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One-pot Preparation of Homopropargylic *N*-Sulfonylamines Catalyzed by Zinc Powder

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A new one-pot method for synthesis of homopropargylic *N*-sulfonylamines from aldehydes catalyzed by zinc powder is described. The procedure is lauded by its simplicity, good yields, and adaptability to a wide variety of aldehydes.

Owing to the versatility of homopropargylic *N*-sulfonylamines as intermediates in organic synthesis,[1] extensive studies on their preparation have been well documented.[2] Among them, the addition of organometallic reagents to imines has long been recognized as a highly versatile method. Transition metals such as magensium,[3] silver,[4] chromium,[5] indium,[6] and palladium[7] have been used for this purpose. In addition, ring-opening reactions of aziridines with acetylides also provide a useful protocol.[8] However, the reported methods are associated with one or more of the following drawbacks: harsh conditions, complex experimental manipulations, and the use of hazardous and expensive reagents. Furthermore, some methods require multistep procedures.[9] On the other hand, the aliphatic *N*-tosylimines are labile to decomposition during purification by silica gel column chromatography or during distillation at high temperature. It is difficult to purify aliphatic *N*-tosylimines even though recrystallization is feasible. As a result, the substrate scope of electrophilic addition to imines is limited.

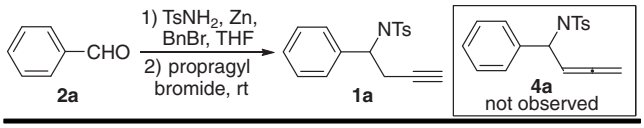
As an important catalyst,[10] zinc has been reported to be applied in the allylation and benzylation of imines. In the presence of zinc powder, homobenzylamines and homoallylamines were prepared in good yields in THF, and the reactions were also carried out under solvent-free conditions.[11] Nevertheless, the propargylation of *N*-sulfonylimines has received much less scrutiny, and only one example of a zinc-mediated addition to imines has been reported.[1c]

We describe herein the first zinc-catalyzed synthesis of homopropargylic *N*-sulfonylamines using an efficient and simple one-pot procedure for the direct condensation of aldehydes with *p*-toluenesulfonamide.

A systematic study was undertaken to define the best condition, and the representative data are listed in Table 1.[12] In general, a mixture of benzyl bromide and activated zinc powder[13] was stirred for 30 min, then *p*-toluenesulfonamide (1 mmol) and benzaldehyde were successively added. The mixture was stirred until the amide disappeared as monitored by TLC. Then, propargyl bromide was added dropwise.

The reactions of organozinc reagents always require strict reaction conditions such as inert atmosphere.[11c] However, our present route proceeded well in air (Table 1, Entries 1 and 2). Then we studied the effect of catalyst amount on the conversion of the reaction. By changing the amount of zinc powder from 2 to 4 equiv, the yield increased to 49% (Entries 2–4), but higher amount of zinc powder (5 equiv) did not improve the yield. Variation of the ratio of aldehyde to *N*-tosylamide had significant impact on the conversion. With a 1.5:1 ratio, the yield was 49%.

Table 1. Examination of reaction conditions[a]



Entry	Aldehyde /equiv	Zn /equiv	Temp /°C[b]	Yield /%[c]
1[d]	1.5	3.0	25	46
2	1.5	3.0	25	44
3	1.5	2.0	25	39
4	1.5	4.0	25	49
5	1.5	5.0	25	48
6	1.1	4.0	25	58
7	1.0	4.0	25	50
8	0.9	4.0	25	38
9	1.1	4.0	40	63
10	1.1	4.0	60	71
11	**1.1**	**4.0**	**reflux**	**76**
12[e]	1.1	4.0	reflux	9

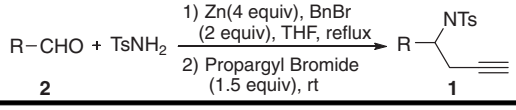
[a]The reactions were conducted on a 1 mmol scale. [b]Temperature of reaction step 1. [c]Isolated yield based on the amide. [d]N_2 atmosphere. [e]No BnBr was used.

The excessive aldehyde led to an increased by-product homopropargyl alcohol 1-phenylbut-3-yn-1-ol (**3a**).[14] When we decreased the amount of aldehyde to a ratio of 1.1:1, the yield did increase significantly (58%) (Entry 6). However, when the ratio reached 1:1 or less, the yields decreased (Entries 7 and 8). By changing the temperature of reaction step 1 from 25 °C to reflux, the yield increased to 76% (Entries 9–11). This suggested that high temperature could enhance the reaction. Due to the weak nucleophilicity of *p*-toluenesulfonamide, high temperature was usually required.[15] To get more information on the optimal catalytic conditions, we also carried out intensive investigations to define the necessity of benzyl bromide. Only 14% conversion of imine was detected by ^{1}H NMR and 9% isolated yield of compound **1a** was obtained without addition of benzyl bromide.

