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One-Step Synthesis of Sulfonamides from *N*-Tosylhydrazones

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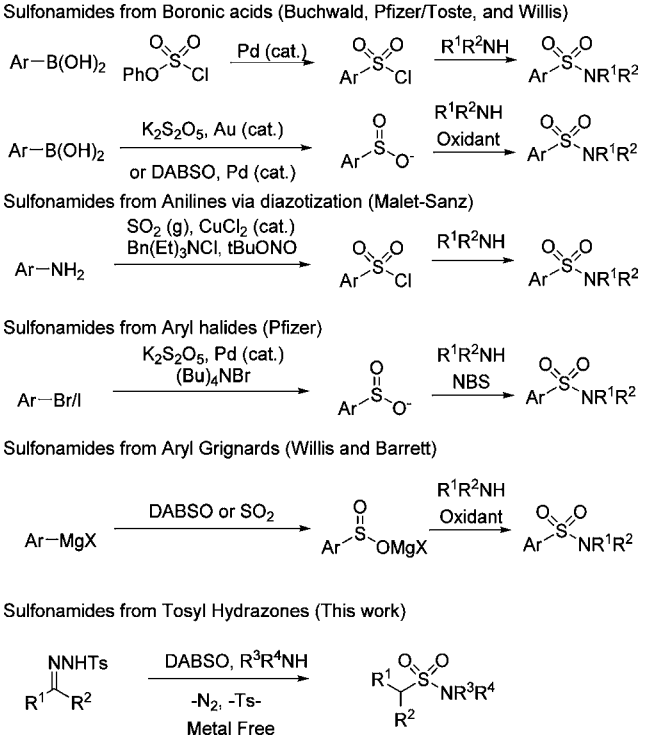
Supporting Information

ABSTRACT: The first described reaction between *N*-tosylhydrazone and SO_2 is reported to provide alkyl sulfonamides in the presence of various amines. In this procedurally simple method, hydrazones of both unsaturated aldehydes and ketones proceed in moderate to excellent yields. Primary and secondary aliphatic amines are accommodated in this reaction, which provides a novel route to sulfonamides.

Sulfonamides have become important structural elements in drug design since the development of sulfa antibiotics in the 1930s.[1] Although the traditional synthesis of sulfonamides from sulfonyl chlorides and amines is straightforward, obtaining the necessary sulfonyl chloride can be cumbersome. Classical methods toward sulfonyl chlorides typically require the oxidation and/or chlorination of less commonly encountered sulfides/thiols/sulfonates or harsh electrophilic aromatic substitution with SO_3.[2] Recently, various groups have reported more streamlined syntheses of aryl sulfonamides through a one-pot combination of an organic fragment, sulfur source, and amine.[3] The organic fragments have ranged from boronic acids (Buchwald, Pfizer/Toste, and Willis),[4a−c] to anilines (Malet-Sanz),[4d] aryl halides (Pfizer),[4e] and aryl Grignards (Willis and Barrett)[4f−h] (Scheme 1).[4] These advances have provided medicinal chemists increased flexibility for the introduction of sulfonamides.

While previous one-pot reactions have focused on aryl sulfonamides, we sought a method to access alkyl variants.[5] With this goal in mind, we were particularly attracted to decades-old reports that showed alkyl diazo species react with SO_2 to purportedly generate sulfenes which undergo further reaction with amines to yield sulfonamides.[6] While a topic of mechanistic study, these reports were not further explored for their synthetic value, likely due to the fact that diazo compounds are difficult to obtain and exhibit explosive potential. We sought to elaborate this chemistry through in situ generation of diazo compounds from *N*-tosylhydrazones which are stable and straightforward to obtain in one step from aldehydes/ketones.[7] Thus, we endeavored to develop a conversion of *N*-tosylhydrazones to sulfonamides through reaction with sulfur dioxide and an amine.[8] To our knowledge, such a transformation would be the first report of a reaction between *N*-tosylhydrazones and sulfur dioxide.

