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A Facile Synthesis of *N*-Sulfonyl and *N*-Sulfinyl Aldimines under Barbier-Type Conditions

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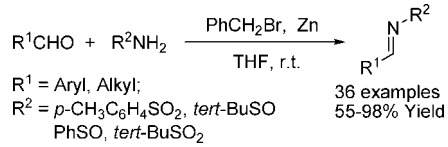

A convenient synthesis of *N*-sulfonyl- and *N*-sulfinylimines by the condensation of aldehydes with sulfonyl or sulfinyl amides in the presence of benzyl bromide and zinc dust at room temperature under the Barbier-type conditions is reported. The procedure is lauded by its simplicity and adaptability to aromatic, α,β-unsaturated, and aliphatic aldehydes.

N-Sulfonyl- and *N*-sulfinylimines are of increasing importance because they are versatile intermediates in organic synthesis.[1] As powerful substrates, they can undergo various nucleophilic addition reactions,[2] radical reactions,[3] and hetero-Diels–Alder reactions[4] to afford the expected *N*-sulfonyl- and *N*-sulfinylamide derivatives. Although there are a variety of methods developed for the preparation of *N*-sulfonylimines,[5,6] the direct condensation of aldehydes with sulfonyl amides is still the ideal procedure.[7] However, due to the weak nucleophilicity of sulfonamide, harsh acidic conditions and high temperature are normally required in the condensation reactions.[8] These conditions are not compatible with the resulting imines, especially with those derived from the aliphatic aldehydes because of their instability and ease of enolization. Although a few existing indirect methods can be applied to synthesize these *N*-sulfonylimines,[5] it is still desired to find an efficient procedure for the direct condensation of aldehydes with sulfonyl amides under mild reaction conditions. We report herein an efficient and simple procedure for the direct condensation reactions of aldehydes with *N*-sulfonyl- and *N*-sulfinylamides under mild Barbier-type conditions using benzyl bromide and zinc dust to synthesize the *N*-sulfonyl- and *N*-sulfinylimines.

Multicomponent reactions of aldehydes, amines, and organometallic reagents are known as a versatile method for the synthesis of amines.[9,10] We have reported a three-component, one-pot benzylation and allylation of aromatic and aliphatic

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SCHEME 1

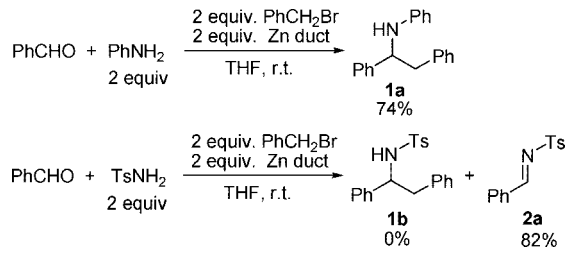
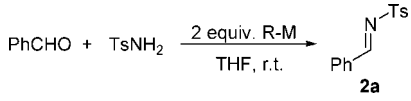


TABLE 1. Condensation Reactions of Benzaldehyde and $TsNH_2$ with Various Organometallic Reagents[a]



entry	R-M	**2a**[b] (%)	entry	R-M	**2a**[b] (%)
1	$PhCH_2Br$, Zn	82	6	*t*-BuLi	trace
2	CH_2=$CHCH_2Br$, Zn	0	7	*n*-BuLi, $ZnBr_2$	11
3	Et_2Zn	trace	8	*t*-BuLi, $ZnBr_2$	65
4	$PhCH_2Br$, Mg	trace	9	$ZnBr_2$	0
5	*n*-BuLi	0	10	$ZnBr_2$, 4Å AMS	0

[a] All reactions were conducted on a 1 mmol scale. [b] Isolated yield based on the benzaldehyde.

aldehydes and amines under Barbier-type conditions.[11] As a part of our program to develop the synthetic application of sulfonamides,[12] we tried to synthesize some homobenzyl *N*-sulfonylamides using the same procedure. However, the reaction of benzaldehyde and 4-methylbenzenesulfonamide under the same conditions did not give rise to the expected benzylation product **1b** but instead *N*-4-methylbenzenesulfonyl imine **2a** in 82% yield (Scheme 1). No homobenzyl *N*-sulfonylamide was obtained even though the amounts of benzyl bromide and zinc dust were increased to 3 equiv with a longer reaction time and a higher temperature.

