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Selective Deprotection of *N*-Tosyl Alkoxyamines Using Bistrifluoromethane Sulfonimide: Formation of Oxime Ethers

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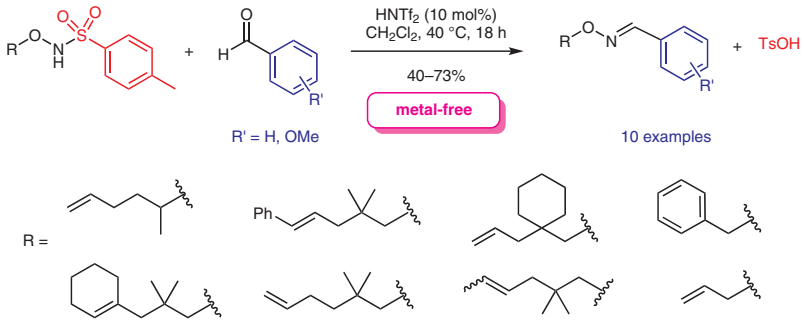

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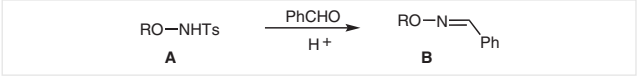
Abstract The detosylation of *N*-tosyl alkoxyamines was realized by treatment with benzaldehyde and bistrifluoromethane sulfonimide as the catalyst to afford the corresponding oxime ethers. The reaction is chemoselective as *N*-tosyl amines are not deprotected. A mechanism is proposed for this deprotection.

Key words *N*-detosylation, bistrifluoromethane sulfonimide, *N*-tosyl-alkoxyamine, benzaldehyde, oxime ethers

Protection and subsequent deprotection of amines are routine procedures used in multistep synthesis of polyfunctionalized molecules. Among the diverse protecting groups of amines, the tosyl group is one of the most versatile one.

N-Tosyl amines are readily formed, easy to purify, and are stable under a variety of conditions. However, the robustness of *N*-tosyl amines can be a disadvantage and they are notoriously difficult to cleave. A number of methods has been reported such as electrolysis,[1] Li/naphthalene,[2] Birch reduction conditions,[3] refluxing in HCl,[4] Ni(acac)$_2$/*i*PrMgCl,[5] $TiCl_4$,[6] Mg/MeOH,[7] Bu_3SnH/AIBN,[8] Na/K metal on silica,[9] Mg/Me_3CoLi,[10] SmI_2/HMPA or SmI_2/DMPU,[11] SmI_2/ROH,[12] and SmI_2/H_2O/amine.[13]

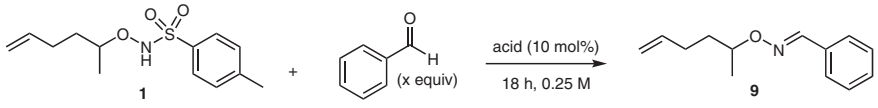
During our study dealing with the reactivity of *N*-tosyl alkoxyamines,[14] we observed that, when a *N*-tosyl alkoxyamine was treated with an aromatic aldehyde under acidic conditions, a detosylation occurred and an oxime ether was formed (Scheme 1).



Scheme 1 One-step *N*-detosylation/oximation under acidic conditions

Our study started with *N*-tosyl alkoxyamine **1** (Table 1). When this *N*-tosyl alkoxyamine was treated with benzaldehyde (PhCHO, 2 equiv) in the presence of different Brønsted

Table 1 Optimization Studies: Effect of the Acid



Entry	Acid	Solvent	Temp (°C)	x equiv	Conversion (%)	Yield (%)[a]
1	$MeCO_2H$	CH_2Cl_2	40	2	5	0
2	CF_3CO_2H	CH_2Cl_2	40	2	13	0
3	PTSA	CH_2Cl_2	40	2	24	18
4	$HNTf_2$	CH_2Cl_2	40	2	100	65
5	$HNTf_2$	CH_2Cl_2	40	1	60	40
6	$FeCl_3$	CH_2Cl_2	40	2	8	0

[a] Isolated yield.