Scheme 1. Summary of One Pot Sulfonamide Syntheses



It was found that heating DABSO (a 1,4-diazabicyclo[2.2.2] octane bis(sulfur dioxide) adduct),[9] a convenient, commercially available, solid source of SO_2, with **1a** and piperidine in DMSO

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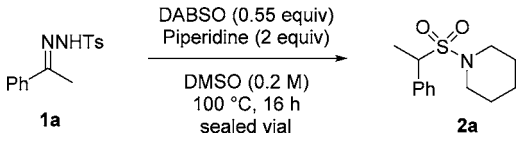
(dimethyl sulfoxide) at 100 °C in a sealed tube afforded direct formation of sulfonamide **2a** in 80% yield (Table 1, entry 1).

Table 1. Deviation from Optimal Conditions



entry	variation from standard conditions	yield[a]
1	none	80%
2	DMF solvent	61%
3	toluene solvent	36%
4	MeCN solvent	35%
5	DCE solvent	0%
6	dioxane solvent	40%
7	1.2 equiv of piperidine	49%
8	DABCO (2 equiv)	73%
9	LiOtBu (2 equiv)	39%
10	Cs_2CO_3 (2 equiv)	50%
11	SO_2 (1 equiv) instead of DABSO	60%
12	open to atmosphere	26%[b]

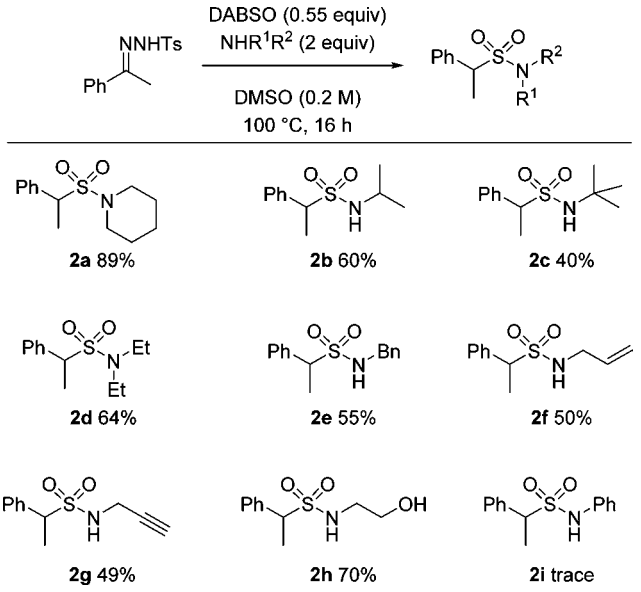
[a]NMR yields based on 2,6-dimethoxytoluene as internal standard. [b]Reaction was connected to a mineral oil bubbler.

DMF, dioxane, acetonitrile, and toluene provided products in lower yields whereas a reaction in dichloroethane provided no sulfonamide product (entries 2−6). The use of 2 equiv of piperidine provided a higher yield than 1.2 equiv (entry 7). As SO_2 is consumed during the reaction, DABSO generates DABCO (1,4- diazabicyclo[2.2.2] octane). Thus, the effect of excess DABCO was explored and a minimal reduction in yield was found (entry 8). Interestingly, this reaction does not require the addition of an inorganic base such as LiOtBu or Cs_2CO_3 which is typically used to initiate the decomposition of the *N*-tosylhydrazone to the diazo species.[7] The addition of such bases actually lead to a decrease in yield (entries 9−10). Use of SO_2 instead of DABSO also provides the sulfonamide product albeit in a slightly lower yield (entry 11). Finally, all reported reactions were carried out in a sealed container to prevent loss of SO_2 gas from DABSO. Heating the reaction while open to the atmosphere provided significantly diminished yields (entry 12).

The substrate scope was next explored using different amines (Scheme 2). While cyclic secondary amines such as piperidine provided the highest yield, useful yields were obtained with isopropyl, *tert*-butyl, diethyl, and benzyl amine (**2a**−**2d**). Versatile functional handles such as alkene, alkyne, and hydroxyl groups were also tolerated, allowing for potential subsequent diversification (**2f**−**2h**). Aryl amines provided only trace products under these conditions (**2i**). Bulky secondary amines such as dibenzyl and diisopropylamine furnished no product (not shown).

