Synthetic Methods

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An Unexpected Reaction of Arenesulfonyl Cyanides with Allylic Alcohols: Preparation of Trisubstituted Allyl Sulfones**

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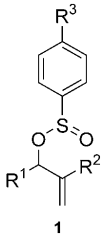
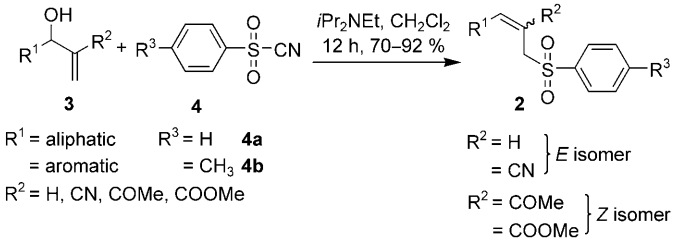
For an ongoing program within our research group we needed to synthesize sulfinates of the type **1**. We reasoned that **1** could be easily prepared by a reaction of Baylis–Hillman adduct **3** with *p*-toluenesulfonyl cyanide (Scheme 1).[1] These reaction conditions, however, led to an unexpected trisubstituted allyl sulfone **2**. To the best of our knowledge, such a reaction of a Baylis–Hillman adduct[2] with *p*-toluenesulfonyl cyanide[1,3] to form substituted allyl sulfones has not been reported. These types of substituted allyl sulfones are important intermediates in organic synthesis[4] and have been recently found to be highly potent against cancer and abnormal cell proliferation diseases.[5] The synthesis of these substituted compounds has received scant attention in the literature, with only two methods outlined. Kabalka et al.[6] reported the nucleophilic addition of sodium *p*-toluene sulfinate to an acetate of the Baylis–Hillman adduct, and found that the reaction only proceeded in ionic liquids at high temperatures. Later, Chandrasekhar et al.[7] reported a nucleophilic addition of sodium *p*-toluene sulfinate to the Baylis–Hillman adduct in polyethylene glycol as the solvent at high temperatures. It is therefore significant that the new method we report herein is unprecedented, quite general, and proceeds efficiently at ambient temperature.

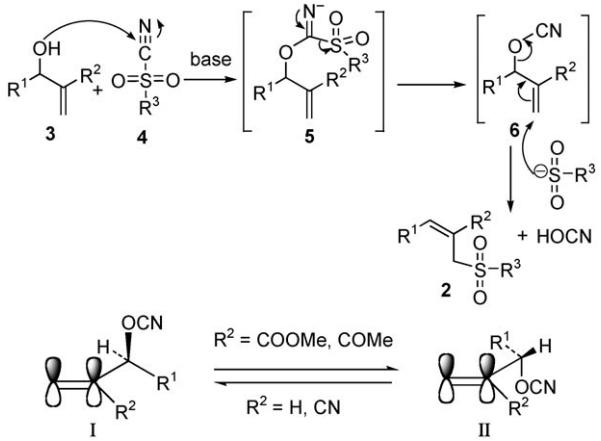


1

Treatment of methyl 2-(hydroxyphenylmethyl) acrylate (**3a**, 1 equiv) with *p*-toluenesulfonyl cyanide (**4b**, 1.2 equiv) in the presence of diisoproylethylamine (1.3 equiv) in dichloromethane at room temperature for 12 hours afforded trisubstituted allyl sulfone **2a** in high yield (92%) with good selectivity (*E*/*Z* 5:95; Table 1, entry 1). The structure of **2a** was assigned based on ^{1}H,^{13}C NMR spectroscopy and mass spectrometry as well as by comparison with literature data.[6,7] The *E*/*Z* ratio was determined to be 5:95 by ^{1}H NMR analysis of the crude product. Similarly, the reaction of **3a** with benzenesulfonyl cyanide (**4a**) in the presence of iPr$_2$NEt in CH_2Cl_2 at room temperature for 12 hours also proceeded to give the trisubstituted allyl sulfone **2b** in 95% yield and with an *E*/*Z* ratio of 6:94 (Table 1, entry 2).



Scheme 1. Reaction of arenesulfonyl cyanides with various allylic alcohols.



Scheme 2. A possible mechanism and conformations.

Encouraged by these results, we turned our attention to other substituted aromatic acrylates. Interestingly, a large number of these acrylates such as *p*-methyl, *o*-bromo, cinnamyl, and furfuryl derivatives reacted cleanly with benzenesulfonyl cyanide (**4a**) or *p*-toluenesulfonyl cyanide (**4b**) in the presence of base leading to the corresponding trisubstituted allyl sulfones **2c–2h** (Table 1, entries 3–8) in high yields (80–86%) and with good selectivity (*E*/*Z* ratio from 6:94 to 2:98). In the same way, aliphatic Baylis–Hillman adducts such as methyl 3-hydroxy-2-methylenehexanoate (**3f**) and methyl 3-hydroxy-2-methyleneoctanoate (**3g**) reacted smoothly with **4a** to afford the corresponding trisubstituted allyl sulfones **2i** (75% yield) and **2j** (72% yield) with an *E*/*Z* ratio of 7:93 and 6:94, respectively (Table 1, entries 9 and 10).

