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Catalyst-Free Alkylation of Sulfinic Acids with Sulfonamides via sp^3 C−N Bond Cleavage at Room Temperature

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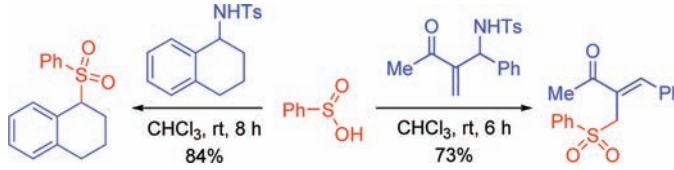
ABSTRACT



An unprecedented catalyst-free alkylation of sulfinic acids with sulfonamides has been developed via sp^3 C−N bond cleavage at room temperature. In the absence of external catalysts and additives, a wide variety of *N*-benzylic and *N*-allylic sulfonamides couple with sulfinic acids to give structurally diversified sulfones in moderate to excellent yields. Furthermore, the reaction of *N*-(2-acyl)allylic sulfonamides with sulfinic acids provides a convenient access to trisubstituted allyl sulfones with exclusive *Z* selectivity.

Although sp^3 C−N bond cleavage can be realized by metals such as Pd, Rh, Ru, and Na, strong bases such as *t*-BuLi and *t*-BuOK, and some other reagents such as CCl_3CH_2OCOCl, DDQ, and PhSeH under various reaction conditions, amines and amine derivatives have rarely been applied to the alkylation of protic nucleophiles.[1] In 1983, Kunakova and co-workers disclosed a palladium-catalyzed coupling reaction of sulfinic acids with allylic amines via sp^3 C−N bond cleavage at 100 °C.[2] This reaction can provide a direct access to sulfones that can serve as versatile building blocks for organic synthesis owing to the useful reactivity of α-sulfonyl carbanions.[3] More than 10 years later, Nagakura and co-workers found that palladium could catalyze the removal of the allyl group from *N*-allyl-*N*-pentylaniline with *p*-toluenesulfinic acid at room temperature.[4] This method, however, has not been extended to the alkylation of sulfinic acids with nonallylic amines and amine derivatives.

When the nitrogen atoms of benzylic (or allylic) primary amines are attached to appropriate electron-withdrawing groups (EWGs), either Brønsted[5] or Lewis acids[6,7] are able to facilitate the amino groups to serve as leaving groups toward a range of nucleophiles. In the course of exploring new reactions with a combination of acids,[7,8] we found, however, that the sulfonyl-activated amines (sulfonamides) could couple with

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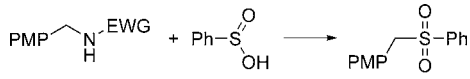
sulfinic acids via sp^3 C−N bond cleavage in the absence of external catalysts and additives at room temperature. This finding is totally out of our expectation because the acidity of a sulfinic acid is much weaker relative to that of a sulfonic acid,[9] which nevertheless failed to catalyze the sp^3 C−N bond cleavage for the alkylation of acetyl acetone with *N*-tosyl benzhydrylamine.[7] In addition, sulfinic acids and their salts are not powerful nucleophiles, and a simple alkylation reaction of sulfinate anions is not trivial and often requires readjusting the reaction conditions.[10] Herein, we describe this unprecedented catalyst-free alkylation of sulfinic acids with sulfonamides, which adds a new and direct entry to the synthesis of structurally diversified sulfones.

As demonstrated by the alkylation of benzenesulfinic acid with 4-methoxybenzylamine derivatives in chloroform at room temperature, the activating group (EWG) attached to the nitrogen atom played a vital role for the benzylic sp^3 C−N bond cleavage to take place in the absence of external catalysts and additives (Table 1, entries 1−5). To our delight, sulfone **2a** was obtained in 67% yield when using the tosyl group, a strong electron-withdrawing group that can be introduced conveniently from inexpensive *p*-toluenesulfonyl chloride (Table 1, entry 1). Nevertheless, the use of another common organic solvent instead of chloroform just led to a lower yield or even no desired sulfone product at all (Table 1, entries 6−12).

Table 1. Survey of EWGs and Solvents[a]



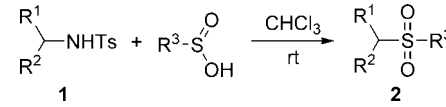
1a-1ae **2a**

entry	**1**, EWG	solvent	time/h	yield/%[b]
1	**1a**, Ts	$CHCl_3$	14	67
2	**1ab**, *p*-Ns	$CHCl_3$	24	55
3	**1ac**, $PO(OPh)_2$	$CHCl_3$	24	13
4	**1ad**, COPh	$CHCl_3$	24	30
5	**1ae**, Cbz	$CHCl_3$	24	0
6	**1a**, Ts	CH_2Cl_2	16	58
7	**1a**, Ts	$(ClCH_2)_2$	24	36
8	**1a**, Ts	toluene	24	13
9	**1a**, Ts	MeCN	24	54
10	**1a**, Ts	THF	24	0
11	**1a**, Ts	EtOAc	24	0
12	**1a**, Ts	$MeNO_2$	24	7

[a] Reaction conditions: amine derivative (0.50 mmol), benzenesulfinic acid (0.60 mmol), solvent (0.50 mL), rt. [b] Isolated yield. PMP = *p*-methoxyphenyl. *p*-Ns = *p*-nitrobenzenesulfonyl.