In order to understand the reaction pathway, several organometallic reagents were examined. When benzyl bromide was replaced by allylic bromide, the allylation product of benzaldehyde was obtained as the only product (Table 1, entry 2). Only trace or no *N*-4-methylbenzenesulfonyl imine **2a** was detected from the reactions of diethylzinc, benzyl Grignard reagent, *n*-butyllithium, and *tert*-butyllithium (Table 1, entries 3–6). When the mixture of 2 equiv of $ZnBr_2$ with *n*-butyllithium was used, the expected product **2a** was isolated in 11% yield, while the butylation product of benzaldehyde was isolated as the byproduct (Table 1, entry 7).[13] The yield of **2a** increased to 65% using a mixture of $ZnBr_2$ with *tert*-butyllithium (Table 1, entry 8). No *N*-4-methylbenzenesulfonyl imine **2a** was formed in the absence of organometallic reagents even in the presence of 4 Å MS as the dehydrating reagent (Table 1, entries 9 and 10).

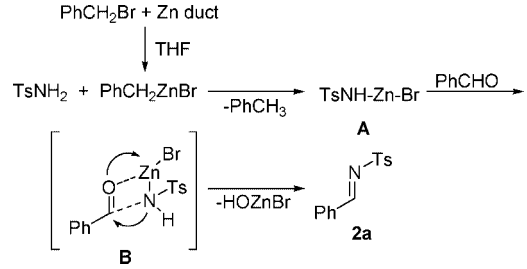
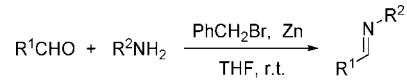


FIGURE 1. Plausible pathway for the condensation of benzaldehyde with $TsNH_2$ under the Barbier-type conditions.

TABLE 2. Condensation of Aldehyde with Amide under the Barbier-Type Conditions[a]



