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Trifluoromethylation of *N*-Benzoylhydrazones

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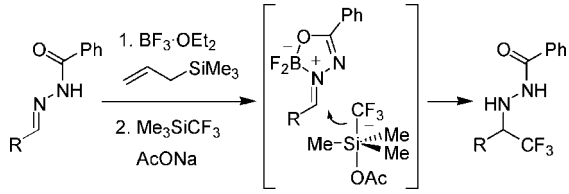

A method for the nucleophilic trifluoromethylation of *N*-benzoylhydrazones using Me_3SiCF_3/AcONa has been described. The *C*═N bond of the hydrazones is activated by difluoroboron group, which is introduced by means of boron trifluoride and allylsilane.

Methods for the introduction of trifluoromethyl group into organic molecules using the Ruppert−Prakash reagent (Me_3SiCF_3)[1] have gained considerable attention in recent years[2,3] due to the importance of CF_3-containing products for the pharmaceutical and agrochemical industries.[4]

The most elaborated reaction of Me_3SiCF_3 is the Lewis base-mediated nucleophilic addition to carbonyl group, which is applicable to a wide variety of compounds such as aldehydes, ketones, esters, and lactones.[2,5] At the same time, analogous addition to the *C*═N bond is quite limited in scope, owing to low electrophilicity of the azomethine fragment, and only certain imines,[5b,6] nitrones,[7] and iminium salts[8] can be successfully trifluoromethylated. Reactions of fluorinated silanes with hydrazones have not been documented.

Our group has focused on the reactions of fluorinated silanes with various imines and iminium ions.[8a,b,9] Recently we described an approach for the activation of the *C*═N bond through the intramolecular complexation with Lewis acidic difluoroboryl group, which enables the interaction of poorly reactive N-alkylimines with Me_3SiCF_3 in the presence of Lewis base.[10] Herein we report the application of this methodology toward the trifluoromethylation of *N*-acylhydrazones.

N-Acylhydrazones are known to serve as useful templates in a number of allylation,[11] cycloaddition,[12] and radical addition[13] processes proceeding through the five-membered chelate structures. In this respect, we proposed that the difluoroboron complex bearing activated *C*═N bond would be amenable to coupling with the Me_3SiCF_3/Lewis base system.

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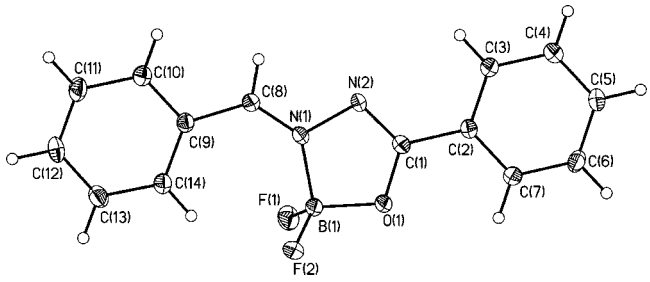
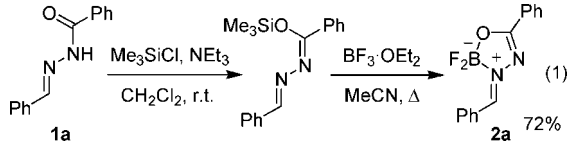
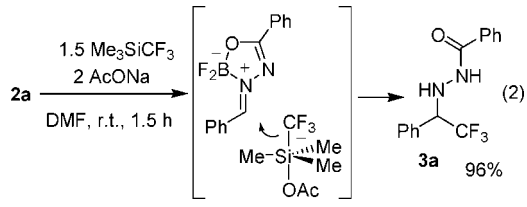


FIGURE 1. X-ray structure of complex **2a** presented in thermal ellipsoids at 50% probability.

For initial evaluation, *N*-benzoylhydrazone of benzaldehyde (**1a**) was selected as a model substrate. The silylation of **1a** followed by treatment of crude silylhydrazone with boron trifluoride etherate afforded difluoroboron complex **2a** in 72% yield after recrystallization (eq 1). The complex **2a** was characterized by NMR spectroscopy and X-ray diffraction analysis (Figure 1). It should be noted, that compound **2a** is the first well-defined boron−hydrazone complex.[14]



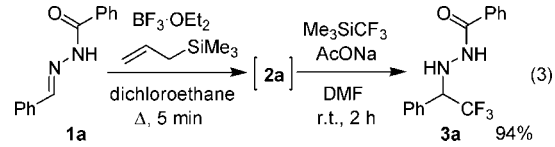
It was rewarding to find that treatment of **2a** with Me_3SiCF_3 and sodium acetate in DMF at room temperature afforded desired product **3a** in excellent yield after aqueous workup (eq 2). In this process, acetate anion behaves as a Lewis basic activator of the silicon reagent.