Interestingly, the reaction of other Baylis–Hillman adducts such as 3-(hydroxymethylphenyl)but-3-en-2-one (**3h**) with **4a** in the presence of iPr$_2$NEt in CH_2Cl_2 at room temperature for 12 hours afforded trisubstituted allyl sulfone **2k** in high yield (85%) and with high selectivity (*E*/*Z* 5:95; Table 1, entry 11). Likewise, the reaction of **4a** with 2-

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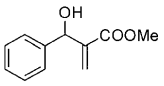
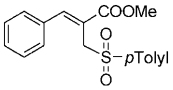
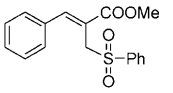
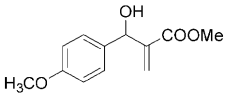
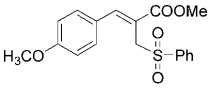
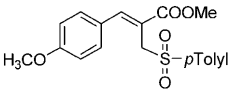
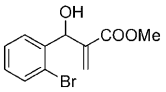
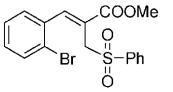
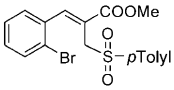
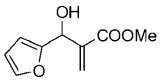
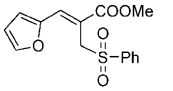
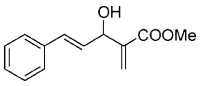
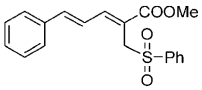
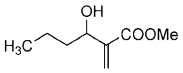
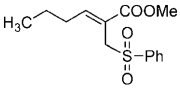
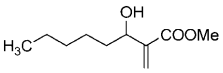
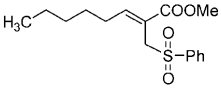
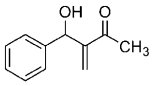
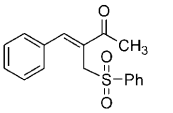
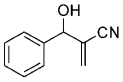
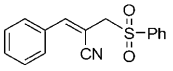
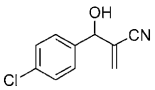
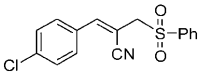
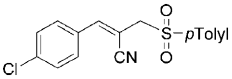
Table 1: Reaction of arenesulfonyl cyanide with Baylis–Hillman adducts.

Entry	Substrate **3**	**4**	Product **2**	Yield [%][a]	*E*/*Z*[b]
1		**3a** **4b**	 **2a**	92	5:95
2		**3a** **4a**	 **2b**	95	6:94
3		**3b** **4a**	 **2c**	86	3:97
4		**3b** **4b**	 **2d**	84	3:97
5		**3c** **4a**	 **2e**	85	2:98
6		**3c** **4b**	 **2f**	84	2:98
7		**3d** **4a**	 **2g**	80	4:96
8		**3e** **4a**	 **2h**	80	6:94
9		**3f** **4a**	 **2i**	75	7:93
10		**3g** **4a**	 **2j**	72	6:94
11		**3h** **4a**	 **2k**	85	5:95
12		**3i** **4a**	 **2l**	81	97:3
13		**3j** **4a**	 **2m**	85	97:3
14		**3j** **4b**	 **2n**	90	97:3

[a] Yield of isolated product. [b] The selectivity was determined by ^{1}H NMR analysis. The *E*/*Z* ratio of 2:98 denotes that signals for only one isomer were observed.

(hydroxymethylphenyl)acrylonitrile (**3i**) or 2-[(4-chlorophenyl) hydroxymethyl]acrylonitrile (**3j**) in the presence of *i*Pr$_2$NEt in CH_2Cl_2 at ambient temperature proceeded to give trisubstituted allyl sulfone **2l** and **2m**, respectively, in good yields (81% and 85%) and with high selectivity (*E*/*Z* 97:3; Table 1, entries 12 and 13). In the same way, the reaction of **4b** with **3j** gave trisubstituted allyl sulfone **2n** in 90% yield and with an *E*/*Z* ratio of 97:3 (Table 1, entry 14).

We also investigated the reaction of simple allylic alcohols **3k** and **3l** with **4a** or **4b** in the presence of *i*Pr$_2$NEt in CH_2Cl_2 at room temperature and obtained the corresponding *E*-selective allyl sulfones **2o**–**2r** in good yields (Table 2, entries 1–4). The structure of **2r** was confirmed by single-crystal X-ray diffraction analysis (Figure 1). Finally, the reactions of **4b** with **3m** or **3n** resulted in highly regiospecific additions and yielded allyl sulfones **2s** and **2t**, respectively (Table 2, entries 5 and 6). Notably, the new carbon–heteroatom bond is formed exclusively from the most substituted end of the allylic system, and led to **2s** and **2t**.