A broad range of tosyl-activated benzylic and allylic primary amines coupled with aromatic and aliphatic sulfinic acids at room temperature to give the corresponding sulfones in good to excellent yields (Table 2, entries 1−15). Notably, no isomerization was observed in the reaction of benzylic propargylic amine derivative **1i** with benzenesulfinic acid, which proceeded cleanly to give sulfone **2i** as a single product in 96% yield (Table 2, entry 9). Furthermore, the displacement of the sulfonamido group of allylic amine derivative **1k** by benzenesulfinic acid took place only at the original allylic position, presumably to maintain a maximum degree of conjugation (Table 2, entry 11).[11] Nevertheless, no reaction took place with simple sulfonamides such as *N*-tosyl benzylamine (**1m**) and *N*-tosyl allylamine (**1n**) (Table 2, entries 16 and 17).

Table 2. Catalyst-Free Alkylation of Sulfinic Acids with Sulfonamides[a]



1 **2**

entry	**1**, R^1, R^2	R^3	product	time /h	yield /%[b]
1	**1a**, PMP, H	Ph	**2a**	14	67
2	**1b**, PMP, Me	Ph	**2b**	10	98
3	**1c**, 2-HOC_6H_4, Me	Ph	**2c**	15	80
4	**1d**, 2-naphthyl, Me	Ph	**2d**	3	81
5	**1e**, 	Ph	**2e**	8	84
6	**1f**, Ph, Ph	Ph	**2f**	24	56
7	**1g**, PMP, Ph	Ph	**2g**	10	87
8	**1h**, 4-ClC_6H_4, Ph	Ph	**2h**	4	96
9	**1i**, Ph, 1-hexynyl	Ph	**2i**	24	96
10	**1j**, (*E*)-PhCH=CH, Ph	Ph	**2j**	2	88
11	**1k**, (*E*)-PhCH=CH, Me	Ph	**2k**	2.5	85
12	**1l**, 	Ph	**2l**	10	80
13	**1b**, PMP, Me	PMP	**2m**	3	99
14	**1b**, PMP, Me	4-ClC_6H_4	**2n**	6	99
15[c]	**1b**, PMP, Me	Me	**2o**	6	72
16	**1m**, Ph, H	Ph		24	0
17	**1n**, vinyl, H	Ph		24	0

[a] Reaction conditions: sulfonamide (0.50 mmol), sulfinic acid (0.60 mmol), $CHCl_3$ (0.50 mL), rt. [b] Isolated yield. [c] MeCN was used as the solvent to dissolve methanesulfinic acid.

The cross-coupling reaction of optically active sulfonamide (***R***)-**1b** (95% ee) with 0.50 equiv of benzenesulfinic acid proceeded at room temperature for 10 h to give sulfone **2b** (Table 2, entry 2) in nearly racemic form (3% ee), and at the same time the optical purity of recovered sulfonamide (***R***)-**1b** decreased from 95% to 66%. Furthermore, the formation of sulfone **2b** was found to be irreversible based on the fact that no reaction took place between sulfone **2b** and *p*-toluenesulfinic acid at room temperature for 24 h.[12] These results suggest that carbocation **3** is generated from sulfonamide **1** via a sulfinic acid-promoted sp^3 C−N bond cleavage (Scheme 1). The resulting sulfinate anion acts as an *S*-nucleophile to couple with carbocation **3** to give sulfone **2** (Scheme 1, path a).

However, a sulfinic acid can also act as an *O*-nucleophile toward a "harder" carbon electrophile relative to *N*-benzylic and

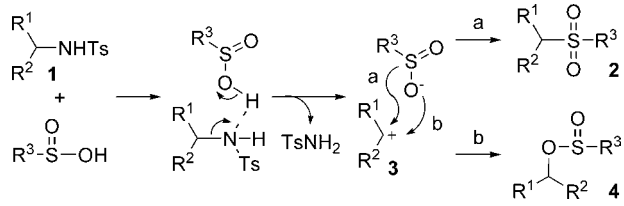
(9) For example, the pK_a value of TfOH is 0.3 in DMSO, and that of $PhSO_2H$ is 7.1. See: Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463.

(10) For a review, see: (a) Solladie, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991, Vol. 6, pp 133−170. For examples, see: (b) Wu, J.-P.; Emeigh, J.; Su, X.-P. *Org. Lett.* **2005**, *7*, 1223–1225. (c) Crandall, J. K.; Pradat, C. *J. Org. Chem.* **1985**, *50*, 1327–1329.

(11) No S_N2' product was detected by ^1H NMR analysis of the reaction mixture.

