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3-DIMETHYLHYDRAZONO-1,1,1-TRIFLUORO-2-PROPANONE AS A USEFUL SYNTHETIC EQUIVALENT OF TRIFLUOROPYRUVALDEHYDE – APPLICATION TO SYNTHESIS OF FLUORINE-CONTAINING HETEROCYCLES

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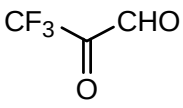
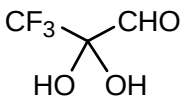
Abstract – 3-Dimethylhydrazono-1,1,1-trifluoro-2-propanone (**4**) which is easily obtainable from formaldehyde dimethylhydrazone and trifluoro-acetic anhydride was found to be an usuful synthetic equivalent of trifluoropyruvaldehyde for the synthesis of fluorine-containing heterocycles. With the use of **4**, 4-trifluoromethylimidazoles and 2-trifluoromethylquinoxaline were successfully synthesized.

Trifluoropyruvaldehyde (**1**) should be one of useful starting materials for syntheses of a variety of fluorinated organic compounds including heterocycles functionalized by trifluoromethyl group. However **1** is available only as aqueous solution of hydrates (**2**) and (**3**), and the known method to prepare them requires expensive 1,1,1-trifluoropropanone as a starting material together with tedious procedures.[1,2] These facts cause negative drawbacks in various organic syntheses using **1**.



1



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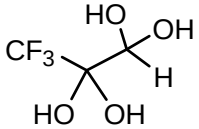


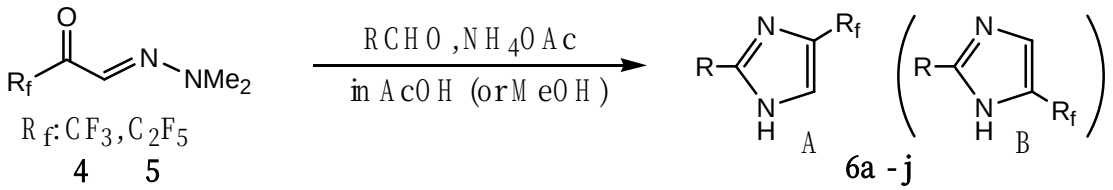
3

Previously we reported successful electophilic substitution reactions at azomethine carbon atoms of a series of aldehyde dialkylhydrazones with the use of several acylating reagents, such as trifluoroacetic anhydride (TFAA).[3,4] Formaldehyde dimethylhydrazone readily obtainable from paraformaldehyde and dimethylhydrazine can be converted easily to 3-dimethylhydrazono-1,1,1-trifluoro-2-propanone (**4**)

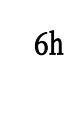
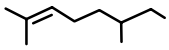
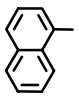
in excellent yield. These results prompted us to elucidate the usefulness of **4** as a synthetic equivalent of trifluoropyruvaldehyde (**1**). We chose fluorine-containing heterocycles as the first synthetic target using hydrazone (**4**). These heterocycles are very fascinating targets because of their potentially high physiological activities.[5-8] Herein we wish to report a convenient synthetic method to prepare imidazoles and quinoxalines with the use of **4**.

By usual manner,[4] trifluoroacetylation of formaldehyde dimethylhydrazone was carried out to afford hydrazone (**4**) in almost quantitative yield. In the presence of NH_4OAc, thus obtained **4** and excess amounts of aldehyde dissolved in AcOH were allowed to react for 18 h at 80°C. After general workup the corresponding imidazloes (**6a** - **g**) were obtained in 42-74% yields. In the cases of **6b** - **d**, MeOH instead of AcOH was used as a solvent.

The present method is applicable to the synthesis of imidazoles bearing pentafluoroethyl group. Similarly to the case of hydrazone (**4**), 4-dimethylhydrazono-1,1,1,2,2-pentafluoro-3-butanone (**5**) is accessible from folmaldehyde dimethylhydrazone and pentafluoropropionic anhydride. The reactions of **5** with aldehydes in the presence of NH_4OAc gave the corresponding imidazoles (**6h** - **j**) in 61 - 68% yield.



