Direct Trifluoromethylation of Nitriles Promoted by Tetrabutylammonium Bifluoride

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Abstract: The direct trifluoromethylation of nitriles using $TMSCF_3$ is reported. This reaction is promoted by TBABF and provides α,α-bistrifluoromethylated amines in moderate to good yields. The reaction conditions are mild and tolerate a range of functional groups. The X-ray crystal structure of a bistrifluoromethylamine was obtained.

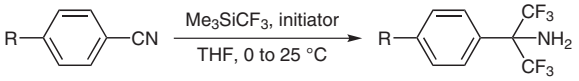
Key words: α,α-bistrifluoromethylated amines, nitriles, tetrabutylammonium bifluoride, trifluoromethyltrimethylsilane

Fluorinated molecules often display unique properties that make them suitable for numerous applications in pharmaceuticals,[1,2] agrochemicals,[3] and materials science.[4] Perfluoroalkyl-containing molecules often exhibit behavior distinct from their hydrocarbon counterparts. For instance, moieties such as the trifluoromethyl group can dramatically influence the polarity, solubility, chemical reactivity, and intermolecular interactions of an entire molecule.[5] Straightforward and reliable procedures for the introduction of the trifluoromethyl group are highly desirable.[6,7] In recent years the utilization of trifluoromethyltrimethylsilane ($TMSCF_3$), also known as the Ruppert–Prakash reagent, as a nucleophilic trifluoromethylating reagent has become the method of choice for introducing trifluoromethyl groups into various organic compounds. Because of the electrophilic nature of the carbonyl carbon, aldehydes and ketones are very reactive to nucleophilic attack by $TMSCF_3$ in the presence of a fluoride source such as tetrabutylammonium fluoride (TBAF).[8] Esters and nitrones were initially thought to be deactivated towards $TMSCF_3$ but were subsequently reported to be good substrates affording trifluoromethyl ketones[9] and trifluoromethylhydroxylamines[10] in good yields. Simple amides are less reactive due to the electron donation from the adjacent nitrogen which leads to deactivation of the carbon–nitrogen bond.[6] With such deactivated substrates, little conversion to product is observed, or low to moderate yields are obtained with the addition of additives such as TMS-imidazole to trap unstable intermediates.[10,11] The direct trifluoromethylation of nitriles to yield α,α-bistrifluoromethylated amines has not been reported in the literature. We wish to report herein the discovery that α,α-bistrifluoromethylated amines can be obtained in moderate to good yields in the presence of tetrabutylammonium bifluoride (TBABF).

During the course of a medicinal chemistry project, we were interested in preparing fluorinated amines. Very few routes for the synthesis of α,α-bis(trifluoromethyl)benzylamines have been reported. One such synthesis is based on the reaction of hexafluoroimine with an aromatic hydrocarbon under extremely vigorous Friedel–Crafts conditions ($AlCl_3$ as a catalyst at temperatures between 150–200 °C in an autoclave).[12] The yields ranged from 15–43%. Another route reported by Nesi et al. involved a multistep conversion of bistrifluoromethyl alcohols to the corresponding bistrifluoromethylamines via triflates followed by the displacement to azides and ultimately reduction to the amines.[13]

Our initial attempts to effect the trifluoromethylation of nitriles using 1 M THF solution of TBAF and $TMSCF_3$ (Table 1, entry 1) led only to starting material. Attempts to dry THF solutions of TBAF using molecular sieves or magnesium sulfate ($MgSO_4$) did not result in any improvement. Substitution of TBAF by tetramethylammonium fluoride (TMAF) also failed to yield any detectable

Table 1 Evaluating Reaction Conditions for Nitrile Trifluoromethylation



Entry[a]	R	Initiator	Yield (%)[b]
1	H	TBAF 1M THF	–
2	H	solid TBAF hydrate	(5)
3	Ph	solid TBAF hydrate	(10)
4	H	'dried' TBAF[c]	46
5	Ph	'dried' TBAF[c]	55
6	Me	'dried' TBAF[c]	48
7	SMe	'dried' TBAF[c]	80
8	Br	'dried' TBAF[c]	63

[a] Reactions were performed with 3 equiv of $TMSCF_3$ and 2 equiv of specified tetraalkylammonium fluoride in anhyd THF at 25 °C.
[b] Isolated yields; values in parentheses denote percent conversions based on integration of unpurified ^1H NMR spectrum.
[c] Heated under vacuum until reaching melting point, cooled and used directly

