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3-(Dimethylhydrazono)-1,1,1,4,4,4-hexafluoro-2-butanone as latent perfluorobiacetyl

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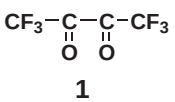
Abstract

Reaction of trifluoroacetaldehyde dimethylhydrazone with TFAA yielded 3-(dimethylhydrazono)-1,1,1,4,4,4-hexafluoro-2-butanone, which could be condensed in situ with diamino compounds to afford 2,3-bis(trifluoromethyl)quinoxaline, 5,6-bis(trifluoromethyl)pyrazine, and 4,5-bis(trifluoromethyl)-1*H*-imidazole.

Keywords: hydrazones; fluorine and compounds; substitution; pyrazines; imidazoles.

Perfluorobiacetyl (1,1,1,4,4,4-hexafluoro-2,3-butanedione, **1**) is a convenient building-block for the synthesis of various fluoroorganic compounds, especially heterocycles bearing two vicinal trifluoromethyl groups. The first synthesis of perfluorobiacetyl (**1**) was reported by Moor and Clark, which involved chromic acid oxidation of 2,3-dichloro-1,1,1,4,4,4-hexafluoro-2-butene.[1,2] However, the method suffered from some drawbacks, including use of a chromium reagent which is unfavorable for the environment, tedious procedures, and insufficient yield. Recently, Saloutin et al. reported an alternative preparation of **1** from octafluoro-2,3-epoxybutane,[3] but the yield of **1** was not significantly improved.



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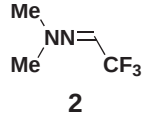

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In previous papers[4,5] we reported a successful electrophilic substitution reaction at azomethine carbon atoms in dialkylhydrazones of aldehyde. We have now investigated the development of a method for trifluoroacetylation of trifluoroacetaldehyde dimethylhydrazones (**2**), which should yield derivatives of perfluorobiacetyl. As a result of the 6-31G* level ab initio calculations[6] for the hydrazone **2**, the HOMO energy level and frontier electron density at the azomethine carbon are estimated as −0.334 au and 0.387, respectively. These values are comparable to those for methyl vinyl sulfide (−0.310 au for the energy level and 0.311 for the frontier electron density at the terminal olefinic carbon atom), which undergoes smooth electrophilic

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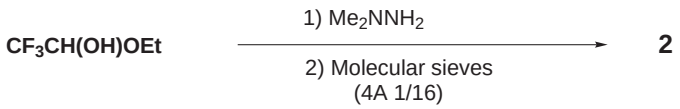
trifluoroacetylation at the terminal olefinic carbon atom.[7] These facts encouraged us to examine the electrophilic trifluoroacetylation of hydrazone (**2**) and its application to synthesis of several fluorine-containing heterocycles (Scheme 1).

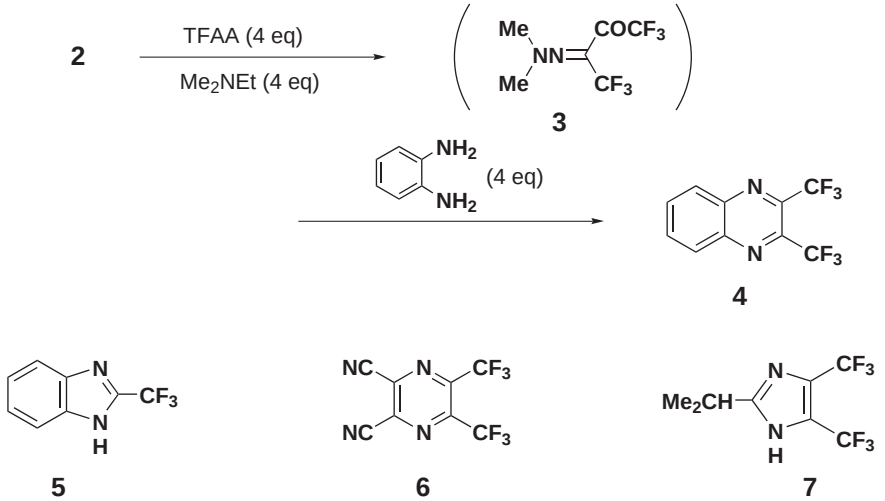


Scheme 1.

