Nucleophilic Trifluoromethylation of *N*-Tosyl Aldimines

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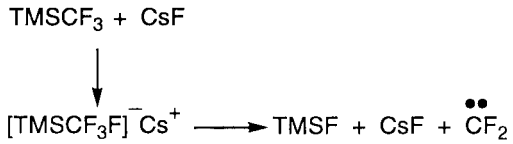
Abstract: $TMSCF_3$ and tetrabutylammonium (triphenylsilyl) difluorosilicate (TBAT) were used for efficient nucleophilic trifluoromethylation to *N*-tosyl aldimines. Aromatic, aliphatic and α,β-unsaturated sulfonaldimines were efficiently trifluoromethylated to obtain the corresponding sulfonamide adducts in good to excellent yields.

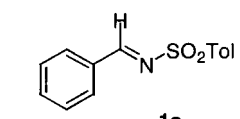
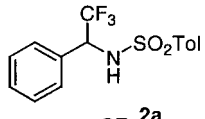
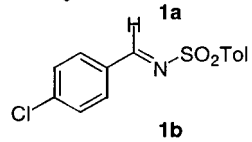
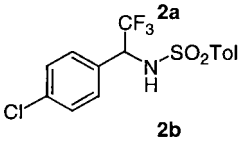
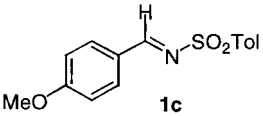
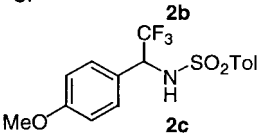
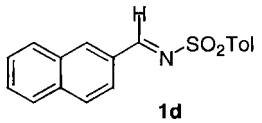
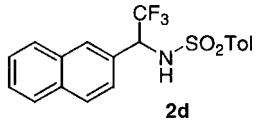
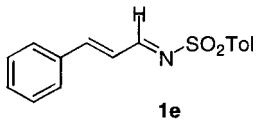
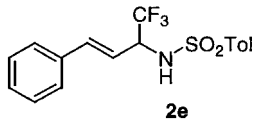
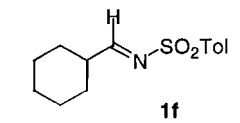
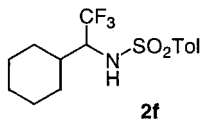
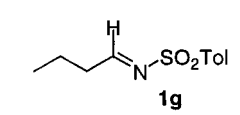
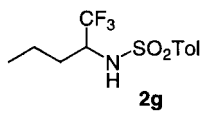
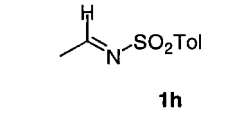
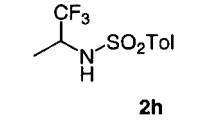
Key words: amines, drugs, imines, nucleophilic addition, sulfonamides

Although, many of synthetic drugs contain nitrogen,[1] introduction of fluorine often results in very special beneficial properties[2] due to fluorine's high electronegativity and lipophilicity of the C-F bond. There have been, however, only few literature reports[3] regarding the preparation of trifluoromethylated amines. As their preparation from imines is advantageous, we were interested in their direct nucleophilic trifluoromethylation. We have recently reported efficient stereoselective trifluoromethylation of *N-tert*-butanesulfinimines[4] using $TMSCF_3$ and CsF or TBAT (tetrabutylammonium (triphenylsilyl) difluorosilicate). In that study[4] with CsF we encountered two problems: a) conversion of imines was incomplete even in presence of excess $TMSCF_3$ and CsF and b) imines with an α-hydrogen failed to undergo reaction with $TMSCF_3$ due to the basic nature of CsF. We surmised that the low electrophilicity of sulfinimines together with instability of pentavalent silicate species (Scheme 1) resulted in the low yields. We have now overcome these problems by the use of following two approaches: a) increasing the electrophilicity of imines by using *N*-tosyl aldimines,[5,6] and b) employing a nonmetallic fluoride source. When sulfonaldimines were reacted with $TMSCF_3$ in the presence of TBAF (tetrabutylammonium fluoride) the desired products were obtained in only low yields with concomitant formation of trifluoromethane (the hydrolysis product of $TMSCF_3$) because of the strong hygroscopic nature of TBAF. We have found that tetrabutylammonium (triphenylsilyl) difluorosilicate (TBAT),[7] a soluble fluoride source, is very effective for our nucleophilic trifluoromethylation reaction.[4] Thus reaction of sulfonaldimines with $TMSCF_3$ in the presence of TBAT afforded the trifluoromethylated product in good to excellent isolated yields (see Table). The reaction temperatures have been optimized and the best results were achieved between 0-5 °C.