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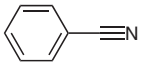
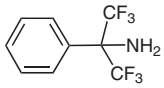
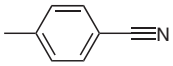
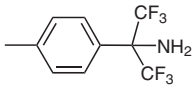
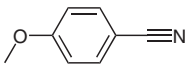
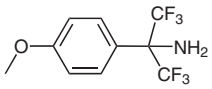
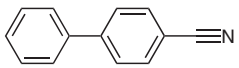
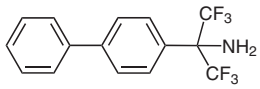
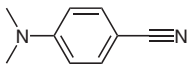
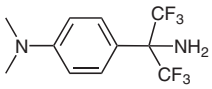
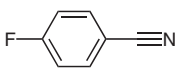
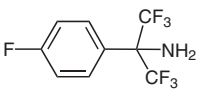
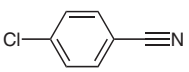
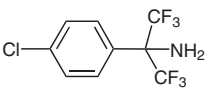
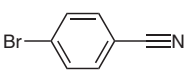
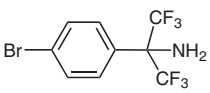
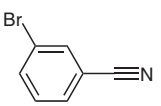
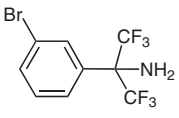
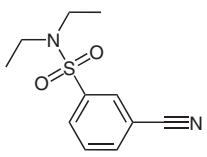
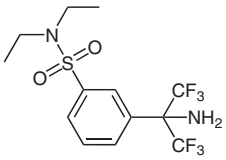
amount of product. Low but detectable conversion was observed when solid TBAF was used (entries 2 and 3).

TBAF is an extremely hygroscopic material, and we reasoned that further drying solid TBAF hydrate could lead to improved yields. Solid TBAF was therefore heated under vacuum until the material melted, cooled, and used directly. We were gratified to observe moderate to good yields of the desired α,α-bistrifluoromethylamines (Table 1, entries 4–8). The fluorinated products are easily detected by NMR and are characterized by a broad singlet by ^{1}H NMR at δ = 2.1–2.3 ppm and a septet by ^{13}C NMR at δ = 63–65 ppm.

References both to the difficulty of removing water from tetraalkylammonium fluorides and to their instability are well documented in the literature.[14] Fry el al.[15] concluded that it is very unlikely that pure, anhydrous tetraalkylammonium fluoride salts have ever been produced in the case of ammonium ions susceptible to E2 elimination. In fact, TBABF is isolated after heating TBAF at temperatures between 44–77 °C. This led us to wonder if the actual promoter for the direct trifluoromethylation of nitriles to the bistrifluoromethylamines was TBABF. We performed ^{19}F NMR experiments in THF to investigate the composition of the 'dried solid TBAF' and the major peak observed was a doublet at δ = –149 ppm (J_{HF} = 123 Hz), which is consistent with the formation of TBABF.[14] Based on this finding, we decided to investigate the use of pure TBABF as a promoter for the direct trifluoromethylation of nitriles to bistrifluoromethylamines. TBABF has been reported to be a mild and efficient fluorinating agent[16] with good solubility in organic solvents such as THF and displays good thermal stability at temperatures below 140 °C. To the best of our knowledge, TBABF has not been reported to initiate trifluoromethylation reactions of C=O or C=N

Table 2 Trifluoromethylation of Various Nitriles Promoted by TBABF

Entry[a]	Substrate	Product	Conversion (%)[b]	Yield (%)[c]
1			69	58
2			92	78
3			57	52
4			86	79
5			27	18
6			75	63
7			64	54
8			77	75
9			91	76
10			92	82

[a] Reactions were performed in anhyd THF with 5 equiv of $TMSCF_3$ and 2.1 equiv of TBABF from 0–25 °C, 2 h.
[b] Conversion based on integration of unpurified ^{1}H NMR spectrum and LC-MS analysis.
[c] Unoptimized yields.