To an ice-cooled 1-ethoxy-2,2,2-trifluoroethanol (100 mmol, 11.9 mL) was added dropwise 1,1-dimethylhydrazine (110 mmol, 8.36 mL), and the mixture was stirred for 30 min at 20°C. Molecular sieves 4A, 1/16 (40 g) were then added, and the mixture was stirred for 3 h at 100°C. After cooling, pentane (100 mL) was added, and the organic layer was filtered. The molecular sieves were washed thoroughly with pentane (100 mL). The combined filtrate and washings were dried over Na_2SO_4, and concentrated in vacuo to give trifluoroacetaldehyde dimethylhydrazone (**2**,[8] 1.080 g) in 77% yield.

In the previous procedure,[4,5] 2,6-lutidine effectively promoted *C*-trifluoroacetylation of the azomethine carbon of dialkylhydrazones. However, the current trifluoroacetylation of **2** was not completed with 2,6-lutidine, leading to the formation of unidentified materials. After some attempts, ethyldimethylamine was found to be useful for this substitution.

To a mixture of **2** (1.6 mmol, 224.8 mg) and ethyldimethylamine (6.42 mmol, 0.70 mL) in $CHCl_3$ (1.6 mL) was added dropwise TFAA (6.42 mmol, 0.91 mL), and the mixture was stirred for 4 h at 20°C. At this time the ^1H NMR spectra of the reaction mixture showed no quartet signal characteristic of the azomethine proton in **2**, indicating complete consumption of hydrazone **2**. After addition of *O*-phenylenediamine (6.42 mmol, 708.2 mg), the mixture was stirred for an additional 20 h and then poured into CH_2Cl_2 (100 mL). The organic phase was washed with water and dried over Na_2SO_4. After concentration in vacuo, the residue was chromatographed on silica gel, affording 315.2 mg (74%) of 2,3-bis(trifluoromethyl)quinoxaline (**4**,[9] benzene). The second fraction gave 414.5 mg of 2-trifluoromethyl-1*H*-benzoimidazole (**5**,[10] benzene/AcOEt 8/2), the formation of which is ascribed to the reaction of *O*-phenylenediamine with TFAA (Scheme 2).



Scheme 2.

Diaminomaleonitrile (4.00 mmol, 432.4 mg) was also condensed with **3** to give 42% (178.8 mg) yield of 5,6-bis(trifluoromethyl)pyrazine-2,3-dicarbonitrile (**6**).[11] Conversely, **3** was cyclized with isobutylaldehyde (4.80 mmol, 0.436 mL) in 28% aq. NH_3 (34.0 mmol, 4.78 mL) to afford 2-isopropyl-4,5-bis(trifluoromethyl)-1*H*-imidazole (**7**)[12] in 35% (137.8 mg) yield. The structures of these heterocycles (**4**, **6**, and **7**) were confirmed by ^1H and ^{13}C NMR and IR spectra,[14] and their combustion analysis.

Although the formation of **3** was apparent by successful synthesis of the heterocycles, unfortunately 3-(dimethylhydrazono)-1,1,1,4,4,4-hexafluoro-2-butanone (**3**), i.e. the monodimethylhydrazone of perfluorobiacetyl, could not be isolated as a pure form from the reaction mixture of **2** and TFAA. Thus, monohydrazone **3** was contaminated with considerable amounts of unidentified materials even after any purification method. In the ^{13}C NMR spectra, this product shows two quartet signals at 179.9 ($^2J_{CF}=35.5$ Hz) and 157.1 ($^2J_{CF}=35.7$ Hz) ppm, which are assigned to the carbonyl and the azomethine carbon atoms of **3**,[13] respectively.