The three-step synthesis of **3a** can be performed without purification of intermediate silylhydrazone and complex **2a** with the overall yield of 88%. However, this procedure is inconvenient, since it requires handling of moisture-sensitive silylhydrazone, the isolation of which even in crude form involves filtration under argon.

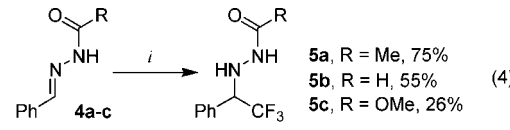
To find a more practical protocol obviating complicated steps we attempted to perform silylation and silicon−boron exchange in one reaction flask followed by reaction with Me_3SiCF_3/AcONa. Disappointingly, after extensive variation of stoichiometry, order of mixing, solvent, and temperature, the yields of **3a** not exceeding 75% were achieved. Application of the borylation procedure using $EtN(i\text{-}Pr)_2$ and $BF_3\cdot OEt_2$ that we reported earlier for salicyl aldimines[10] also gave only 40% yield of the product.

These experiments prompted us to surmise that the decreased yields are associated with the presence of ammonium salts.[15] To circumvent this problem we proposed a different approach for the difluoroborylation. Thus, treatment of hydrazone **1a** with $BF_3\cdot OEt_2$ and allyltrimethylsilane cleanly proceeded in chlorinated solvents affording the complex **2a**, with propene and Me_3SiF being the sole byproducts (eq 3).



Although in the case of **1a** the difluoroborylation occurred within 30 min at room temperature, for some other substrates brief heating was required. Consequently, the reflux in dichloroethane for 5 min was selected as a general procedure for the formation of boron complexes. Evaporation of solvent followed by addition of DMF, Me_3SiCF_3, and sodium acetate furnished compound **3a** in 94% yield.[16]

To probe the influence of the acyl group on the efficiency of the reaction, hydrazones **4a**−**c** bearing at nitrogen different substituents were evaluated under similar conditions (eq 4). Although in the case of acetyl group a reasonable yield of 75% was obtained, substrates with formyl and methoxycarbonyl groups gave products in notably decreased yields.



i: $BF_3\cdot OEt_2$, $CH_2{=}CHCH_2SiMe_3$, dichloroethane, Δ, 5 min; Me_3SiCF_3, AcONa, DMF, r.t., 2 h

A variety of *N*-benzoylhydrazones were involved in the trifluoromethylation reaction using the $BF_3\cdot OEt_2$/allylsilane system for the generation of difluoroboron complexes (Table 1, method A). Hydrazones derived from aromatic, α,β-unsaturated, heteroaromatic, and α-branched aldehydes furnished very good yields of products (entries 1−8). However, reactions of α-unbranched substrates were accompanied by unidentified impurities, removal of which by conventional column chromatography was problematic.[17] In this case, employment of silylation and silicon−boron exchange for the generation of borane complexes (method B) cleanly provided the desired trifluoromethylated products (entries 10, 12).

N-Benzoylhydrazones obtained from typical ketones were also tested in the trifluoromethylation process (Table 2). Although the formation of boron complexes proceeded cleanly, they proved to be significantly less reactive compared to aldehyde-derived counterparts, and elevated temperatures (50−55 °C) were required for their reactions with Me_3SiCF_3. Hydrazones of cyclohexanone, cyclopentanone, and acetone worked quite well, whereas lower yields were noted for acetophenone and cyclopropylmethyl ketone hydrazones.[18]

(14) Silicon and tin hydrazone complexes are known; see refs 11c and (a) Kalikhman, I.; Gostevskii, B.; Girshberg, O.; Sivaramakrishna, A.; Kocher, N.; Stalke, D.; Kost, D. *J. Organomet. Chem.* **2003**, *686*, 202. (b) Dey, D. K.; Lycka, A.; Mitra, S.; Rosair, G. M. *J. Organomet. Chem.* **2004**, *689*, 88.