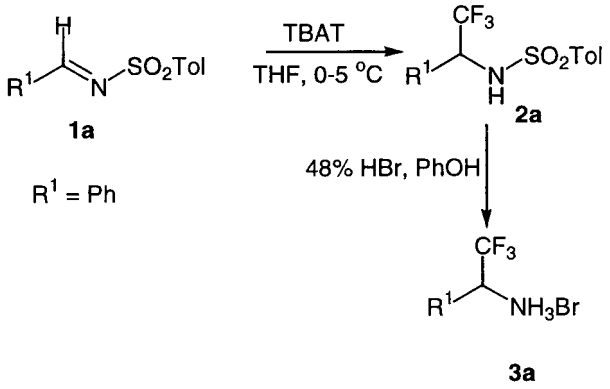
Scheme 1

Table Nucleophilic Trifluoromethylation of *N*-Tosyl Aldimines.

Subtrate	Product	Yield (%)
 **1a**	 **2a**	90
 **1b**	 **2b**	87
 **1c**	 **2c**	85
 **1d**	 **2d**	95
 **1e**	 **2e**	83
 **1f**	 **2f**	80
 **1g**	 **2g**	50
 **1h**	 **2h**	45

In a typical reaction, 0.36 mmol TBAT was dissolved in 4 mL of dry THF and cooled to 0 °C under inert conditions. In a separate flask, 0.3 mmol of the imine and 0.39 mmol $TMSCF_3$ were mixed in 3 mL THF. The mixture of imine and $TMSCF_3$ was slowly added via a syringe to the

solution of TBAT. The reaction mixture was stirred for 45 min to 1 h while maintaining the reaction temperature at 0-5 °C. Saturated NH_4Cl (2 mL) was added at 0 °C and the reaction mixture was slowly warmed to ambient temperature. The quenched reaction mixture was extracted three times with ethyl acetate and the combined organic layer was dried over anhydrous Na_2SO_4. Evaporation of the solvent under vacuum followed by column chromatography (silica gel, hexanes\ethyl acetate 10\1) gave the sulfonamides as white solids. In one case, the *p*-toluenesulfonyl group of **2a** was removed by treatment with phenol and 48% HBr to obtain **3a**[8] as a hydrobromide salt in 90% isolated yield (Scheme 2).



Scheme 2

Trifluoromethylation of benzaldimine **1a**, which contains no α hydrogen adjacent to the imine group, proceeded smoothly to give adduct **2a** in excellent yield. Aromatic imines with electron withdrawing as well as electron donating group underwent similar trifluoromethylation. Even sterically bulky naphthyl sulfonaldimine **1d** reacted smoothly to give **2d**[9] in 95% isolated yield. Most interestingly, α,β-unsaturated imine **1e**, gave exclusively the 1,2 -addition product in good yield. Even sulfonaldimines containing an enolizable α hydrogen reacted smoothly, for example, **1f** giving the trifluoromethylated adduct in 80% yield. Aliphatic sulfonaldimines, **1g** and **1h**, however, gave lower yield of the product because of their inherent instability. *N*-Tosyl ketimines, on the other hand, under the similar reaction conditions gave very poor yield of the trifluoromethylated adduct.

In summary, we have developed a very efficient method for the preparation of trifluoromethylated amine derivatives by trifluoromethylation of corresponding *N*-tosyl aldimines.

Acknowledgement

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References and Notes

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(8) Spectral data for **3a**: ^{1}H NMR (500 MHz, CD_3OD) δ 5.37 (q, 1H, J = 7.9 Hz), 7.55 (m, 5H), the NH_3^+ protons could not be observed due to rapid proton-deuteron exchange with the methanol solvent; ^{13}C NMR (125 MHz, CD_3OD) δ 56.6 (q, $^2J_{C\text{-}F}$ = 32.8 Hz), 124.8 (q, $^1J_{C\text{-}F}$ = 278 Hz), 129.5, 129.6, 130.6, 132.1; ^{19}F (500 MHz, CD_3OD) δ −73.2 (d, $J_{F\text{-}H}$ = 5.6 Hz).
(9) Spectral data for **2d**: ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.15 (s, 3H), 5.07 (m, 1H), 6.18 (d, 1H, J = 8.9 Hz), 6.96 (d, 2H, J = 8.2 Hz), 7.24-7.75 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1, 60.7 (q, $^2J_{C\text{-}F}$ = 31.8 Hz), 125.8 (q, $^1J_{C\text{-}F}$ = 281 Hz), 125.9, 127.5, 127.8, 127.9, 128.5, 129.0, 129.3, 129.5, 130.1, 130.6, 131.2, 134.1, 134.5, 136.3, 139.2, 144.5; ^{19}F (360 MHz, $CDCl_3$) δ −73.9 (d, $J_{F\text{-}H}$ = 7.14 Hz); HRMS (DEI) m/z calc for $C_{19}H_{16}F_3NO_2S$ (M^+) 379.0853, found 379.0863.

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