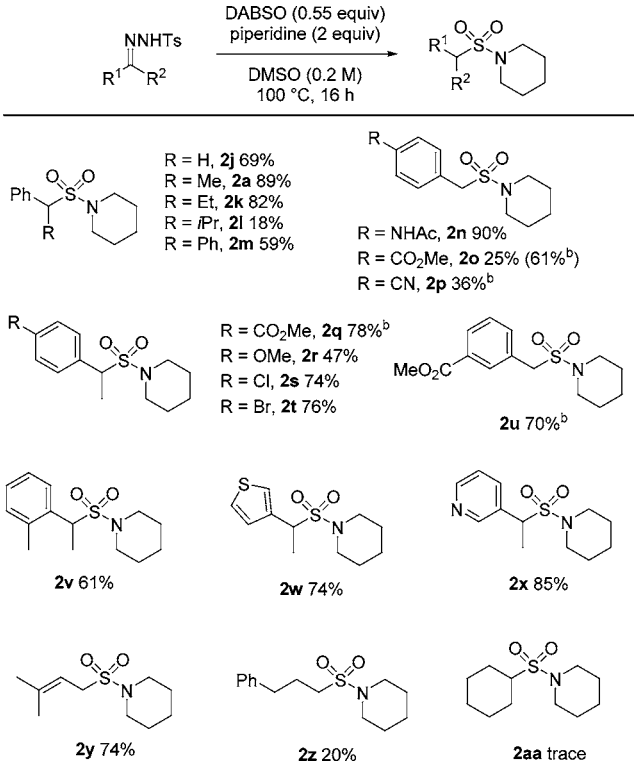
Various *N*-tosylhydrazones of aromatic aldehydes and ketones are accommodated (Scheme 3, **2j**−**2k**), though sterically congested hydrazones such as that derived from isobutyrophenone provided significantly lower yields (**2l**). Electronically diverse aryl hydrazones provided the sulfonamide products in moderate to good yields (**2n**−**2r**, **2u**). Of note, it was empirically discovered that electron-deficient substrates provided higher yields in dioxane instead of DMSO.[10] This method tolerated aryl chlorides, bromides, and ortho

Scheme 2. Substrate Scope in Amine[a]



[a]Yields are for products isolated after chromatography.

Scheme 3. Substrate Scope in Hydrazone[a]



[a]Yields are for products isolated after chromatography. [b]Reaction was performed in dioxane.

substitution (**2s**, **2t**, **2v**). Diaryl hydrazones (**2m**), thiazoles (**2w**), and pyridines (**2x**) were all accommodated. Good yields were obtained for the reaction of α,β-unsaturated hydrazones providing homovinyl sulfonamide, **2y**, which could be leveraged for consequent reactions. Yields were significantly decreased for the hydrazones of alkyl aldehydes (**2z**) and completely repressed for dialkyl ketones (**2aa**). In these low yielding reactions, the starting hydrazone was largely consumed and

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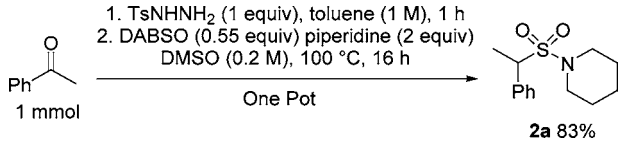
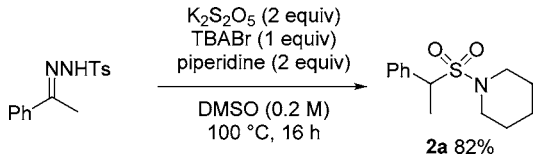
significant amounts of tosyl piperidine were obtained. No elimination or carbene dimerization products were observed. However, the bulk of the mass balance is unaccounted for. Furthermore, in substrates bearing the ester moiety (i.e., **2o**, **2q**), no amidation products were observed, suggesting that the amine may be sequestered during the reaction. Finally, a two-step, one-pot conversion of acetophenone to sulfonamide **2a** was demonstrated to provide the product in comparable yields to that found in Scheme 2 (Scheme 4).