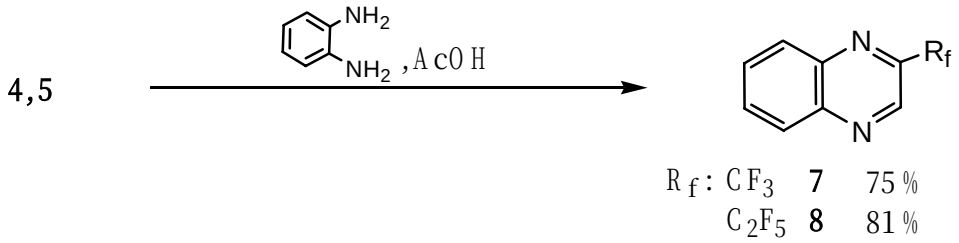
6a - j

R	(R_f = CF_3)	Yield (%)	R	(R_f = C_2F_5)	Yield (%)
H	**6a**	42		**6h**	61
Et	**6b**	74			
iso-Pr	**6c**	69			
	**6d**	51	*p*-Tol	**6i**	62
Ph	**6e**	57	O_2N- 	**6j**	68
p-Tol	**6f**	61			
	**6g**	53			

A tautomeric equilibrium between A and B is possible for imidazoles (**6a** - **j**). On the basis of our *ab initio* calculations (RHF/6-31G*),[9] tautomer B (R = H, R_f = CF_3) is predicted to be 3.0 Kcal/mol less stable than A (R = H, R_f = CF_3). This suggests that imidazoles (**6a** - **g**) are predominantly present as tautomer A (4-trifluoromethylimidazole). In the ^{13}C NMR spectra of **6b**, each imidazole ring carbon atom appears as one signal at 153.1, 132.3 ($^2J_{CF}$ = 36.6 Hz), and 118.2 ppm. These are assignable as

signals for C2, C4, and C5, respectively, of 2-ethyl-4-trifluoromethylimidazole (**6b**) rather than those for C2, C5, and C4, respectively, of 2-ethyl-5-trifluoromethylimidazole.[10]

Hydrazone (**4**) was also found to be useful for the synthesis of 2-trifluoromethyquinoxaline (**7**). In the presence of AcOH, hydrazone (**4**) successfully reacted with equimolar amounts of 1,2-phenylene-diamine to afford **7** in 74% yield. Quite similarly, 2-pentafluoromethylquinoxaline (**8**) was obtainable from **5** and 1,2-phenylenediamine.



In conclusion, hydrazones (**4**) and (**5**) which are easily obtainable from formaldehyde dimethylhydrazone were found to be an useful synthetic equivalents of trifluoropyruvaldehyde (**1**) and 3,3,4,4,4-pentafluoro-2-oxobutyraldehyde, respectively, for the synthesis of 4-perfluoroalkylimidazoles and 2-perfluoroalkylquinoxalines. The present method should be extended to syntheses of heterocycles bearing longer perfluoroalkyl substituent. Utilization of **1** for syntheses of another type of heterocycles as well as more generalized fluorinated organic compounds are now under investigation.

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. 3-Dimethylhydrazono-1,1,1-trifluoro-2-propanone (**4**) was prepared according to a literature method.[4]

Preparation of 4-dimethylhydrazono-1,1,1,2,2-pentafluoro-3- butanone (5).

To an ice-cooled mixture of formaldehyde dimethylhydrazone (1.303 g, 18.6 mmol) and 2,6-lutidine (2.989 g, 27.9 mmol) in dry $CHCl_3$ (120 mL) was added dropwise a solution of pentafluoropropionic anhydride (5.50 mL, 27.9 mmol) in dry $CHCl_3$ (40 mL) with continuous stirring. After stirring for 10 min at 0°C, the mixture was washed with 0.5 M HCl (200 mL), then with water (200 mL), and finally with 0.1 M aq. Na_2CO_3 (200 mL). The mixture was dried over Na_2SO_4 and the solvent was removed. Kugelrohr distillation (oven temperature 80°C / 5 torr) of the crude materials gave 3.412 g (84 %) of **5**.

