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Pd-Catalyzed Selective Synthesis of Cyclic Sulfonamides and Sulfinamides Using $K_2S_2O_5$ as a Sulfur Dioxide Surrogate

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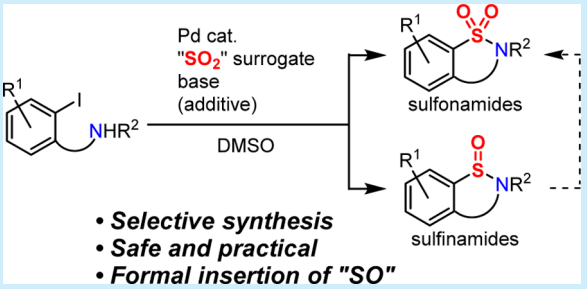
Supporting Information

ABSTRACT: A variety of cyclic sulfonamides and sulfinamides could be selectively synthesized under Pd catalysis using haloarenes bearing amino groups and a sulfur dioxide (SO_2) surrogate. The amount of base was key in determining the selectivity. Mechanistic studies revealed that sulfinamides were initially formed via an unprecedented formal insertion of sulfur monoxide and were oxidized to sulfonamides in the presence of an iodide ion and DMSO.



Sulfonamides and sulfinamides are important classes of organosulfur compounds in medicinal and synthetic chemistry.[1] Both sulfonamides and sulfinamides can be employed as amide isosteres in peptidomimetics.[2] Since sulfa drugs were discovered as antibacterial agents,[3] sulfonamides have been applied in the development of many types of drugs such as antimicrobials, diuretics, and anti-retrovirals.[1a] On the other hand, because of the characteristic chiral sulfur atom, sulfinamides are also used in synthetic chemistry as chiral auxiliaries[4] and chiral ligands.[5]

Sulfonamides are generally synthesized by the condensation of sulfonyl chlorides and amines.[6] Sulfinamides can also be synthesized by the condensation of sulfinyl chlorides, by multistep procedures starting from disulfides or sulfinates[7] or by the reaction of sulfonyl chlorides and amines in the presence of reductants.[8] However, the corrosive, easily hydrolyzable nature of sulfonyl and sulfinyl chlorides makes their handling troublesome. Formation of these chlorides often requires highly hazardous chlorine or strong chlorinating agents,[9] which restricts the synthetic utility. Considering the disadvantages of the aforementioned synthetic procedures, an alternative method to access sulfonamides and sulfinamides is highly desired.

Recently, Willis and co-workers elegantly demonstrated the Pd-catalyzed synthesis of *N*-aminosulfonamides from iodoarenes using hydrazines and DABSO, a complex of sulfur dioxide (SO_2) and 1,4-diazabicyclo[2.2.2]octane, as a SO_2 surrogate.[10] Thereafter, the use of potassium metabisulfite ($K_2S_2O_5$) as a SO_2 surrogate was reported in the synthesis of *N*-aminosulfonamides from organic halides.[11] Because these methods avoid the use of sulfonyl chlorides or toxic SO_2 gas, they have accelerated the development of synthetic methods for the introduction of sulfonyl moieties using SO_2 surrogates.[12]

While the Pd-catalyzed, one-step synthesis of sulfonamides from organic halides with amines and SO_2 surrogates is operationally simple and has good functional group compatibility, most reported methods for sulfonamide synthesis from organic halides use hydrazines as amine sources, resulting in the synthesis of only *N*-aminosulfonamides.[10,11,12d,e,g,i,k,n,s] To obtain sulfonamides from simple amines, multistep procedures via the corresponding sulfonyl halides are required.[12j,l,m,o,r,t,13] Moreover, only a few examples have disclosed the catalytic synthesis of sulfinamides using thiols or disulfides.[14] A one-step catalytic method from organic halides and amines has not been reported to date.

During our investigation on practical synthetic methods using toxic gas surrogates,[15] the lack of direct synthetic methods for sulfonamides from organic halides, a SO_2 surrogate, and amines piqued our interest. We recently reported that a variety of cyclic carbonyl compounds could be synthesized from haloarenes bearing nucleophilic groups via Pd-catalyzed external-CO-free carbonylation.[16] Likewise, if the introduction of a sulfonyl group were achieved under Pd catalysis, the formation of sulfonamides would proceed via an entropically favored intramolecular nucleophilic cyclization to afford a benzo-fused cyclic sulfonamide (sultam), which is present in many biologically interesting molecules.[17] Herein, we report the direct synthesis of cyclic sulfonamides using a Pd catalyst, a SO_2 surrogate, and various haloarenes with amino groups (Scheme 1). Furthermore, we describe the selective synthesis of cyclic sulfinamides where the SO_2 surrogate is used as a formal sulfur monoxide (SO) source to introduce a sulfinyl group.[18]