entry	aldehyde	amide	imine[b] (%)
1	PhCHO	$TsNH_2$	**2a** (93)
2	4-$CH_3C_6H_4CHO$	$TsNH_2$	**2b** (81)
3	3-$CH_3C_6H_4CHO$	$TsNH_2$	**2c** (76)
4	4-$CH_3OC_6H_4CHO$	$TsNH_2$	**2d** (75)
5	4-$(CH_3)_2NC_6H_4CHO$	$TsNH_2$	**2e** (88)
6	4-ClC_6H_4CHO	$TsNH_2$	**2f** (73)
7	2-ClC_6H_4CHO	$TsNH_2$	**2g** (55)
8	2-BrC_6H_4CHO	$TsNH_2$	**2h** (61)
9	4-FC_6H_4CHO	$TsNH_2$	**2i** (68)
10	1-naphthyl	$TsNH_2$	**2j** (73)
11	2-thiophene	$TsNH_2$	**2k** (61)
12	$(CH_3)_2C$=CHCHO	$TsNH_2$	**2l** (67)
13	(*E*)-CH_3CH=$C(CH_3)CHO$	$TsNH_2$	**2m** (66)
14	$CH_3C(CH_3)_2CHO$	$TsNH_2$	**2n** (85)[c,d]
15	$CH_3CH(CH_3)CH_2CHO$	$TsNH_2$	**2o** (81)[c,d]
16	$CH_3(CH_2)_2CH(CH_3)CHO$	$TsNH_2$	**2p** (80)[c,d]
17	PhCHO	*t*-$BuSONH_2$	**3a** (92)
18	4-$CH_3C_6H_4CHO$	*t*-$BuSONH_2$	**3b** (92)
19	4-$CH_3OC_6H_4CHO$	*t*-$BuSONH_2$	**3d** (89)
20	4-ClC_6H_4CHO	*t*-$BuSONH_2$	**3f** (96)
21	2-Cl-C_6H_4CHO	*t*-$BuSONH_2$	**3g** (98)
22	2-BrC_6H_4CHO	*t*-$BuSONH_2$	**3h** (98)
23	4-FC_6H_4CHO	*t*-$BuSONH_2$	**3i** (96)
24	1-naphthyl	*t*-$BuSONH_2$	**3j** (88)
25	2-furan	*t*-$BuSONH_2$	**3q** (83)
26	2-thiophene	*t*-$BuSONH_2$	**3k** (94)
27	2-pyridine	*t*-$BuSONH_2$	**3r** (57)
28	3-pyridine	*t*-$BuSONH_2$	**3s** (60)
29	$(CH_3)_2C$=CHCHO	*t*-$BuSONH_2$	**3l** (91)
30	$CH_3C(CH_3)_2CHO$	*t*-$BuSONH_2$	**3n** (56)
31	$CH_3CH(CH_3)CH_2CHO$	*t*-$BuSONH_2$	**3o** (76)
32	$CH_3(CH_2)_2CH(CH_3)CHO$	*t*-$BuSONH_2$	**3p** (91)
33	$CH_3(CH_2)_6CHO$	*t*-$BuSONH_2$	**3t** (92)
34	$CH_3CH_2CH(CH_2CH_3)CHO$	*t*-$BuSONH_2$	**3u** (78)
35	PhCHO	$PhSONH_2$	**3v** (82)
36	PhCHO	*t*-$BuSO_2NH_2$	**2q** (70)

[a] Reactions were conducted on a 1 mmol scale. [b] Isolated yield based on the amide. [c] 1 equiv of aldehyde was used. [d] Conversion yield based on the amide determined from the ^1H NMR of the crude products after workup.

A plausible pathway is shown in Figure 1. $PhCH_2ZnBr$ acted as a base to deprotonate 4-methylbenzenesulfonamide to form a zinc species **A** and $PhCH_3$. The zinc atom in **A** would activate benzaldehyde as a Lewis acid, and then the intermediate **A** reacted with benzaldehyde via a four-membered ring transition state **B** to generate the condensation product **2a**. In this

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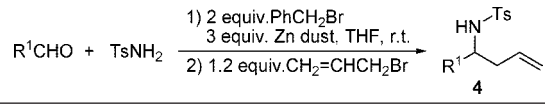
TABLE 3. One-Pot Condensation and Allylation Reactions[a,b]



entry	aldehyde	4[c] (%)
1	PhCHO	**4a** (91)
2	4-$CH_3OC_6H_4CHO$	**4d** (82)
3	4-FC_6H_4CHO	**4i** (81)
4	$(CH_3)_2C{=}CHCHO$	**4l** (88)
5	(*E*)-$CH_3CH{=}C(CH_3)CHO$	**4m** (87)
6	$CH_3C(CH_3)_2CHO$	**4n** (81)
7	$CH_3CH(CH_3)CH_2CHO$	**4o** (76)
8	$CH_3(CH_2)_2CH(CH_3)CHO$	**4p** (71)
9	$CH_3(CH_2)_6CHO$	**4t** (72)

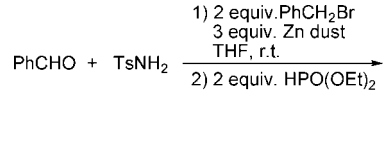
[a] 1.1 equiv of aldehyde was used. [b] Reactions were conducted on a 1 mmol scale. [c] Isolated yield based on the amide.

condensation reaction, $PhCH_2ZnBr$ worked not only as the dehydrating agent but as a Lewis acid to promote the reaction.