(15) Ammonium salt may inhibit either formation or reaction of difluoroboron complex. For example, mixing of **2a** with Et_3NHCl, Me_3SiCF_3, and AcONa gave product in only 82% yield.

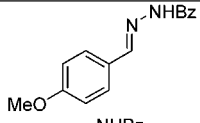
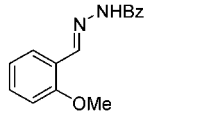
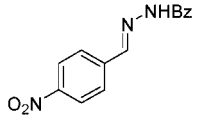
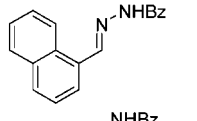
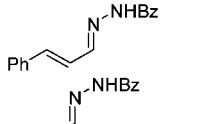
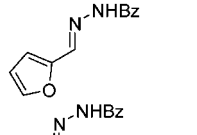
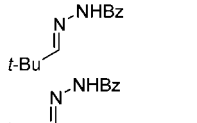
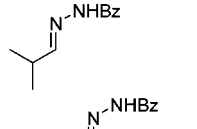
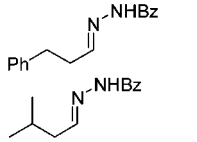
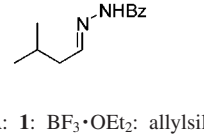
(16) Difluoroborylation with $BF_3\cdot OEt_2$ and allyltrimethylsilane cannot be performed in DMF, presumably due to high Lewis basicity of this solvent.

(17) We may propose that the side products originate from cycloaddition of boron complex with allylsilane, see ref 12b. However, when hydrazone **1j**, $BF_3\cdot OEt_2$, and allylsilane were refluxed in dichlorethane for 6.5 h, a complex mixture was formed.

(18) The reactions of these substrates provided complex mixtures, which may be associated with enolization of the methyl group followed by interaction of enamine fragment with the difluoroboryl group.

TABLE 1. Trifluoromethylation of *N*-benzoylhydrazones 1[a]

A: $BF_3{\cdot}OEt_2$, $CH_2{=}CHCH_2SiMe_3$, dichloroethane, Δ, 5 min
B: Me_3SiCl/NEt_3; $BF_3{\cdot}OEt_2$

entry	substrate		method	yield of **3**, %[b]
1		**1b**	A	79
2		**1c**	A	94
3		**1d**	A	88
4		**1e**	A	80
5		**1f**	A	91
6		**1g**	A	70
7		**1h**	A	96
8		**1i**	A	80
9		**1j**	A	68[c]
10			B	78
11		**1k**	A	66
12			B	87

[a] Method A: **1**: $BF_3{\cdot}OEt_2$: allylsilane = 1: 1.5: 1.5. Method B: **1**: NEt_3: Me_3SiCl: $BF_3{\cdot}OEt_2$ = 1: 1.2: 1.2: 1.2. For the second step, 2 equiv Me_3SiCF_3, 4 equiv AcONa. [b] Isolated yield. [c] Determined by NMR spectroscopy.

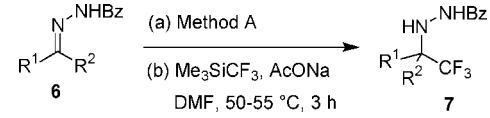
Besides the trifluoromethyl group, various other fluorinated substituents can be transferred from corresponding silanes, as demonstrated for the hydrazone **1a** (Table 3, entries 1−3). Even poorly reactive trifluorovinylsilane[19] was used as a source of trifluorovinyl fragment when reaction was carried out at harsher conditions (entry 4). At the same time, the reaction with the ketone hydrazone **6c** turned out to be notably less efficient (entry 5).[20]

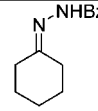
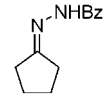
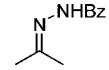
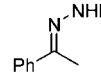
In summary, a convenient method for the addition of a trifluoromethyl group, as well other fluorinated fragments, to *N*-benzoylhydrazones has been described. Hydrazones derived from aldehydes are the best substrates for the reaction, leading to the fluorine-containing products inaccessible by other means. The intermediacy of the difluoroboron complexes constitutes the key feature of the reaction.

(19) Ritter, S. K.; Kirchmeier, R. L.; Shreeve, J. M.; Oberhammer, H. *Inorg. Chem.* **1996**, *35*, 4067.

(20) The low yield is due to incomplete conversion. This is likely owing to increased steric interactions upon the C−C bond-forming event between ketohydrazone electrophile and pentafluorophenyl nucleophile.