5: pale yellow oil: ^{1}H NMR δ 3.27 (s, 6H, Me), 6.72 (s, 1H, CH). *Anal*. Calcd for $C_6H_7N_2OF_5$: C, 33.04; H, 3.23; N, 12.84; F, 43.55. Found: C, 32.85; H, 3.38; N, 12.71; F, 43.27.

General procedure for preparation of imidazoles (6a - j) from 4 and 5.

To a solution of **4** or **5** (1 mmol) and NH_4OAc (3.083 g, 40 mmol) in AcOH (8 mL), aldehydes (2 mmol) was added. In the cases of **6b** - **d**, MeOH (6 mL) was used instead of AcOH. The mixture was stirred for 1 h at 20°C, and then, 18 h at 80°C (42 h at 50°C in the cases of **6b** - **d**). After cooling, CH_2Cl_2 (100 mL) was added, and the mixture was washed with saturated aq. Na_2CO_3 (100 mL) and dried over Na_2SO_4. Removal of the solvent and fractionation of the residual materials by silica gel column chromatography (benzene / AcOEt = 1 / 1) afforded imidazoles (**6a** - **j**).

4-Trifluoromethyl-1*H*-imidazole (6a): pale yellow crystals (benzene), mp 128 - 132°C (lit.,[1] 148.5 - 149.5°C) : ^{1}H NMR ($CDCl_3$ / CD_3CN = 1 / 1) δ 7.38 (s, 1H, NC**H**=C), 7.60 (s, 1H, N=C**H**N), 7.70 - 9.40 (br, 1H, NH); IR (KBr) ν 2215 - 3200 (NH), 1137 (CF_3) cm^{-1}. *Anal*. Calcd for $C_4H_3N_2F_3$: C, 35.31; H, 2.22; N, 20.59. Found: C, 35.59; H, 2.59; N, 20.82.[11]

2-Ethyl-4-trifluoromethyl-1*H*-imidazole (6b): colorless crystals (cyclohexane), mp 130 - 131°C: ^{13}C NMR (acetone-d_6) δ 13.6 (CH_3), 23.2 (CH_2), 118.2 (N**C**H=C), 124.5 ($^1J_{CF}$= 264.8 Hz, CF_3), 132.3 ($^2J_{CF}$=36.6 Hz, NCH=**C**), 153.1 (N=**C**N); ^{1}H NMR δ 1.20 (t, *J*= 7.0 Hz, 3H, CH_3), 2.74 (q, *J*= 7.0 Hz, 2H, CH_2), 7.21 (s, 1H, CH), 9.20 - 10.50 (br, 1H, NH); IR (KBr) ν 2360 - 3250 (NH), 1167, 1142, 1118 (CF_3) cm^{-1}. *Anal*. Calcd for $C_6H_7N_2F_3$: C, 43.91; H, 4.30; N, 17.07. Found: C, 43.90; H, 4.27; N, 17.02.

2-*iso*-Propyl-4-trifluoromethyl-1*H*-imidazole (6c): colorless crystals (benzene), mp 149 - 150°C, (lit.,[1] 201 - 202°C): ^{1}H NMR ($CDCl_3$ / CD_3CN = 5 / 1) δ 1.31 (d, *J*= 7.0 Hz, 6H, CH_3), 3.06 (hept, *J*= 7.0 Hz, 1H, CH), 7.17 (s, 1H, NCH), 8.20 - 8.90 (br, 1H, NH); IR (KBr) ν 2240 - 3280 (NH), 1125 (CF_3) cm^{-1}. *Anal*. Calcd for $C_7H_9N_2F_3$: C, 47.19; H, 5.09; N, 15.72. Found: C, 47.02; H, 4.97; N, 15.70.[11]

2-(2,6-Dimethylhept-5-enyl)-4-trifluoromethyl-1*H*-imidazole (6d): syrupy oil: ^{1}H NMR δ 0.70 - 2.12, 1.58, 1.66 (m, s, and s, 16H, CH, CH_2, CH_3), 5.07 (t, *J*= 7.2 Hz, 1H, C=CH), 7.29 (s, 1H, NCH), 9.60 - 10.70 (br, 1H, NH).