Optimization of the reaction conditions showed that no further activation of the zinc powder was necessary, and the best ratio among benzaldehyde, $TsNH_2$, benzyl bromide, and zinc was 1.5:1:2:3, in which the yield of **2a** increased to 93%. As shown in Table 2, entries 1–16, the scope of the condensation reactions of aldehydes with 4-methylbenzenesulfonamide was explored. It turned out that our proposed reaction system could adapt to various aldehydes. For aromatic aldehydes containing either electron-withdrawing or -donating substituents, or the hetaryl aldehydes (Table 2, entries 1–11), the reactions proceeded smoothly and gave rise to the aromatic *N*-Ts imines in moderate to high yields, comparable with the reactions of other methods. Because of the mild condensation reaction conditions, α,β-unsaturated aldehydes and nonenolizable or enolizable aliphatic aldehydes were also good candidates for the reactions (Table 2, entries 12–16) despite their low reactivity and inherent instability. This protocol could also be applied in the synthesis of *N*-*tert*-butanesulfinylimine,[14] *N*-benzenesulfinylimine,[15] and *N*-*tert*-butanesulfonylimine[5b] (Table 2, entries 17–36). The procedure was effective for a wide range of aldehydes, including electron-rich aldehydes and unreactive sterically demanding aldehydes.

After the reaction, benzyl bromide was converted into toluene, and the zinc salt formed in the reaction could be removed by a simple wash with brine. The resulting stable imines could be purified by recrystallization or column chromatography. Aliphatic *N*-Ts imines **2n**, **2o**, **2p**, and **2t** were not purified because of their instability. Further investigation indicated that the condensation reactions and allylation of the resulting *N*-Ts imines could be carried out in one pot (Table 3). Because of the excess of zinc dust in the condensation reactions, the addition of allylic bromide was enough to make the allylation reactions occur. Homoallylic *N*-sulfonylamides **4** derived from various aldehydes were obtained from the one-pot reactions. The formations of **4n**, **4o**, **4p**, and **4t** in good yields also verified the formations of the unstable aliphatic *N*-Ts imines **2n**, **2o**, **2p**, and **2t**.

The basic zinc salts formed in the condensation reaction could act as a base and a Lewis acid to promote the subsequent one-pot nucleophilic addition. When diethyl phosphate was used as the nucleophile, no other base or Lewis acid was required in the addition step (1).[16]



(1)

In summary, we have developed an efficient and simple method for the synthesis of *N*-sulfonyl- and *N*-sulfinylimines by the condensation of aldehydes with sulfonyl- and sulfinylamides in the presence of benzyl bromide and zinc dust at room temperature under Barbier-type conditions. The potential of this reaction system can be evaluated by its adaptability to a wide variety of aldehydes and the mild reaction conditions. In addition, the one-pot procedure for the condensations and the following nucleophilic additions offers manipulability by avoiding the isolation of the unstable imine intermediates. The further development of asymmetric reactions is ongoing and will be reported in due course.

Experimental Section

General Procedure for the Condensation of Aldehyde with Amide under the Barbier-Type Conditions. A Schlenk tube was charged with zinc dust (195 mg, 3 mmol), evacuated, and backfilled with argon. Benzyl bromide (238 μL, 2 mmol) and THF (2 mL) were added. After the mixture was stirred at room temperature for 15 min, amide (1 mmol) and aldehyde (1.5 mmol) were successively added. The reaction mixture was stirred at room temperature until the amide disappeared as monitored by TLC. The mixture was quenched with brine and extracted with ethyl acetate (100 mL × 3). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel or recrystallization to provide the desired product. *N*-Benzylidene-4-methylbenzenesulfonamide **2a**: ^1H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 1H), 7.88–7.94 (m, 4H), 7.62 (t, $J = 7.5$ Hz, 1H), 7.49 (t, $J = 7.6$ Hz, 2H), 7.35 (d, $J = 8.2$ Hz, 2H), 2.44 (s, 3H). The spectral data are consistent with those reported in the literature.[5a]

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Supporting Information Available: Experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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