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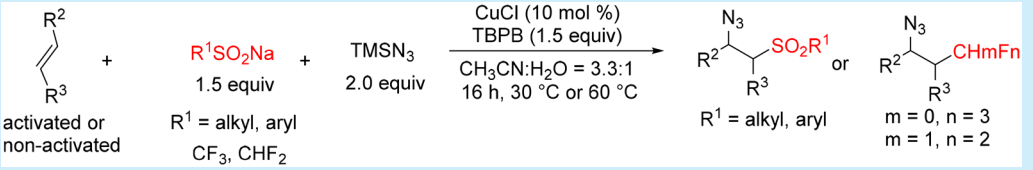
Copper-Catalyzed Synthesis of β-Azido Sulfonates or Fluorinated Alkanes: Divergent Reactivity of Sodium Sulfinates

Yang Xiong, Youwen Sun, and Guozhu Zhang*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Center for Excellence in Molecular Synthesis, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, P. R. China

Supporting Information



ABSTRACT: A new and general method for the synthesis of β-azidosulfonates has been achieved through Cu(I)-mediated radical oxidative sulfonylation−azidation of alkenes with sodium sulfinates. Under identical conditions, azido fluoroalkyated products could be readily obtained instead using CF_3SO_2Na or CHF_2SO_2Na as reagents. The starting materials of sulfinate compounds, alkenes, and azidotrimethylsilane are stable and cheap. This method can be easily adapted for large-scale preparation.

Sulfones are key synthons in many synthetic transformations, such as Junia−Lythgoe olefination,[1] electrophilic substitution,[2] reductive cleavage of the sulfone group,[3] and more recent fruitful exercises in photoredox and fluorination chemistry.[4] More importantly, sulfones display diverse biological activities, making them one of the major components in the pharmaceutical and agro-chemical agents.[5] Despite many well established sulfone preparation methods,[6] new strategies for expedient sulfonyl introduction are still highly desired.

Difunctionalization of alkenes represents one of the most powerful and straightforward methods for rapidly increasing the molecular complexity as two chemical bonds are formed in one step.[7] One important class of such transformations is amino difunctionalization, including diamination,[8] amino-oxygenation,[9] amino-halogenation,[10] and carbo-amination,[11] with generation of valuable N-containing molecules. However, examples of alkene sulfonyl amination for producing linear N-containing sulfones are scarce and remain a challenge, despite the fact that molecules bearing both amino and sulfone groups have extensively been used in pharmaceuticals (Figure 1).[12]

Sulfonyl radicals are transient intermediates that undergo a range of reactions, including those with alkenes and alkynes.[13] Radical nature Cu-catalyzed azido difunctionalization of alkenes has been well established using an azide reagent,[14] leading to valuable organo-azides.[15,16] We propose that a Cu-catalyzed radical process, utilizing readily available sulfonyl and azido radical precursors in the presence of a suitable oxidant, would enable us to achieve the azido sulfonylation of alkenes.

We initiated our studies with the azido sulfonylation reaction of styrene with readily available $TMSN_3$ and $NaSO_2Me$ in the presence of oxidants and a Cu catalyst. After extensive

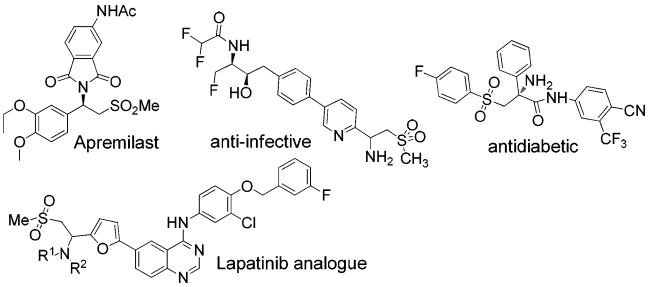


Figure 1. Representative active pharmaceutical compounds.