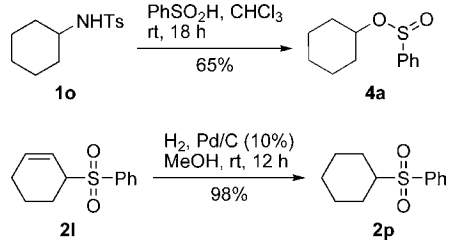
(12) Determined by ^1H NMR analysis of the reaction mixture.

Scheme 1. Proposed Reaction Pathways



N-allylic sulfonamides (Scheme 1, path b).[13] While no reaction took place between acyclic *N*-alkyl sulfonamides and sulfinic acids, *N*-cyclohexyl sulfonamide **1o** coupled smoothly with benzenesulfinic acid at room temperature, and the resulting product was identified as sulfinate **4a** rather than expected sulfone **2p** (Scheme 2), which could alternatively be synthesized

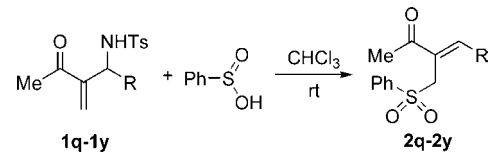
Scheme 2. Synthesis of Sulfinate **4a** and Sulfone **2p**



by catalytic hydrogenation of allylic sulfone **2l**, previously prepared from alcohol **1l** and benzenesulfinic acid (Table 2, entry 12).

Furthermore, a third reaction pathway was observed in the reaction of sulfinic acids with *N*-allylic sulfonamides bearing activated terminal C=C double bonds.[14] As shown in Table 3, a range of *N*-(2-acetyl)allylic sulfonamides coupled with benzenesulfinic acid to give the corresponding trisubstituted allyl sulfones with exclusive *Z* selectivity.[15,16] Obviously, such an S_N2'-type process is allowed to take place by the activation of a terminal C=C double bond with the acetyl group, and tentatively, the *Z* selectivity originates from reactive conformation **A**, which is energetically favored relative to reactive conformation **B** by relieving the allylic 1,2-strain (Figure 1).[5c,15c]

Table 3. Catalyst-Free Alkylation of Benzenesulfinic Acid with *N*-(2-Acetyl)allylic Sulfonamides[a]



entry	**1q**−**1y**, R	product	time/h	yield/%[b]
1	**1q**, Ph	**2q**	6	73
2	**1r**, PMP	**2r**	6	61
3	**1s**, 4-MeC_6H_4	**2s**	6	80
4	**1t**, 4-ClC_6H_4	**2t**	24	51
5	**1u**, 4-$O_2NC_6H_4$	**2u**	5	58
6	**1v**, 2-MeC_6H_4	**2v**	6	70
7	**1w**, 2-furyl	**2w**	24	51
8	**1x**, (*E*)-PhCH=CH	**2x**	6	58
9	**1y**, 1-hexyl	**2y**	24	49

[a] Reaction conditions: sulfonamide (0.50 mmol), benzenesulfinic acid (0.60 mmol), $CHCl_3$ (0.50 mL), rt. [b] Isolated yield.

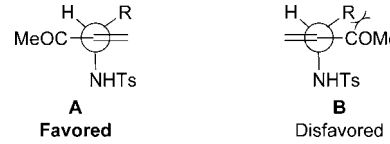


Figure 1. Reactive Conformations **A** and **B**.

In summary, we have developed a catalyst-free alkylation reaction of sulfinic acids with sulfonamides via sp^3 C−N bond cleavage at room temperature. In the absence of external catalysts and additives, a wide variety of *N*-benzylic and *N*-allylic sulfonamides couple with sulfinic acids to give structurally diversified sulfones in moderate to excellent yields. Furthermore, the reaction of *N*-(2-acyl)allylic sulfonamides with sulfinic acids provides a convenient access to trisubstituted allyl sulfones with exclusive *Z* selectivity.

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

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(13) For examples on the ambident nucleophilicity of sulfinate anions toward carbon electrophiles, see: (a) Reference 10b. (b) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Parisi, L. M. *Synlett* **2003**, 361–364. (c) Watanabe, S.; Kurosawa, H. *Organometallics* **1998**, *17*, 479–482.

(14) For reviews on the preparation and application of such highly functionalized sulfonamides, see: (a) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4614–4628. (b) Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* **2009**, *109*, 1–48.

(15) For the stereoselective synthesis of trisubstituted allyl sulfones, see: (a) Kabalka, G. W.; Venkataiah, B.; Dong, G. *Tetrahedron Lett.* **2003**, *44*, 4673–4675. (b) Chandrasekhar, S.; Saritha, B.; Jagadeshwer, V.; Narsihmulu, C.; Vijay, D.; Sarma, G. D.; Jagadeesh, B. *Tetrahedron Lett.* **2006**, *47*, 2981–2984. (c) Reddy, L. R.; Hu, B.; Prashad, M.; Prasad, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 172–174.

(16) The stereochemistry of new products **2v**, **2w**, and **2y** was assigned by 2D NOESY analysis, and the stereochemistry of new product **2s** was assigned by analogy. For details, see the Supporting Information.