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The First Example of Saccharin-Lithium Bromide Catalysis: Direct Synthesis of *N*-Tosylimines from Alcohols

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Abstract: The first procedure to access *N*-tosylimines directly from alcohols under mild and neutral conditions is reported. The protocol involves saccharin-lithium bromide-catalyzed oxidation of alcohols to aldehydes/ketones with chloramine-T followed by their condensation with the *in situ* generated oxidation by-product *p*-toluenesulfonamide in the same reaction vessel to afford *N*-tosylimines in 40–90% overall yields. The present work opens up a new and efficient synthetic route to *N*-tosyimines directly from alcohols in a one-pot procedure.

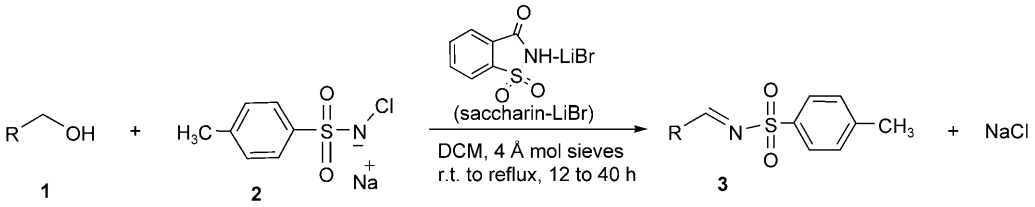
Keywords: alcohols; catalysis; chloramine-T; oxidation; saccharin-lithium bromide; *N*-sulfonylimines

Imines bearing electron-withdrawing *N*-substituents are useful intermediates in organic synthesis.[1] *N*-Sulfonylimines have been increasing in importance in the last two decades[2] as they are one of the few types of electron-deficient imines[3] that are stable enough to be isolated but reactive enough to undergo addition reactions.[4] They are used in numerous reactions such as nucleophilic addition,[5] hetero-Diels–Alder,[6] or ene reactions.[7] In addition, *N*-sulfonylimines are excellent precursors for the preparation of aziridines[8] and oxaziridines.[9] Thus, various synthetic routes to *N*-sulfonylimines have been developed, which include Lewis acid-catalyzed reactions[10] of sulfonamides with aldehydes, rearrangement of oxime *O*-sulfinates,[11] tellurium-mediated reaction of aldehydes with chloramine-T,[12] reaction of *N*-TMS-imines with sulfonyl chloride,[13] microwave-facilitated, acid-catalyzed direct condensations,[14] and utilization of acetic anhydride as dehydrating and acylation agent.[15]

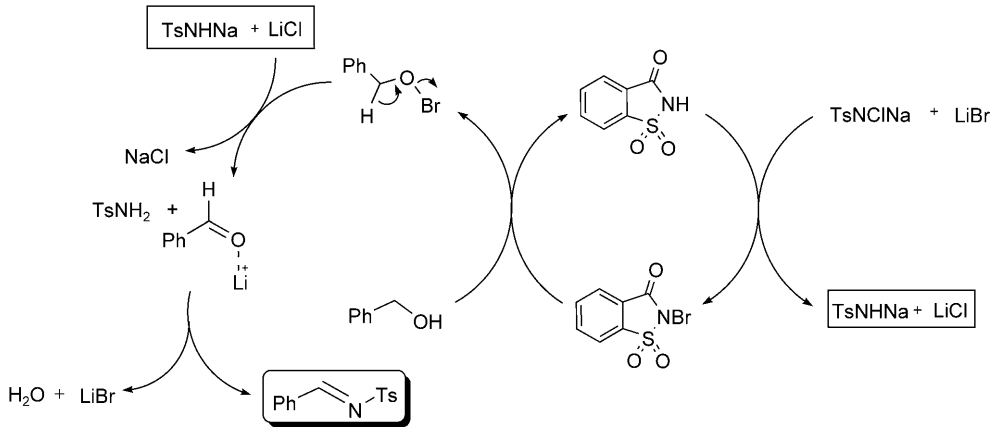
The direct condensation of carbonyl compounds with sulfonamides is used as the straightforward route for the preparation of *N*-sulfonylimines,[16] which usually requires harsh acidic conditions, high temperatures and often dehydrating apparatus. Furthermore, some other methods need cumbersome experimental and multi-step procedures. Recently, a few examples of the catalytic *N*-alkylation of sulfonamides with benzylic alcohols have been reported to proceed *via* *N*-sulfonylimine formation, but in none of these cases have the sulfonylimines been isolated.[17]

