_6H_4$), 27.2, 27.7 (CH_2), 84.8, 85.8 (CH), 92.5, 92.9 ($^2J_{CF}$=32.9 Hz and 33.1 Hz, respectively **C**CF_3), 123.9, 125.1 ($^1J_{CF}$=284.5 Hz and 288.5Hz, respectively, CF_3), 124.3 125.3 (C1' of *p*-CH_3**C**$_6H_4$), 128.5, 129.0, 129.2, (C2', C3', C5', and C6' of *p*-CH_3**C**$_6H_4$), 134.0, 135.2 (N=C-), 141.2 (C4' of *p*-CH_3**C**$_6H_4$); ^{1}H NMR (acetone-d_6) δ 0.90 (t, *J*= 7.4 Hz, 3H, C**H**$_3CH_2$), 1.20-2.15 (m, 2H, CH_3C**H**$_2$), 2.33 (s, 3H, *p*-C**H**$_3C_6H_4$), 3.90, 4.23 (br d, *J*= 5.5 Hz, 1H, NH), 4.80 - 5.10 (m, 1H, CH), 6.42 - 7.42 (br, 1H, OH), 7.16 (d, *J*= 8.0 Hz, 2H, *p*-CH_3C_6**H**$_4$), 8.08, 8.43 (d, 1H, *J*= 8.0 Hz, 2H, *p*-CH_3C_6**H**$_4$); IR (KBr) ν 2050-3625 (OH), 1182, 1131 (CF_3) cm^{-1}. *Anal*. Calcd for $C_{13}H_{15}N_2O_2F_3$: 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-6*H*-[1,2,5]oxadiazines (**5a - b**).

A mixture of **2** (1 mmol), acetone (5 mL, 68.1 mmol), and NH_4OAc (246.1mg, 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 (CH_2Cl_2) afforded 4-trifluoromethyl-6*H*-[1,2,5]oxadiazines (**5a - b**).

6,6-Dimethyl-3-(*p*-methylphenyl)-4-trifluoromethyl-6*H*-[1,2,5]oxadiazine (**5a**): pale yellow crystals (*n*-hexane), mp 76-77°C: ^{1}H NMR δ 1.66 (s, 6H, 6-CH_3), 2.35 (s, 3H, *p*-C**H**$_3C_6H_4$), 7.20, 7.57 (d, *J*= 8.0 Hz, 4H, *p*-CH_3C_6**H**$_4$); IR (KBr) ν 1208, 1138, 1118 (CF_3) cm^{-1}. *Anal*. Calcd for $C_{13}H_{13}N_2OF_3$: 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-6*H*-[1,2,5]oxadiazine (**5b**): pale yellow crystals (*n*-hexane), mp 91-92°C: ^{1}H NMR δ 1.67 (s, 6H, 6-CH_3), 2.14 (s, 3H, *o*-C**H**$_3C_6H_4$), 7.07 - 7.40 (m, 4H, *o*-CH_3C_6**H**$_4$); IR (KBr) ν 1205, 1138 (CF_3) cm^{-1}.

REFERENCES AND NOTES

1. Review: R. Filler, "Organofluorine Chemicals and their Industrial Applications", ed. by R. E. Banks, Ellis Horwood, London, 1979, p. 123.
2. V. N. Pathak and V. Grover, *Pharmazie*, 1979, **34**, 568 (*Chem Abstr*., 1980, **92**, 181060n).
3. H. V. Secor and J. F. De Bardeleben, *J. Med. Chem.*, 1971, **14**, 997.

4. Y. Kamitori, M. Hojo, and T. Yoshioka, *Heterocycles*, 1998, **48**, 2221.
5. Y. Kamitori, M. Hojo, R. Masuda, T. Fujitani, S. Ohara, and T. Yokoyama, *J. Org. Chem*., 1988, **53**, 129. Y. Kamitori, M. Hojo, R. Masuda, T. Yoshida, S. Ohara, K. Yamada, and T. Yokoyama, *J. Org. Chem*., 1988, **53**, 519.
6. Imidazole ring carbon atoms of 1-methyl-5-(*p*-methylphenyl)-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*-methyl-phenyl)-5-trifluoromethyl-1*H*-imidazole (as a reference compound of 2-*iso*-propyl-4-(*p*-methyl-phenyl)-5-trifluoromethylimidazol-1-ol which is the regioisomer of **3d**) are observed at 140.5 (C2), 145.1 (C4), and 116.5 ($^2J_{CF}$= 39.1 Hz, C5) ppm.
7. Y. Kamitori, M. Hojo, R. Masuda, S. Ohara, K. Kawasaki, Y. Kawamura, and M. Tanaka, *J. Heterocycl. Chem*., 1990, **27**, 487.
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*-MeC_6H_4, syn / anti= 1 / 1): mp 89-101°C: ^{13}C NMR ($CDCl_3$ / TMS) δ 21.4 (*p*-**C**$H_3C_6H_4$), 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*-CH_3**C**$_6H_4$), 123.6, 125.7 (C1' of *p*-CH_3**C**$_6H_4$), 141.0, 142.3 (C4' of *p*-CH_3**C**$_6H_4$), 152.7, 153.5 (**C**=N), 179.1 ($^2J_{CF}$=35.3 Hz, **C**=O), 186.6 ($^2J_{CF}$=40.6 Hz, **C**=O); ^{1}H NMR ($CDCl_3$ / TMS) δ 2.32 (s, 3H, *p*-C**H**$_3C_6H_4$), 7.13, 6.80 - 7.40 (s and br, 5H, *p*-CH_3C_6**H**$_4$ and OH); IR (KBr) ν 2000 - 3700 (OH), 1188, 1152 (CF_3) cm^{-1}.