2-Phenyl-4-trifluoromethyl-1*H*-imidazole (6e): colorless crystals (benzene), mp 210 - 211°C (lit.,[1] 210 - 211°C): ^{1}H NMR (CD_3CN) δ 7.26 - 8.01, 7.46 (m and s, 6H, C_6H_5 and NCH), 9.00 - 10.50 (br, 1H, NH); IR (KBr) ν 2460 - 3210 (NH), 1135, 1116 (CF_3) cm^{-1}.

2-*p*-Tolyl-4-trifluoromethyl-1*H*-imidazole (6f): colorless crystals ($CHCl_3$), mp 222 - 223°C: ^{1}H NMR (CD_3CN) δ 2.34 (s, 3H, CH_3), 7.17, 7.68 (d, *J*= 8.0 Hz, 4H, *p*-CH_3C_6**H**$_4$), 7.41 (s, 1H, NCH), 9.70 - 11.00 (br, 1H, NH); IR (KBr) ν 2250 - 3280 (NH), 1140, 1114 (CF_3) cm^{-1}. *Anal*. Calcd for $C_{11}H_9N_2F_3$: C, 58.41; H, 4.01; N, 12.38. Found: C, 58.33; H, 3.86; N, 12.27.

2-Naphthalen-1-yl-4-trifluoromethyl-1*H*-imidazole (6g): colorless crystals (benzene), mp 207 - 209°C: ^{1}H NMR ($CDCl_3$ / CD_3CN = 1 / 1) δ 7.50, 7.20 - 7.93, 8.33 - 8.70 (s, m, and m, 8H, NCH and $C_{10}H_7$), 9.50 - 10.50 (br, 1H, NH); IR (KBr) ν 2510 - 3200 (NH), 1140, 1106 (CF_3) cm^{-1}. *Anal*. Calcd for $C_{14}H_9N_2F_3$: C, 64.12; H, 3.46; N, 10.68. Found: C, 63.95; H, 3.20; N, 10.62.

2-(1-Ethylpentyl)-4-pentafluoroethyl-1*H*-imidazole (6h): colorless crystals (*n*-pentane), mp 107 - 108°C: ^{1}H NMR δ 0.64 - 1.86, 0.86 (m and d, *J*= 6.2 Hz, 14H, CH_2, CH_3), 2.32 – 2.95 (m, 1H, CH), 7.16 (s, 1H, NCH), 9.90 – 11.00 (br, 1H, NH); IR (KBr) ν 2480 - 3220 (NH), 1197, 1133 (C_2F_5) cm^{-1}. *Anal*. Calcd for $C_{12}H_{17}N_2F_5$: C, 50.70; H, 6.03; N, 9.85. Found: C, 51.06; H, 6.06; N, 10.02.

2-*p*-Tolyl-4-pentafluoroethyl-1*H*-imidazole (6i): colorless crystals ($CHCl_3$), mp 203 - 206°C: ^{1}H NMR (acetone-d_6) δ 2.34 (s, 3H, CH_3), 7.17, 7.80 (d, J= 8.0 Hz, 4H, *p*-CH_3C_6**H_4**), 7.53 (s, 1H, NCH), 10.50 – 11.50 (br, NH); IR (KBr) ν 2480 - 3250 (NH), 1197, 1133 (C_2F_5) cm^{-1}. *Anal*. Calcd for $C_{12}H_9N_2F_5$: C, 52.18; H, 3.28; N, 10.14. Found: C, 51.88; H, 3.10; N, 10.07.