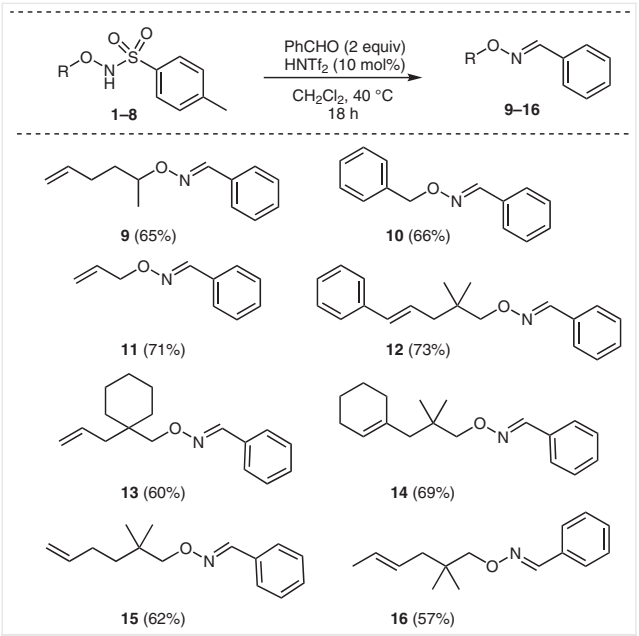
acids (10 mol%) with increasing acidity such as CH_3CO_2H, CF_3CO_2H, PTSA only a low conversion of **1** was noticed and no identifiable compounds were formed, except in the presence of PTSA as **9** was isolated with a yield of 18% (Table 1, entry 3). By using a very strong Brønsted acid such as bistrifluoromethane sulfonimide[15] ($HNTf_2$, 10 mol%), in CH_2Cl_2 at 40 °C, the conversion of **1** was total and oxime **9** was isolated with a yield of 65% (Table 1, entry 4). By decreasing benzaldehyde from 2 to 1 equivalent, the conversion of **1** was decreased (60% instead of 100%) and the yield of **9** was only 40% (Table 1, entry 5). It is worth mentioning that the use of a Lewis acid such as $FeCl_3$ induced a very low conversion of **1** and **9** was not observed (Table 1, entry 6).

As $HNTf_2$ was revealed to be the best Brønsted acid to convert **1** into oxime **9**,[16,17] in the presence of 2 equivalents of benzaldehyde, a screening of the conditions, e.g., solvent, temperature, and concentration of **1** was undertaken (Table 2). This screening revealed that CH_2Cl_2 was the best solvent (Table 2, entries 1–3) and 40 °C the optimum temperature (Table 2, entries 4and 5). The best yield of **9** was obtained when 10 mol% of $HNTf_2$ were used (Table 2, entry 6). In addition, a decrease in the concentration of **1** led to a decrease in the yield of **9** (Table 2, entry 7).

Having optimized conditions,[18] the generalization of the reaction was studied. *N*-Tosyl alkoxyamine **1** was applied in the detosylation/oxime formation with different aldehydes in the presence of 10 mol% of bistrifluoromethane sulfonimide ($HNTf_2$, 10 mol%), and the results are reported in Table 3.

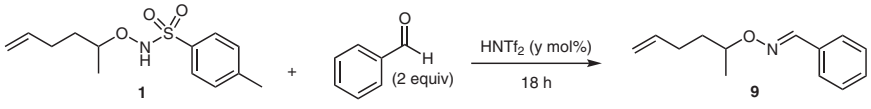
When electron-rich aromatic aldehydes were used, the conversion of **1** and the yield in the corresponding oxime ethers (**17**[19] and **18**[20]) was lower than when using benzaldehyde (Table 3, entries 2–4). When aliphatic aldehydes were reacted with **1**, the conversion of **1** was low and no traces of the corresponding oxime ethers were detected by ^1H NMR analysis of the crude reaction mixtures (Table 3, entries 5–8).

With the optimized conditions, the scope was further examined by treating different *N*-tosyl alkoxyamines with 2 equivalents of benzaldehyde and 10 mol% of $HNTf_2$, at 40 °C in CH_2Cl_2. Whatever the nature of the *N*-tosyl alkoxyamine, the yields were in the range of 57–73%. The results are reported in Scheme 2.



Scheme 2 Scope of the reaction. Isolated yields are given.

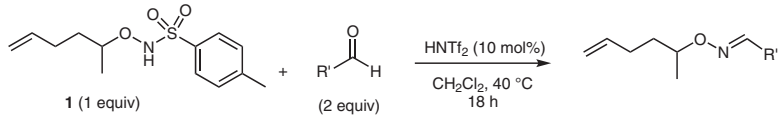
Table 2 Optimization Studies: Reaction Conditions

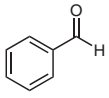
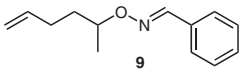
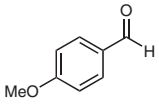
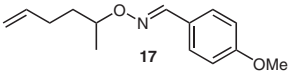
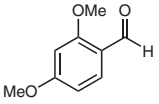
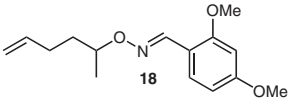
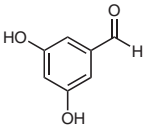


Entry	Solvent	Temp (°C)	c (M)	y	Conversion (%)	Yield (%)[a]
1	CH_2Cl_2	40	0.25	10	100	65
2	$C_2H_4Cl_2$	40	0.25	10	86	60
3	THF	40	0.25	10	55	37
4	CH_2Cl_2	r.t.	0.25	10	52	38
5	CH_2Cl_2	70[b]	0.25	10	82	53
6	CH_2Cl_2	40	0.25	5	60	40
7	CH_2Cl_2	40	0.10	10	60	36

[a] Isolated yield.
[b] With microwave irradiation.