All the methods available for the synthsis of *N*-sulfonylimines utilize an aldehyde or a ketone as one of the starting materials. However, some of the aldehydes are volatile, toxic, or unstable, especially because of aerial oxidation. Thus, in many cases aldehydes must be purified just before their use because the presence of other products affects not only the concentration of the active aldehyde but also the impurities often interfere with chemical reactions involving the aldehyde. Alcohols are usually more stable, less volatile, and less toxic than the corresponding aldehydes and, meanwhile, the oxidation of alcohols is an important method for forming aldehydes. Moreover, one-pot multi-step reactions are of increasing academic, economical and ecological interest because they address fundamental principles of synthetic efficiency and reaction design.

Several methods for the formation of imines by coupling alcohols with amines in the presence of an oxidant have been reported[18] but, to the best of our knowledge, there is no report on the formation of *N*-sulfonylimines starting directly from alcohols. This is presumably because of the weak nucleophilicity of sulfonamides requiring activation of the condensing aldehydes/ketones and operationally special conditions to combine the oxidation and condensation steps in a domino process. Thus, it is an interesting target of investigation, which prompted us to develop a convenient one-pot synthesis of *N*-tosylimines directly from alcohols as an endeavour in continuation of our work on one-pot multi-step syntheses.[19] We reasoned that chloramine-T would be a well suited oxidant for the conversion of alcohols to the corresponding aldehydes or ketones for the present study because it leaves $TsNH_2$ as a by-product, which could be utilized in the subsequent step to afford *N*-tosylimines in a one-pot operation (Scheme 1).



Scheme 1. Direct synthesis of *N*-tosylimines from alcohols.



Scheme 2. A plausible mechanism for the conversion of an alcohol to an *N*-sulfonylimine.

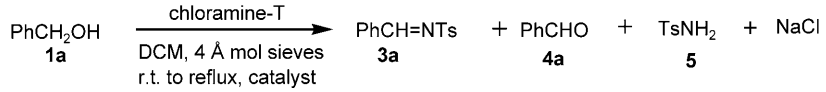
In order to realize the envisaged protocol, we investigated the direct synthesis of *N*-sulfonylimines *via* oxidative coupling of benzyl alcohol (5 mmol) with chloramine-T (5 mmol) using the saccharin-LiBr catalyst system in dichloromethane (DCM). In this reaction chloramine-T oxidizes benzyl alcohol to benzaldehyde and itself is reduced to *p*-toluenesulfonamide. The freshly generated aldehyde and sulfonamide condense to form *N*-tosylimines in the same reaction vessel (Scheme 1). Plausibly, the alcohol is oxidized to the corresponding aldehyde by *in situ* generated *N*-bromosaccharin as depicted in Scheme 2.

A systematic study was undertaken to screen the catalyst system for the synthesis of *N*-sulfonylimine **3a** with various imides and metal halides (Table 1). It was found that among the catalysts tested, saccharin-LiBr gave the best result (Table 1 entry 6), whereas the other structurally analogous imides gave comparatively low yields (Table 1, entries 4 and 5). This is probably due to more electrophilic nature of *N*-bromosaccharin compared with *N*-bromosuccinimide and *N*-bromophthalimide. Out of metal halides tested, LiBr showed better catalytic activity than KBr (Table 1, entries 3 and 6), presumably due to the higher Lewis acidity of lithium ions. Likewise, LiCl and LiI were found to be far less effective than LiBr under the same reaction conditions. On the other hand, among several suitable solvents tested, DCM was found to be most suitable (Table 2, entry 4).

The present optimized synthesis of *N*-sulfonylimine **3a** involves the stirring of equimolar mixture of benzyl alcohol and chloramine-T in DCM using saccharin-LiBr (30 mol%) as the catalyst at room temperature for 3 h followed by addition of molecular sieve (4 Å) and refluxing for 9 h. After several minute of stirring at room temperature, the reaction mixture became thick then it turned yellowish to red and in the course of completion of the reaction it became yellowish at reflux. As shown in Table 3, the scope of the reaction of alcohols with chloramine-T was explored. For benzyl alcohol and substituted benzyl alcohols containing either electron-withdrawing or electron-donating substituents, or heteroaryl alcohols (Table 3, entries 1–9 and 14) the reactions proceeded smoothly and afforded *N*-sulfonylimines **3** in moderate to high yields. For the nitro- and chloro-substituted benzyl alcohols, the reaction proceeded comparatively slower and gave moderate yields (Table 3, entries 2, 3 and 8). Similarly, *ortho*-substituted benzyl alcohols gave relatively low yields (Table 3, entries 7 and 8).