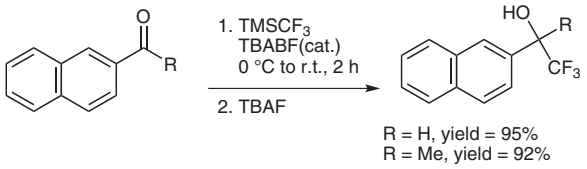
groups with $TMSCF_3$. We treated a variety of nitriles with $TMSCF_3$ and commercially available TBABF as a promoter in anhydrous THF at room temperature, and our findings are summarized in Table 2.[17]

Evaluation of the reaction scope highlights a substrate profile that tolerates a variety of substitutions. In general, the yields vary from moderate to high. Electron-withdrawing groups are likely to polarize the nitrile bond, which would facilitate the trifluoromethylation reaction (entries 6–10). In the case of electron-donating groups, the observed yields were low to moderate, with the dimethylaniline being the least reactive substrate tested. The X-ray structure[18] of the sulfonamide product (Table 2, entry 10) was obtained and unambiguously shows the formation of the bistrifluoromethylated amine.

With a few exceptions, N–H imines have been reported as unstable and difficult to isolate. However, Gosselin et al.[19] reported that solvolysis of *N*-TMS-ketimines in MeOH proceeds readily with cleavage of the nitrogen–silicon bond and isolation of stable N–H trifluoromethylimines. We believe that the trifluoromethylation reaction goes through similar intermediates (Figure 1) where the initial addition of the CF_3 group to the nitrile provides trifluoromethylimine intermediates followed by a second CF_3 addition to afford the desired bistrifluoromethylamines.

Figure 1 Potential imine intermediates for the addition of $TMSCF_3$ to aryl nitriles

Since the discovery of the direct trifluoromethylation reaction of carbonyl compounds with $TMSCF_3$ by Prakash et al.,[8] the most commonly used sources of fluorine include TBAF and cesium fluoride. We wondered if TBABF could also catalyze the trifluoromethylation of aldehydes and ketones. Examples of substrates containing an aldehyde and a ketone are shown in Scheme 1. 2-Naphthylaldehyde and 2′-acetonaphthone reacted in the presence of $TMSCF_3$ and a catalytic amount of TBABF to provide the desired trifluoromethyl alcohols in 95% and 92% yields, respectively.



Scheme 1 TBABF-catalyzed trifluoromethylation of aldehydes and ketones

In conclusion, we report the first example of direct trifluoromethylation of nitriles using $TMSCF_3$. This reaction is promoted by TBABF and provides bistrifluomethylated amines in moderate to good yields. TBABF is not as hydroscopic as TBAF and is more thermally stable. We also showed that TBABF could be used instead of TBAF in the trifluoromethylation of aldehydes and ketones. Further expansion of the reaction scope using electrophiles such as imines and nitrones and examination of other perfluoroalkylation reactions will be reported in due course.

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References and Notes

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(16) Bosh, P.; Camps, F.; Chamarro, E. *Tetrahedron Lett.* **1987**, *28*, 4733.
(17) **Typical Procedure for Trifluoromethylation of Various Nitriles Promoted by TBABF**
Biphenyl-4-carbonitrile (110 mg, 0.61 mmol) was dissolved in THF (4 mL). Under nitrogen at 0 °C (trifluoromethyl)trimethylsilane (0.45 mL, 3.05 mmol, 5 equiv) was added. To this mixture was then added TBAF·HF (0.360 g, 1.28 mmol, 2.1 equiv) solution in THF (4 mL). The cooling bath was removed, and the reaction mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated under rotary vacuum to give a light yellow gum. Column chromatography of the residue (silica gel, hexane–EtOAc = 5:1) provided 2-biphenyl-4-yl-1,1,1,3,3,3-hexafluoropropan-2-amine (154 mg, 79%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.3 Hz, 2 H), 7.63–7.69 (m, 2 H), 7.56–7.63 (m, 2 H), 7.42–7.50 (m, 2 H), 7.35–7.42 (m, 1 H), 2.20 (br s, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.2, 140.3, 129.7, 129.3, 128.3, 128.2, 127.7, 127.6, 124.3 (q, *J* = 286.9 Hz), 65.4 (spt, *J* = 27.8 Hz). HRMS (ESI$^+$): *m/z* calcd for $C_{15}H_{12}F_6N$ [M + H]$^+$: 320.08684; found [M + H]$^+$: 320.08670.
(18) CCDC 729907 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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