experiments, the 1,2-azido sulfonate **1a** was obtained in 20% yield in 1 mL of CH_3CN in the presence of CuCl using $NaSO_2Me$ and TPBP (*tert*-butyl benzoperoxoate) (Table 1, entry 1). In the hope of increasing the solubility of Na salt, an equal amount of H_2O was added and the product yield was significantly improved (Table 1, entry 2). Fine-tuning of the CH_3CN/H_2O ratio resulted in 3.3/1 being optimal. Examination of different oxidants revealed that TPBP was a unique oxidant and radical initiator for this reaction;[17a] a combination of Cu(I) and TBHP (*tert*-butyl hydroperoxide), often used in organo-azido radical reactions,[4a−d] did not work well under these conditions (Table 1, entry 5). Other oxidants, such as BPO (benzoyl peroxide), DTBP (di-*tert*-butyl peroxide), and NFSI (*N*-fluorobenzene-sulfonimide), were not effective (Table 1, entries 6−8). No detectable amount of product was found from reactions running in different solvents other than CH_3CN (Table 1, entries 9−11). CuCl exceeded other

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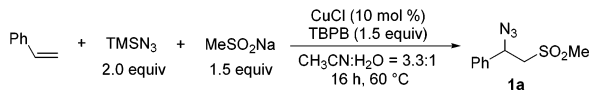
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Optimization of the Reaction Conditions



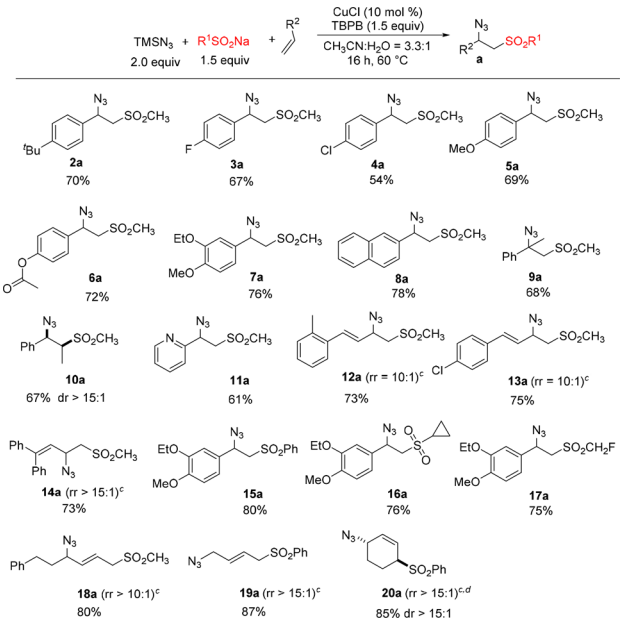
entry[a]	catalyst	oxidant	solvent	yield (%)[b]
1	CuCl	TBPB	CH_3CN	20
2	CuCl	TBPB	CH_3CN/H_2O (1/1)	40
3	CuCl	TBPB	CH_3CN/H_2O (2/1)	72
4	CuCl	TBPB	CH_3CN/H_2O (3.3/1)	78
5	CuCl	TBHP	CH_3CN/H_2O (3.3/1)	trace
6	CuCl	BPO	CH_3CN/H_2O (3.3/1)	ND
7	CuCl	DTBP	CH_3CN/H_2O (3.3/1)	ND
8	CuCl	NSFI	CH_3CN/H_2O (3.3/1)	ND
9	CuCl	TBPB	EtOAc	trace
10	CuCl	TBPB	toluene	trace
11	CuCl	TBPB	DMF	trace
12	CuBr	TBPB	CH_3CN/H_2O (3.3/1)	54
13	$(CH_3CN)_4CuPF_6$	TBPB	CH_3CN/H_2O (3.3/1)	72
14	$Cu(OTf)_2$	TBPB	CH_3CN/H_2O (3.3/1)	68
15	no	TBPB	CH_3CN/H_2O (3.3/1)	ND
16[c]	CuCl	TBPB	CH_3CN/H_2O (3.3/1)	76[d]

[a]Reactions were carried out in 0.2 mmol scale. [b]Measured by ^1H NMR analysis using diethyl phthalate as internal standard. [c]0.4 mmol scale. [d]Isolated yield.

copper salts (Table 1, entries 12−14). The reaction did not occur without a Cu catalyst (Table 1, entry 15). Therefore, heating the reactants in CH_3CN/H_2O (3.3/1) at 60 °C for 16 h using 10 mol % CuCl as the catalyst and TPBP as the oxidant was chosen as the optimized reaction conditions.