It is known that propargylic organometallic reagents exist as an equilibrium mixture of allenic and propargylic species.[16] Hence, the use of metal-catalyzed additions of propargylic reagents to electrophiles has been previously limited by low regioselectivity. Interestingly, in our work its regioisomer (i.e., **4a**) was not observed by ^{1}H NMR. Significantly, both ^{1}H NMR and GC-MS for the reaction mixture confirmed the formation of toluene, which should be the product of BnBr.

After optimization of the reaction conditions, a range of structurally diverse aromatic and aliphatic aldehydes were studied, and the results are summarized in Table 2.[12] It was clear from the table that the reactions proceeded efficiently and the desired products were obtained in good yields. For aromatic

Table 2. Substrate scope of the reaction[a]



2 1

Entry	2 (R=)	Product	Yield /%[b]
1	4-$(CH_3)C_6H_4$	**1b**	74
2	2-$(CH_3)C_6H_4$	**1c**	65
3	4-$(CH_3O)C_6H_4$	**1d**	72
4	3,4-$(CH_3O)_2C_6H_3$	**1e**	69
5	4-ClC_6H_4	**1f**	71
6	4-BrC_6H_4	**1g**	78
7	2-BrC_6H_4	**1h**	60
8	4-$CF_3C_6H_4$	**1i**	73
9		**1j**	69
10	$CH_3(CH_2)_5CH_2$	**1k**	65
11	$BnO(CH_2)_2CH_2$	**1l**	68
12	$TBSO(CH_2)_2CH_2$	**1m**	62
13	*t*-Bu	**1n**	61
14	Cy	**1o**	63

[a]The reactions were conducted on a 1 mmol scale under the conditions shown in Table 1, Entry 11. [b]Isolated yield based on the amide.

aldehydes such as electron-donating group and electron-withdrawing group substituted benzaldehydes, the reaction proceeded smoothly and gave rise to the aromatic *N*-tosylamines in isolated yields ranging from 69 to 78% (Table 2, Entries 1, 3–6). In the case of 2-methylbenzaldehyde (Entry 2) and 2-bromobenzaldehyde (Entry 7), *ortho*-substitutions did decrease the reaction yields substantially, likely due to steric hindrance, although the reaction was still serviceable. When 2-furaldehyde was used, good isolated yield was obtained (**1j**, 69%) (Entry 9). Many synthetically important nonenolizable or enolizable aliphatic aldehyde substituent groups were well tolerated with yields of the desired, isolated products ranging from 61 to 68%, despite their low reactivity and inherent instability (Entries 10–14). Interestingly, the reactions with substrates bearing bulky groups such as tertiary butyl group or cyclohexenyl group also proceeded smoothly (Entries 13 and 14).

In view of the mechanism of the previously reported benzylation of aldehydes[10a] and allylation of aldehydes,[10b] we have postulated a plausible mechanism. As shown in Figure 1, $TsNH_2$ was deprotonated by BnZnBr to generate zinc-containing intermediate **A** that could react with aldehydes to form imines, which after addition of propargyl bromide would generate the desired amines **1**.

In conclusion, we have developed a simple and practical method for the preparation of homopropargylic *N*-sulfonylamines by reaction of aldehydes with *p*-toluenesulfonamide in the presence of benzyl bromide and zinc powder, and further propargylation of the resulting *N*-sulfonylimines. A wide variety of aldehydes are tolerated in this reaction system, including electron-deficient and electron-rich aromatic aldehydes, and aliphatic aldehydes. In addition, the one-pot procedure offers manipulability by avoiding the isolation of the labile imine intermediates.

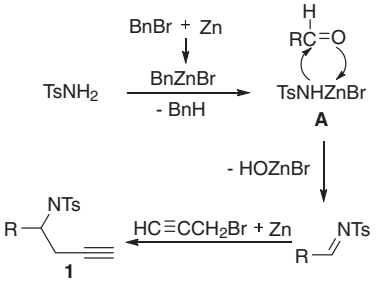


Figure 1. Proposed mechanism for the reaction.

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12 Experimental details are shown in the Supporting Information. Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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