A variety of aliphatic alcohols were also examined to explore the scope of this reaction. Primary alcohols showed good reactivity and gave good yields of the corresponding imines (Table 3, entries 10 and 11). In case of secondary alcohols, the reaction proceeded slower and gave low yields of the corresponding ketimines (Table 3, entries 12 and 13).

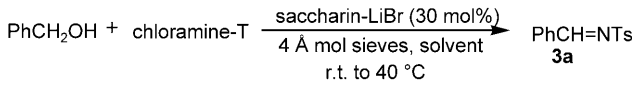
Table 1. Optimization of catalyst for the synthesis of *N*-sulfonylimines.[a]



Entry	Catalyst [mol%][b]	Time [h]	Yield [%][c] of		
			3a	**4a**	**5**
1	succinimide-KBr [30 mol%]	26	30	50	52
2	phthalimide-KBr [30 mol%]	25	32	52	53
3	saccharin-KBr [30 mol%]	20	35	62	63
4	succinimide-LiBr [30 mol%]	16	70	15	17
5	phthalimide-LiBr [30 mol%]	14	78	17	18
6	saccharin-LiBr [30 mol%]	12	90	5	6
7	KBr [50 mol%]	24	–	44	8
8	LiBr [50 mol%]	24	40	10	13
9	LiBr [100 mol%]	24	56	15	17
10	saccharin [40 mol%]	22	–	53	56
11	saccharin-LiBr [20 mol%]	16	65	15	18
12	saccharin-LiBr [40 mol%]	12	90	6	7

[a] *Reaction conditions:* benzyl alcohol (5 mmol), chloramine-T (5 mmol), DCM (3 mL), 4 Å mol sieves (200 mg).
[b] Mol% of each catalyst.
[c] Yields of the isolated pure compounds.

Table 2. Optimization of solvent.



Entry	Solvent	Time [h]	Yield [%][a]
1	acetonitrile	18	70
2	1,4-dioxane	23	65
3	THF	17	58
4	DCM	12	90
5	toluene	24	68
6	DMF	30	trace

[a] Yield of isolated and purified compound **3a**.

In summary, we have developed the first saccharin-LiBr catalyzed convenient synthesis of *N*-sulfonylimines directly from alcohols. The protocol involves oxidation of alcohols to aldehydes or ketones with chloramine-T followed by their condensation with the *in situ* formed oxidation by-product *p*-toluenesulfonamide to afford *N*-tosylimines in a one-pot operation. The present work opens up a new and efficient one-pot synthetic route to *N*-sulfonylimines directly from alcohols.

Experimental Section

General Procedure for One-Pot Synthesis of *N*-Sulfonylimines Directly from Alcohols

In a mixture of alcohol **1** (5 mmol), chloramine-T (5 mmol) and saccharin (30 mol%) in 3–5 mL of DCM was added LiBr (30 mol%) portionwise with stirring at room temperature. After stirring the reaction mixture for 3 h at room temperature, 4 Å molecular sieve (200 mg) was added and stirred for 9–37 h at reflux temperature. The reaction progress was monitored by TLC. Upon completion (Table 3), the solvent was evaporated under reduced pressure, the residue dissolved in 10 mL THF, filtered and *n*-hexane (5–10 mL) was added to afford a crude product. The crude product was recrystallized/from THF-*n*-hexane (1:1) to afford analytically pure *N*-sulfonylimines **3**. The oily compounds (Table 3, entries 11–13) were purified by flash chromatography (silica gel, Et_2O-hexane, 3:2). The structures of the products were confirmed by comparison of their mp, TLC, IR or ^{1}H NMR data with authentic samples obtained commercially or prepared by the literature methods.[10–12,16d,f]

Since all the products are known, the spectral data of only some typical compounds are given below:

***N*-Benzylidene-*p*-toluenesulfonamide**: white solid; yield: 90%; mp 111–112 °C; IR (KBr): ν_{max} = 1650, 1570, 1380, 1326, 1160 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 9.04 (s, 1H), 7.92–7.87 (m, 4H), 7.61 (t, J = 7.5 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 23.3, 127.4, 129.1, 130.2, 131.1, 131.9 133.2, 139.8, 145.7, 171.1; MS (EI): m/z = 259 [M$^+$].