The substrate scope of azido sulfonylation was promptly examined, and the results are summarized in Scheme 1. Substrates **2a**−**8a**, having various substituents (R) on the aromatic ring, either electron-donating or electron-withdrawing groups, were compatible with the current transformation. In particular, product **7a**, bearing two alkoxy groups, could serve as the advanced intermediate for the synthesis of drug Apremilast.[12]

Scheme 1. Scope Studies[a,b]



[a]All reactions were performed in CH_3CN/H_2O (3.3/1, 0.02 M) at 60 °C. [b]Isolated yield. [c]The temperature was 30 °C, ratio of regioisomer (rr) and major isomer are shown. [d]Configuration was assigned by NOE.

For the 1,1-disubstituted substrate, the reaction proceeded well to give the β-Ms-substituted tertiary alkyl azide **9a** in 68% yield. In addition, (*E*)-prop-1-en-1-ylbenzene with an internal alkene was also suitable for this transformation, thus giving the product **10a** in 67% yield with good dr. A valuable pyridine moiety was successfully incorporated (**11a**). The 1,3-dienes are capable substrates as well, and an arrangement of substituted dienes are engaged in this azido sulfonylation reaction to provide the desired products in moderate yields with good 1,2-selectivity (**12a**−**14a**). Notably, better 1,2-regioselectivity was observed for aryl substituted 1,3-dienes by lowering the reaction temperature to 30 °C likely under kinetic control. No detectable 1,4-isomer was found for **14a**, possibly due to increased steric hindrance.

Various aliphatic and aromatic sodium sulfinates were proven to be suitable sulfonylation reagents as well, leading to diversified precursors for drug analogues (**15a**−**17a**). Success in using sodium fluoromethanesulfinate would offer a potent entry to tuning the properties of related molecules for medicinal purposes by introduction of a F atom. Interestingly, for simple aliphatic 1,3-butadiene and cyclohexa-1,3-diene, thermodynamically more stable 1,4-addition regioisomers were observed (**18a**−**20a**). Notably, alkenes with aliphatic substitutions did not react well under the current reaction conditions.

The use of fluorinated alkyl groups including CF_3 and CHF_2 has become increasingly important in a variety of research fields[18] due to the versatile beneficial effects rendered by the presence of a F atom on the materials.[19] Langlois reagent, $NaSO_2CF_3$, has been found to undergo oxidative trifluoromethylation in many events through SO_2 extrusion, but to be limited in the difunctionalization of alkenes.[20] We envisioned that the successful extension of the above-established strategy to induce 1,2-azido fluoroalkylation of alkenes with the $NaSO_2CF_3$ would offer new opportunities for readily available Langlois reagent, and also enrich the alkene difunctionalization research field. The desired trifluoromethylated azide indeed formed under the standard conditions using $NaSO_2CF_3$ instead of nonfluorinated sulfinate salt.

Under almost identical conditions, the generality of the method with alkenes was explored and an even broader substrate scope was revealed (Scheme 2). Activated alkenes such as monoarylated alkenes, including naphthalene, substituted phenyl, and pyridine were suitable substrates for this trifluoromethyl azidation reaction (**1b**−**3b**). 1-Aryl and 1,2-dialkyl trisubstituted alkene also reacted well to provide the desired product in good dr (**4b**). A range of alkylated alkenes proved to be capable substrates (**5b**−**8b**). Notably, ester and amide groups are tolerated under current reaction conditions. Three arylated 1,3-dienes were successfully transformed into products in good 1,2-selectivity (**9b**−**11b**). Again, for an aliphatic diene, a 1,4-disubstituted adduct was isolated (**12b**).

We then turned our attention to the unprecedented difluoro-methyl azidation using $NaSO_2CHF_2$ under the optimized conditions.[21] Again, difluoromethyl azidation proceeded smoothly to provide the desired products in good yields (Scheme 3).