2-(4-Nitrophenyl)-4-pentafluoroethyl-1*H*-imidazole (6j): yellow crystals (CCl_4), mp 140 - 142°C: ^{1}H NMR (acetone-d_6) δ 7.77 (s, 1H, NCH), 8.26 (s, 4H, *p*-$O_2NC_6H_4$), 11.00-11.50 (br, 1H, NH); IR (KBr) ν 2500 - 3600 (NH), 1516, 1337, 1321 (NO_2), 1202, 1116 (C_2F_5) cm^{-1}. *Anal*. Calcd for $C_{11}H_6N_3O_2F_5$: C, 43.01; H, 1.97; N, 13.68. Found: C, 42.90; H, 1.84; N, 13.57.

General procedure for preparation of quinoxalines (7 and 8) from 4 and 5, respectively.

To a solution of **4** or **5** (1 mmol) and AcOH (72 mg, 1.2 mmol) in CH_3CN (1 mL), 1,2-phenylenediamine (108 mg, 1 mmol) was added. The mixture was stirred for 66 h at 20°C, and then, poured into CH_2Cl_2 (100 mL). The whole mixture was washed with saturated aq. Na_2CO_3 (100 mL) and dried over Na_2SO_4. Removal of the solvent and fractionation of the residual materials by silica gel column chromatography (benzene) afforded quinoxalines (**7** - **8**).

2-Trifluoromethylquinoxaline (7):[12] colorless crystals (sublimation, 60°C / 1 atm), mp 54 - 55°C: ^{1}H NMR δ 7.67 - 8.30 (m, 4H, CH), 9.07 (s, 1H, NCH); IR (KBr) ν 1170, 1122 (CF_3) cm^{-1}. *Anal*. Calcd for $C_9H_5N_2F_3$: C, 54.55; H, 2.54; N, 14.14. Found: C, 54.34; H, 2.42; N, 14.00.

2-Pentafluoroethylquinoxaline (8): colorless oil, bp 60°C/10 torr (oven temperature of Kugelrohr): ^{1}H NMR δ 7.64 - 8.29 (m, 4H, CH), 9.06 (s, 1H, NCH); IR (KBr) ν 1203 (C_2F_5) cm^{-1}. *Anal*. Calcd for $C_{10}H_5N_2F_5$: C, 48.40; H, 2.03; N, 11.29; F, 38.28. Found: C, 48.13; H, 1.94; N, 11.36; F, 38.57.

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9. Calculations were accomplished using the computer program package PC SPARTAN pro (Wavefunction, Inc). Calculations including geometry optimizations were performed with the 6-31G* basis set at Hartree-Fock levels.
10. Because of a tautomeric equilibrium, ring carbon atoms of parent imidazole appear as only two signals at 135.4 (C2) and 121.9 (C4 and C5) ppm. On the other hand, ring carbon chemical shifts of 1-methylimidazole are measured as 138.3 (C2), 129.6 (C4), and 120.3 (C5) ppm. The additional shifts on the chemical shifts of sp_2-hybridized carbons (benzene) induced by substituents are reported about Et ($\Delta\delta_{ipso}$= +15.6) and CF_3 group ($\Delta\delta_{ipso}$= +2.5, $\Delta\delta_{ortho}$= –3.2). On the basis of these values, ring carbon chemical shifts of 2-ethyl-1-methyl-4-trifluoromethylimidazole are roughly estimated as 154 (C2), 132 (C4), and 117 (C5) ppm, and those of 2-ethyl-1-methyl-5-trifluoromethylimidazole are as 154 (C2), 126 (C4), and 123 (C5) ppm. Review: H-O. Kalinowski, S. Berger, and S. Braun, 'Carbon-13 NMR Spectroscopy,' John Wiley & Sons, Inc., New York, 1988, pp. 311, 383.
11. These values are considerably different from the literature values. So, we carried out additional micro combustion analysis about **6a** and **6c**.
12. H. Watanabe, F. Yamasita, and K. Uneyama, *Tetrahedron Lett*., 1993, **34**, 1941.