The present method is expected to be useful for the synthesis of various derivatives of perfluorobiacetyl such as interesting heterocycles bearing two vicinal trifluoromethyl groups. Preparation of pure 3-(dimethylhydrazono)-1,1,1,4,4,4-hexafluoro-2-butanone (**3**) and its conversion to perfluorobiacetyl (**1**) is now under investigation.

References

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6. Y. Kamitori, unpublished results. 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.
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8. Compound **2**: bp 100°C/100 Torr (oven temperature of Kugelrohr); ^1H NMR (CCl_4/TMS) δ 2.97 (s, 6H, Me), 6.08 (q, $^3J_{HF}=4.0$ Hz, 1H, CH).
9. Compound **4**: mp 119°C (Lit. mp 117–118°C: Ref. 1. Cushman, M.; Wong, W. C.; Bacher, A. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1043); ^1H NMR ($CDCl_3$/TMS) δ 7.85–8.33 (m, 4H, ArH); IR (KBr) 1422 (w), 1343 (m), 1281 (s), 1185 (s), 1158 (s), 1135 (s), 1104 (s), 1001 (s), 780 (m), 745 (m) cm^{-1}; MS, m/z (M^+) 266. Anal. calcd for $C_{10}H_4F_6N_2$: C, 45.13; H, 1.51; F, 42.83; N, 10.53. Found: C, 45.11; H, 1.66; F, 43.16; N, 10.38.
10. Compound **5**: mp 209°C (Lit. mp 210.0–210.5°C: Smith, W. T.; Steinle, E. C. *J. Am. Chem. Soc.* **1953**, *75*, 1292); ^1H NMR ($CDCl_3$/TMS) δ 7.17–7.70 (m, 4H, ArH), 9.43–9.73 (br, 1H, NH); IR (KBr) 2100–3300 (m, br), 1553 (m), 1505 (m), 1460 (m), 1402 (m), 1190 (s), 1170 (s), 1143 (s), 978 (m), 740 (s) cm^{-1}.
11. Compound **6**: mp 115°C (cyclohexane/benzene); ^{13}C NMR ($CDCl_3$/TMS) δ 111.3 (CN), 118.9 ($^1J_{CF}=277.7$ Hz, CF_3), 134.1 (CCN), 144.1 ($^2J_{CF}=41.2$ Hz, CCF_3); IR (KBr) 2250 (w), 1314 (s), 1275 (s), 1239 (s), 1187 (s), 1130 (s), 972 (m), 741 (m) cm^{-1}; MS, m/z (M^+) 266. Anal. calcd for $C_8F_6N_4$: C, 36.11; F, 42.84; N, 21.05. Found: C, 36.37; F, 42.79; N, 21.14.
12. Compound **7**: mp 200–201°C ($CHCl_3$); ^1H NMR ($CDCl_3$/TMS) δ 1.32 (d, $J=7$ Hz, 6H, Me), 3.06 (hept, $J=7$ Hz, 1H, CH), 10.58–11.60 (br, 1H, NH); IR (KBr) 2600–3100 (br, m), 1540 (m), 1443 (m), 1350 (m), 1274 (m), 1190 (s), 1147 (s), 1004 (s) cm^{-1}; MS, m/z (M^+) 246. Anal. calcd for $C_8H_8F_6N_2$: C, 39.04; H, 3.28; F, 46.31; N, 11.38. Found: C, 38.95; H, 3.34; F, 46.60; N, 11.32.

13. Compound **3** (with contaminants): ^{13}C NMR ($CDCl_3$/TMS) δ 42.1 (CH_3), 116.9 ($^1J_{CF}=287.6$ Hz, CF_3), 117.0 ($^1J_{CF}=287.2$ Hz, CF_3), 157.1 ($^2J_{CF}=35.7$ Hz, $N\underline{C}CF_3$), 179.9 ($^2J_{CF}=35.5$ Hz, $\underline{C}OCF_3$); ^1H NMR ($CDCl_3$/TMS) δ 3.22 (s, Me).
14. ^1H 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. IR spectra were taken with a Hitachi model G3. Mass spectra were obtained on a Shimadzu QP-5000 mass spectrometer.