For the sake of understanding this reaction, the use of other bases was explored (Table 3). No reaction was observed in the absence of base, or with pyridine or 2,6-lutidine (Table 3, entries 1–3). The reaction did not proceed to completion with triethylamine or DBU, and thereby gave low yields (Table 3, entries 4 and 5). A possible mechanism[8,9] for this reaction is depicted in Scheme 2. In the first step, allylic alcohol **3** reacts with **4** in the presence of base to form intermediate **5**, then an arene sulfinate nucleophile and intermediate **6** are subsequently generated. Next, the addition of the nucleophile to the allylic double bond occurs with the elimination of HOCN to form allyl sulfones **2**. This mechanism also explains the observed selectivity[2,10] (*E* and *Z*). When R^2 is a large group (R^2 = COOMe, COMe), conformation **II** is favored and thus predominantly forms the *Z* isomer. If R^2 is a small group (R^2 = H, CN), then conformation **I** is favored and therefore predominantly forms the *E* isomer.

In summary, a general method and a practical protocol for the preparation of substituted allyl sulfones in both high yields and selectivity was described. The reaction used arenesulfonyl cyanides

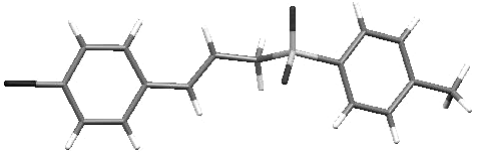
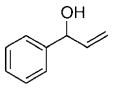
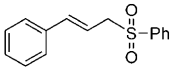
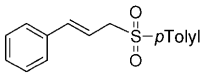
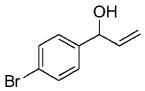
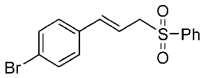
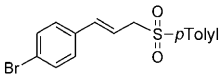
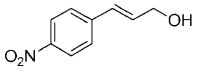
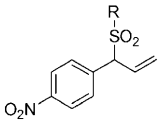
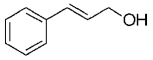
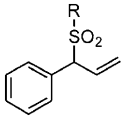


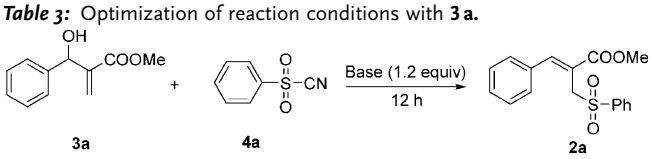
Figure 1. X-ray crystal structure of **2r**.

Table 2: Reaction of arenesulfonyl cyanide with allylic alcohols.

Entry	Substrate **3**		**4**	Product **2**		Yield [%][a]	*E*/*Z*[b]
1		**3k**	**4a**		**2o**	80	98:2
2		**3k**	**4b**		**2p**	82	98:2
3		**3l**	**4a**		**2q**	81	98:2
4		**3l**	**4b**		**2r**	80	98:2
5[c]		**3m**	**4b**		**2s**	84	–
6[c]		**3n**	**4b**		**2t**	80	–

[a] Yield of isolated product. [b] The selectivity was determined by ^{1}H NMR analysis. The *E*/*Z* ratio of 98:2 denotes that signals for only one isomer were observed. [c] R = $C_6H_4CH_3$.

Table 3: Optimization of reaction conditions with **3a**.



3a **4a** **2a**

Entry	Base	Yield [%][a]
1	none	no reaction[b]
2	pyridine	no reaction[b]
3	2,6-lutidine	no reaction[b]
4	triethylamine	50
5	DBU	78
6	iPr$_2$NEt	95

[a] Yield of isolated product. [b] Starting material was recovered quantitatively. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

with Baylis–Hillman adducts and simple allylic alcohols. Extension of this work to other related systems is currently underway.

Experimental Section

General Procedure for the synthesis of substituted allyl sulfones **2**: iPr$_2$NEt (6.5 mmol) was slowly (over 5 min) added dropwise to a stirred mixture of allylic alcohol **3** (5.0 mmol) and arenesulfonyl cyanide **4** (6.0 mmol) in CH_2Cl_2 (20 mL) at 23 °C under nitrogen. After stirring for 12 hours at 23 °C, the reaction mixture was quenched with water (20 mL) then extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with 20% citric acid (1 × 20 mL), water (1 × 10 mL), and the solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel (ethyl acetate/hexanes) to afford pure **2**.

Crystallography data: CCDC-697287 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Keywords: allyl sulfones · bases · Baylis–Hillman adducts · synthetic methods

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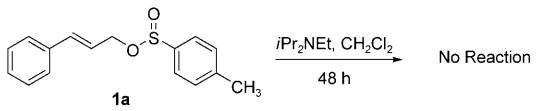

[9] Based on a control experiment where allylic alcohol **3k** was treated with benzenesulfonyl cyanide **4a** in the presence of sodium *p*-toluene sulfinate, a mixture of allyl sulfones **2o** and **2p** was observed. In view of this scrambling a cyclic mechanism was ruled out.
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