Scheme 4. One-Pot Conversion of Ketones to Sulfonamide



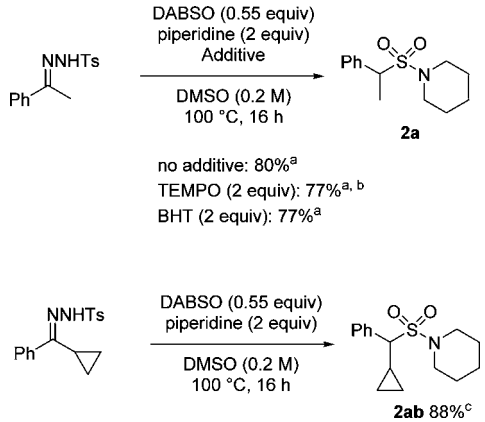
Additionally, alternate sources of SO_2 were viable for this reaction. Use of commonly available potassium metabisulfite and tetrabutylammonium bromide in place of DABSO provided sulfonamide **2a** in good yield (Scheme 5).[4e]

Scheme 5. Potassium Metabisulfite as Sulfur Source



To elucidate the mechanism, reactions were first carried out to probe for radical intermediates which have been reported for amine−SO_2 adducts.[11] Addition of TEMPO had little effect on yield, and no TEMPO adducts were observed (Scheme 6).

Scheme 6. Mechanistic Studies To Probe Existence of Radical Intermediates

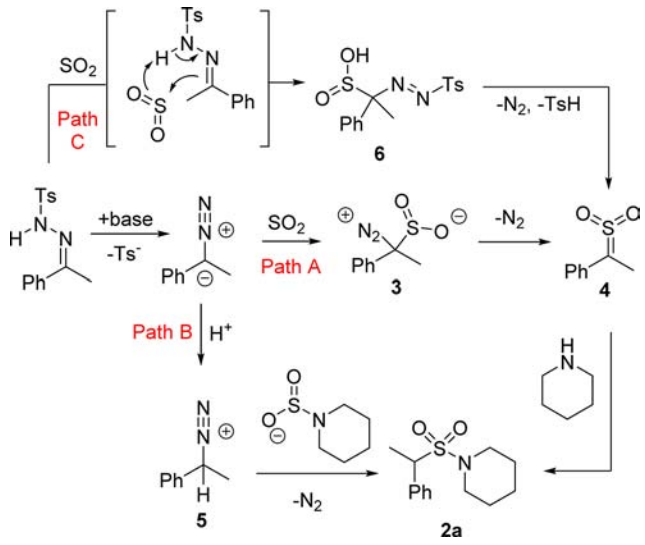


[a]NMR yields based on 2,6 dimethoxytoluene as internal standard. [b]No TEMPO adducts observed. [c]Yield obtained after chromatography.

Addition of BHT (butylated hydroxytoluene) as a radical inhibitor did not suppress the reaction. Finally, use of phenyl cylcopropyl ketone provided the expected sulfonamide product (**2ab**) without ring opening of the cyclopropyl group. Combined, these observations suggest that radical processes are not operative during this transformation.

Several plausible nonradical mechanisms might be considered for the reported reaction (Scheme 7). Path A is based on

Scheme 7. Possible Mechanisms



previous reports from reactions of SO_2 with nucleophilic diazo species.[6] In this pathway, the diazo species generated from the amine-initiated decomposition of the *N*-tosylhydrazone[7] acts as a nucleophile in a reaction with SO_2, forming intermediate **3**. Loss of N_2 gas then yields a sulfene (**4**) which reacts with piperidine to generate **2a**. Alternatively in path B, the diazo intermediate may act as a base and be protonated to generate **5**. Displacement with a nucleophilic amine−SO_2 complex would also provide **2a**.[12] Finally in path C, SO_2 may undergo an ene reaction with the *N*-tosylhydrazone to generate intermediate **6** which could decompose to sulfene **4**. Similar ene reactivity with SO_2 has been reported previously with alkenes.[5] Other mechanistic possibilities include formation of a free carbene which could react with SO_2 to generate sulfene **4** directly. This may be less likely, as no carbene side products (i.e., alkenes) were observed in the couplings. Further investigation is ongoing to elucidate the mechanism.

In conclusion, the first reported reaction between *N*-tosylhydrazones, SO_2, and amines is shown to generate sulfonamides. Unsaturated hydrazones provide moderate to excellent yields, and the mild reaction conditions accommodate a variety of useful functional groups. Of note, this reaction neither requires nor benefits from the addition of commonly used transition metals such as Pd, Cu, or Rh,[10] and it adds to a growing list of metal-free coupling reactions with *N*-tosylhydrazones. Ultimately, this method affords a new route to sulfonamides from readily available ketones and aldehydes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03545.

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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