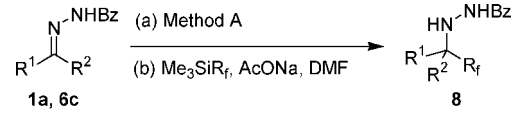
TABLE 2. Trifluoromethylation of *N*-benzoylhydrazones 6

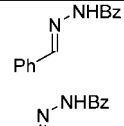
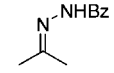


entry	substrate		yield of **7**, %[a]
1		**6a**	75
2		**6b**	61
3		**6c**	80
4		**6d**	46
5		**6e**	27

[a] Isolated yield.

TABLE 3. Variation of fluorinated silanes



Entry	Substrate	R_f	Condtns.[a]	Yield of **8**, %[b]
1	 **1a**	C_2F_5	r.t., 2 h	91
2		C_6F_5	r.t., 2 h	99
3		CCl_2F	r.t., 2 h	72
4		$CF{=}CF_2$	70 °C, 5 h	68
5	 **6c**	C_6F_5	50-55 °C, 3 h	17

[a] Conditions for the reaction of boron complexes with silanes. [b] Isolated yield.

Experimental Section

General Procedures for the Trifluoromethylation of *N*-Benzoylaldohydrazones. Method A. Allyltrimethylsilane (166 μL, 1.05 mmol) and $BF_3{\cdot}OEt_2$ (133 μL, 1.05 mmol) were successively added to a suspension of *N*-bezoylhydrazone (0.7 mmol) in 1,2-dichloroethane (1.4 mL), and the mixture was heated at gentle reflux for 5 min. The solvent was evaporated in vacuum, the residue was dissolved in DMF (1.4 mL) followed by addition of Me_3SiCF_3 (207 μL, 1.4 mmol) and NaOAc (230 mg, 2.8 mmol). The mixture was stirred for 2 h at room temperature, quenched with 1 mL of saturated aqueous Na_2CO_3, and stirred for additional 5 min. The mixture was diluted with water (∼10 mL) and extracted with ether (for **3a−c,e,g−k**) or ethyl acetate (for **3d,f**) (4 × 4 mL). The combined organic phase was dried with Na_2SO_4, concentrated, and the residue was flash chromatographed on silica gel.

Method B. Chlorotrimethylsilane (306 μL, 2.4 mmol) was added in one portion to a vigorously stirred mixture of hydrazone (2 mmol) and NEt_3 (334 μL, 2.4 mmol) in CH_2Cl_2 (4 mL). The resulting suspension was stirred for 10 min and then evaporated in vacuum. The residue was extracted with hexane (3 × 5 mL), filtering the hexane phases under argon, and the combined hexane extracts were concentrated, affording silylhydrazone as an oil. The crude silylhydrazone was dissolved in 1,2-dichloroethane (2 mL), and $BF_3 \cdot OEt_2$ (304 μL, 2.4 mmol) was added. This mixture was refluxed for 5 min and then concentrated in vacuum. The residue was dissolved in DMF (4 mL) followed by successive addition of Me_3SiCF_3 (443 μL, 3.0 mmol) and NaOAc (492 mg, 6.0 mmol). The mixture was stirred for 2 h at room temperature, quenched with 2 mL of saturated aqueous Na_2CO_3, and worked up as described in Method A.

***N′*-(2,2,2-Trifluoro-1-phenylethyl)benzohydrazide (3a).** Chromatography: hexanes/EtOAc, 3:1, R_f = 0.32 (hexane/EtOAc, 3:1). Mp = 97−98 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 4.61 (q, 1H, J = 6.9), 5.15 (d, 1H, J = 5.8), 7.31−7.57 (m, 8H), 7.70 (dd, 2H, J = 7.6, 1.5), 8.01 (d, 1H, J = 5.8). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 66.7 (q, J = 27.8), 125.0 (q, J = 281.4), 127.0, 128.6, 128.7, 128.9, 129.6, 131.9 (q, J = 1.7), 132.1, 132.2, 167.8. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −73.8 (d, J = 6.9). Calcd for $C_{15}H_{13}F_3N_2O$ (294.27): C 61.22, H 4.45, N 9.52. Found: C 61.24, H 4.50, N 9.24.

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Supporting Information Available: Experimental procedures; spectroscopic, analytical, and X-ray data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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