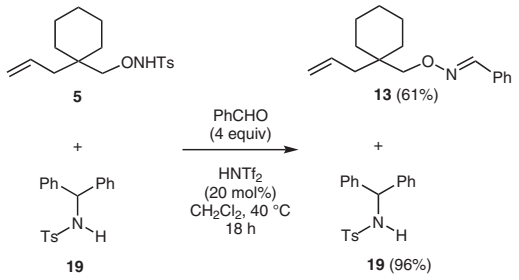
Table 3 Optimization Studies: Effect of the Aldehyde



Entry			Yield (%)[a]
1		 **9**	65
2		 **17**	51
3		 **18**	40
4		–	0
5		–	0
6		–	0
7		–	0

[a] Isolated yield.

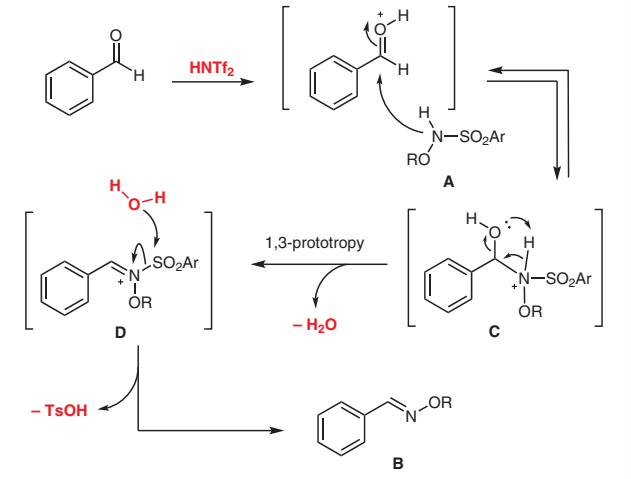
It is worth mentioning that the reaction is chemoselective. When **5** and *N*-tosyl sulfonamide **19** were treated with benzaldehyde in the presence of $HNTf_2$, only the *N*-tosyl alkoxyamine **5** was transformed into the oxime ether **13**,[21] and **19** was recovered (Scheme 3).



Scheme 3 Reactivity of *N*-tosyl alkoxyamine vs *N*-tosyl amine

With this latter result, we can exclude the activation of the *N*-tosyl group by $HNTf_2$. Thus, the formation of oxime ethers **B** from *N*-tosyl alkoxyamines **A** can be explained by the activation of benzaldehyde by $HNTf_2$, with **A** being nucleophilic enough to attack the activated benzaldehyde. Intermediate **C** can be produced, which after 1,3-prototropy, leads to **D**. The nucleophilic attack of H_2O on **D** then produces **B** and TsOH (Scheme 4).

In summary, the use of bistrifluoromethane sulfonimide in the presence of benzaldehyde allows the chemoselective *N*-detosylation/oximation of *N*-tosyl-alkoxyamines. This metal-free method can be useful to prepare biologically active oxime ether derivatives.



Scheme 4 Proposed mechanism

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610298.

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(16) Compound **9** was isolated as a mixture of *E*- and *Z*-isomers in a ratio 96:4.

(17) **Spectral Data of (*E*)-9**
IR: ν = 2923, 1640, 1446, 1373, 1335, 1210, 1089, 967, 910, 900 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.06 (s, 1 H), 7.60–7.50 (m, 2 H), 7.40–7.30 (m, 3 H), 5.85 (m, 1 H), 5.04 (dq_{app}, *J* = 17.0, 1.8 Hz, 1 H), 4.97 (m, 1 H), 4.32 (m, 1 H), 2.18 (m, 2 H), 1.83 (m, 1 H), 1.59 (m, 1 H), 1.30 (d, *J* = 6.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.2, 138.4, 130.8, 129.7, 128.4 (2 C), 126.9 (2 C), 114.6, 79.9, 34.8, 29.7, 19.2. MS (EI): *m/z* = 203 (13) [$M^{+\bullet}$], 202 (40), 188 (8), 158 (8), 132 (3), 122 (7), 121 (10), 120 (9), 104 (42), 94 (4), 89 (5), 82 (6), 78 (9), 77 (47), 67 (15), 65 (8), 55 (100), 51 (13).