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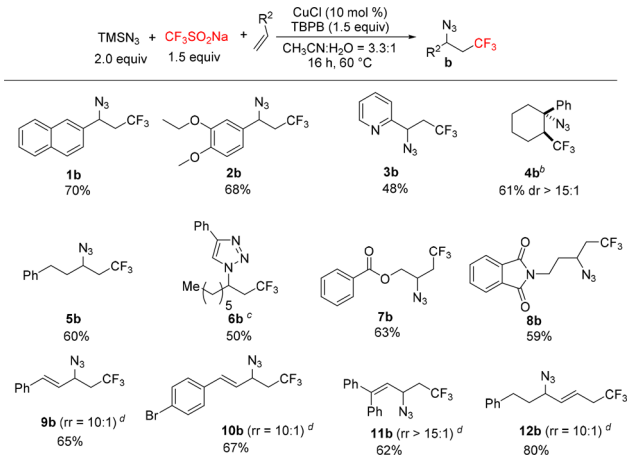
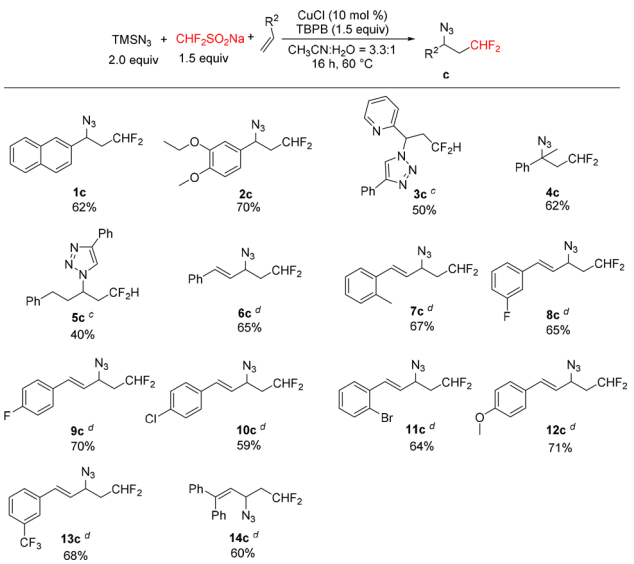
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Scope Studies[a,b]



[a]All reactions were performed in CH_3CN/H_2O (3.3/1, 0.02 M), except **6b** performed in CH_3CN/H_2O (3.3/1, 0.03 M) at 60 °C; Isolated yield. [b]Configuration was assigned by comparison with reported example. [c]Isolated yield of triazole over two steps, for second step [CuI (12.1 mg, 0.06 mmol), phenylacetylene (66 μL, 0.6 mmol) in THF (2 mL)], stirred at 60 °C for 6 h]. [d]The temperature was 30 °C, ratio of regioisomer.

Scheme 3. Scope Studies[a,b]

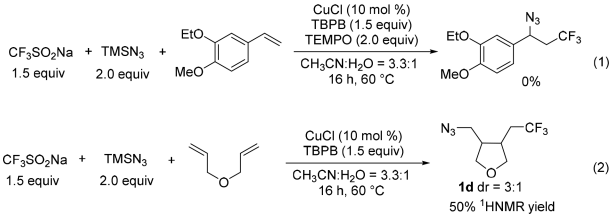


[a]All reactions were performed in CH_3CN/H_2O (3.3/1, 0.02 M), except **3c** and **5c** performed in CH_3CN/H_2O (3.3/1, 0.03 M) at 60 °C. [b]Isolated yield. [c]Configuration was assigned by comparison with reported example. Isolated yield of triazole over two steps, for second step [CuI (12.1 mg, 0.06 mmol), phenylacetylene (66 μL, 0.6 mmol in THF (2 mL), stirred at 60 °C for 6 h]. [d]The temperature was 30 °C, ratio of regioisomer (>15:1).