***N*-(*p*-Chlorobenzylidene)-*p*-toluenesulfonamide**: white solid; yield: 69%; mp 174–176 °C; IR (KBr): ν_{max} = 1652, 1565, 1370, 1320, 1163 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 9.02 (s, 1H), 7.90–7.87 (m, 4H), 7.49 (d, J = 7.4 Hz, 2H), 7.36 (d, J = 7.1 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 23.2, 128.5, 129.7, 130.1, 131.3, 132.7 135.2, 140.2, 145.6, 170.2; MS (EI): m/z = 295 [(M + 2)$^+$], 293 [M$^+$].

***N*-(*p*-Methoxybenzylidene)-*p*-toluenesulfonamide**: white solid; yield: 87%; mp 128–129 °C; IR (KBr): ν_{max} = 1665, 1563, 1375, 1325, 1168 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.97 (s, 1H), 7.91–7.88 (m, 4H), 7.36 (d, J =

Table 3. One-pot synthesis of *N*-sulfonylimines.[a]

Entry	Alcohol	Product **3**	Time [h][b]	Yield [%][c,d]	mp [°C]	Ref.
1	$C_6H_5CH_2OH$	C_6H_5CH=NTs	12	90	111–112	[10]
2	*m*-$O_2NC_6H_4CH_2OH$	*m*-$O_2NC_6H_4CH$=NTs	25	60	141–142	[16d]
3	*p*-$ClC_6H_4CH_2OH$	*p*-ClC_6H_4CH=NTs	25	69	174–176	[10]
4	*p*-$BrC_6H_4CH_2OH$	*p*-BrC_6H_4CH=NTs	19	85	181–183	[12]
5	*p*-$MeOC_6H_4CH_2OH$	*p*-$MeOC_6H_4CH$=NTs	20	87	128–129	[12]
6	*m*-$MeOC_6H_4CH_2OH$	*m*-$MeOC_6H_4CH$=NTs	20	88	78–79	[16f]
7	*o*-$BrC_6H_4CH_2OH$	*o*-BrC_6H_4CH=NTs	24	70	140–141	[16f]
8	*o*-$ClC_6H_4CH_2OH$	*o*-ClC_6H_4CH=NTs	27	63	133–134	[16d]
9	*p*-$MeC_6H_4CH_2OH$	*p*-MeC_6H_4CH=NTs	16	89	110–112	[15]
10	$(CH_3)_3CCH_2OH$	$(CH_3)_3CCH$=NTs	19	82	101–102	[12]
11	*n*-$C_3H_7CH_2OH$	*n*-C_3H_7CH=NTs	24	80	oil	[16d]
12	$(CH_3)_2CHOH$	$(CH_3)_2C$=NTs	35	40	oil	[11]
13	cyclohexanol	cyclohexyl=NTs	40	43	oil	[11]
14	2-furylCH_2OH	2-furylCH=NTs	17	83	99–100	[16d]

[a] See Experimental Section for general procedure.
[b] Total stirring time.
[c] All the products are known compounds[10–12,16d,f] and were characterized by comparison of their mp, TLC, IR and ^{1}H NMR data with those of authentic samples.
[d] Yields of the isolated pure compounds.

8.0 Hz, 2H), 6.99 (d, J=8.8 Hz, 2H), 3.91 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ=23.1, 56.7, 116.5, 126.1, 128.7, 130.5, 135.1, 139.6, 145.2, 165.1, 170.3; MS (EI): m/z=289 [M$^+$].

2,2-Dimethyl-*N*-tosylpropan-1-imine: white solid; yield: 82%; mp 101–102 °C; IR (KBr): ν_{max}=1630, 1327, 1165 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=9.02 (s, 1H), 7.83 (d, J=8.7 Hz, 2H), 7.35 (d, J=8.7 Hz, 2H), 2.44 (s, 3H), 1.2 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ=23.4, 27.8, 33.2, 128.9, 131.3, 139.3, 145.1, 169.8; MS (EI): m/z=239 [M$^+$].

***N*-Tosylpropan-2-imine**: yellowish oil; yield: 40%; IR (neat): ν_{max}=1646, 1330, 1153 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=7.84 (d, J=8.6 Hz, 2H), 7.34 (d, J=8.6 Hz, 2H), 2.51 (s, 3H), 2.49 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ=18.1, 23.2, 27.9, 129.0, 130.2, 140.1, 145.2, 170.1; MS (EI): m/z=211 [M$^+$].

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