(18) **General Procedure for the Synthesis of Oxime Ethers from *N*-Tosyl Alkoxyamines**
In a round-bottom flask, a mixture of a solution of *N*-tosyl alkoxyamide (0.2 mmol, 1 equiv) in anhydrous CH_2Cl_2 (*c* = 0.25 M), aldehyde (2 equiv), and a solution of $HNTf_2$ (0.1 equiv) in anhydrous CH_2Cl_2 was stirred at 40 °C for 18 h. The reaction mixture was cooled to r.t. and saturated aqueous Na_2CO_3 was added. The two phases were separated, and the aqueous layer was extracted four times with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate) to obtain the desired oxime ether.

(19) **Spectroscopic Data for 17**
^1H NMR (400 MHz, $CDCl_3$): δ = 8.02 (s, 1 H), 7.52–7.49 (m, 2 H), 6.90–6.70 (m, 2 H), 5.85 (m, 1 H), 5.04 (dq_{app}, *J* = 17.1, 1.8 Hz, 1 H), 4.96 (m, 1 H), 4.29 (m, 1 H), 3.82 (s, 3 H), 2.20–2.15 (m, 2 H), 1.81 (m, 1 H), 1.60 (m, 1 H), 1.29 (d, *J* = 6.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.7, 147.5, 138.5, 128.3 (2 C), 125.4, 114.5, 114.1 (2C), 78.7, 55.3, 34.9, 29.7, 19.8. MS (EI): *m/z* = 233 (22) [$M^{+\bullet}$], 232 (33), 218 (26), 188 (11), 174 (13), 162 (10), 151 (41), 150 (22), 147 (15), 146 (9), 136 (20), 135 (58), 134 (78), 108 (50), 107 (20), 92 (19), 91 (12), 77 (36), 67 (6), 55 (100), 51 (7). HRMS (ESI): *m/z* calcd for $C_{14}H_{20}NO_2$ [M + H]$^+$: 234.1489; found: 234.1485.

(20) **Spectroscopic Data for (*E*)-18**

IR: ν = 3077, 2969, 2936, 2838, 1607, 1572, 1504, 1463, 1438, 1418, 1372, 1311, 1283, 1270, 1208, 1159, 1120, 1107, 1068, 1034, 993, 965 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.37 (s, 1 H), 7.72 (d, *J* = 8.6 Hz, 1 H), 6.48 (dd, *J* = 8.6, 0.5 Hz, 1 H), 6.42 (d, *J* = 2.3 Hz, 1 H), 5.85 (m, 1 H), 5.03 (dq_{app}, *J* = 17.1, 1.8 Hz, 1 H), 4.95 (m, 1 H), 4.28 (m, 1 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 2.17 (m, 2 H), 1.81 (m, 1 H), 1.60 (m, 1 H), 1.29 (d, *J* = 6.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.1, 158.7, 143.9, 138.6, 127.2, 114.4, 114.3, 105.3, 98.2, 78.5, 55.5, 55.4, 34.9, 29.7, 19.8. MS (EI) *m/z*: 263 ($M^{+\cdot}$, 12), 204 (10), 192 (11), 177 (14), 166 (10), 164 (37), 163 (15), 150 (18), 149 (100), 137 (12), 134 (14), 122 (14), 121 (44), 120 (18), 107 (16), 92 (10), 91 (10), 79 (11), 77 (22), 67 (10), 55 (59). HRMS (ESI): *m/z* calcd for $C_{15}H_{22}NO_3$ $[M + H]^+$: 264.1594; found: 264.1591.

(21) **Spectroscopic Data for 13**

IR: ν = 3073, 2925, 1573, 1448, 1340, 1273, 1210, 1046, 944, 913 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.09 (s, 1 H), 7.60–7.55 (m, 2 H), 7.40–7.30 (m, 3 H), 5.87 (m, 1 H), 5.06–5.00 (m, 2 H), 4.04 (s, 2 H), 2.17 (dt_{app}, *J* = 7.5 Hz, 0.9 Hz, 2 H), 1.43 (m, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.7, 134.8, 132.5, 129.5, 128.6 (2 C), 126.8 (2 C), 117.3, 79.5, 40.1, 37.2, 32.7 (2 C), 26.2, 21.4 (2 C). MS (EI): *m/z* = 257 (14), 256 (36), 132 (5), 122 (62), 106 (100), 104 (58), 95 (30), 93 (12), 81 (64), 79 (20), 69 (13), 55 (30), 51 (13).