Investigation of the alkene scope exhibits broad generality. Both aryl and alkyl substituted alkenes reacted readily to afford the desired products in moderate to good yields (**1c**−**5c**). Good 1,2-regioselecvitities were observed for a range of 1,3-dienes tested (**6c**−**14c**).

With addition of TEMPO, the reaction was inhibited and no desired product was observed [Scheme 4, eq 1]. To further understand this reaction, the reaction of 3-(allyloxy)prop-1-ene was investigated [Scheme 4, eq 2], and cyclized product **1d** was obtained in 3:1 dr. These results are consistent with a stepwise radical process.[16,17]

Scheme 4. Preliminary Mechanistic Study



A plausible reaction mechanism is illustrated in Figure 2. As previously suggested, CuCl first reduces TBPB to provide a

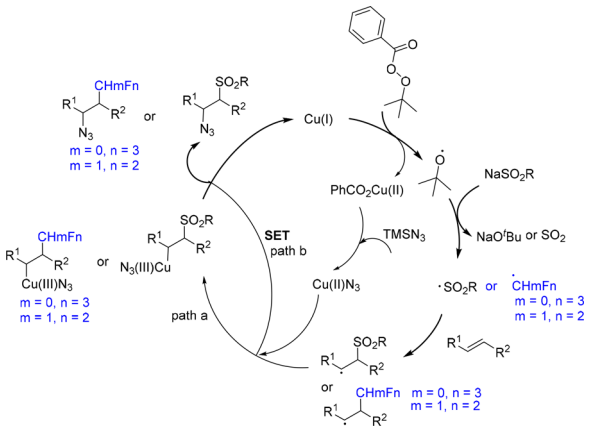


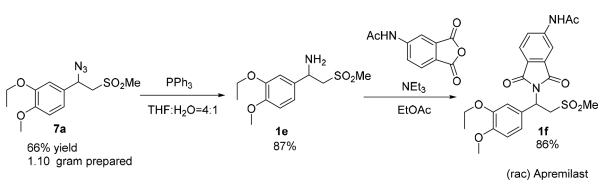
Figure 2. Proposed reaction mechanism.

tert-butoxyl radical and a Cu(II)OBz species.[17a] A radical relay process then occurs between RSO_2Na and the *tert*-butoxyl radical to afford a sulfonyl radical that adds to the olefin, generating an internal radical.[22] The Cu(II)OBz species undergoes ligand exchange with $TMSN_3$ to give $Cu(II)N_3$.[17a] In path a, rejoining of $Cu(II)N_3$ and an internal radical would provide a Cu(III) complex,[17b] which undergoes reductive elimination to eventually deliver product with regeneration of the Cu(I) catalyst. In path b, a direct SET process possibly leads to the same products.

Alternatively, the internal radical is oxidized to a cationic intermediate that is trapped by $TMSN_3$ to form the same product,[14f] which is, however, less likely, considering the good dr value for internal alkenes.[23] In the case of CF_3SO_2Na and CHF_2SO_2Na, fluorinated methyl radicals are formed through SO_2 expulsion and are added onto the alkene to continue the catalytic cycle.[4,20,21]

To illustrate the synthetic utility of the azidosulfonylation products, the synthesis of Apremilast was pursued. As shown in Scheme 5, Apremilast could be obtained in a three-step sequence in gram scale.[12]

Scheme 5. Approach for the Synthesis of Apremilast



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In summary, general and highly effective, Cu-catalyzed azido sulfonylation or fluoroalkylation reactions of alkenes have been achieved. This reaction can be applied to a variety of sodium sulfinates and a broad range of alkenes. Sulfinates were used efficiently in the radical difunctionalization of alkenes, and valuable divergent azido difunctionalized products could be obtained in high selectivity. Owing to the ready availability of starting material, mild reaction conditions, the significance of resulting functionalities, and high flexibility, the application of this novel strategy established here in synthetic and medicinal chemistry is positively expected.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02735.

Research details, experimental procedures, full characterization of products, and NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: guozhuzhang@sioc.ac.cn.

ORCID

Guozhu Zhang: 0000-0002-2222-6305

Notes

The authors declare no competing financial interest.

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