Initial trials to synthesize cyclic sulfonamides were conducted using compound **1a** and $K_2S_2O_5$ (**2**) (Scheme 2). 1,4-Dioxane and tetra-*n*-butylammonium bromide (TBAB) were previously reported to be effective for the synthesis of *N*-aminosulfonamides.[11] However, desired sulfonamide **3a** was not obtained under these conditions. When 1,4-dioxane was replaced with DMSO, **3a** was obtained in 21% yield. Surprisingly, in DMF, sulfinamide **4a** was obtained instead of sulfonamide **3a**, albeit in a

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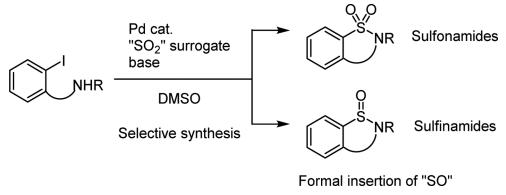
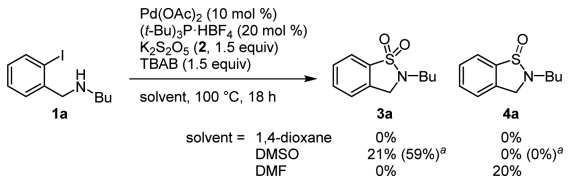
Scheme 1. Synthesis of Cyclic Sulfonamides and Sulfinamides Using SO_2 Surrogates



Scheme 2. Formation of Sulfonamide 3a and Sulfinamide 4a: Initial Studies

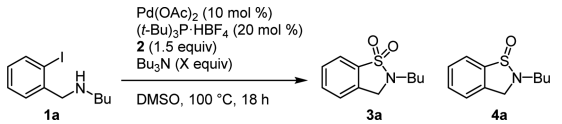


[a]Bu_3N (1.0 equiv) was used instead of TBAB.

low yield. This unexpected change in products encouraged us to develop a selective method for the synthesis of either sulfonamides or sulfinamides. Notably, when 1.0 equiv of tri-*n*-butylamine (Bu_3N) was used instead of TBAB to trap in situ generated hydrogen iodide, the yield of **3a** was improved to 59%.

Next, the effect of the amount of Bu_3N was examined (Table 1). Surprisingly, sulfonamide **3a** was obtained when 1.0 equiv or

Table 1. Effect of the Amount of Bu_3N



entry	X (equiv)	yield of **3a** (%)	yield of **4a** (%)
1	0	25	0
2	0.10	33	0
3	0.50	20	0
4	1.0	48	0
5[a]	1.0	59	0
6	1.5	0	39
7	2.0	0	54
8	3.0	0	48
9[b]	2.0	0	75

[a]$K_2S_2O_5$ (2.0 equiv) was used. [b]PCy_3 (20 mol %) was used instead of $(t\text{-Bu})_3P{\cdot}HBF_4$.

less Bu_3N was used, and sulfinamide **4a** was obtained when 1.5 equiv or more Bu_3N was utilized. Since the selective formation of **3a** or **4a** was feasible, we further optimized the conditions (for details, see Tables S1−S4 in Supporting Information (SI)) and finally found the best conditions for sulfonamide **3a** (entry 5) and for sulfinamide **4a** (entry 9).

We also evaluated other SO_2 surrogates (for details, see Table S5 in SI). $Na_2S_2O_5$ and DABSO afforded sulfonamide **3a** and sulfinamide **4a**, albeit in yields (up to 45% for **3a** and up to 43% for **4a**) lower than that of $K_2S_2O_5$. The formation of the products with all SO_2 sources suggests that SO_2 was generated in situ and used to produce **3a** and **4a**.

The selective synthesis of sulfonamides or sulfinamides was tested with various substrates (Figure 1). Method A and method B were applied for the synthesis of sulfonamides **3a−o** and

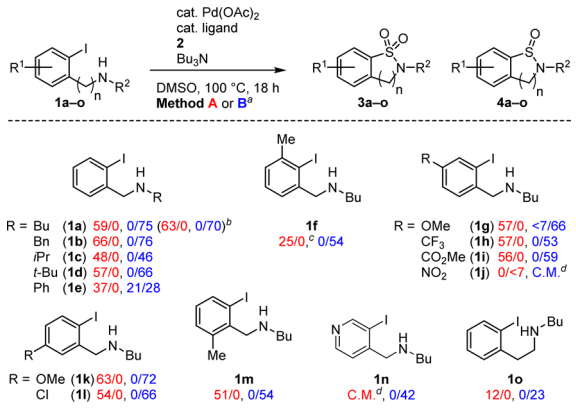


Figure 1. Substrate scope. Isolated yields of products (%) are described as "sulfonamide **3**/sulfinamide **4** in method A, sulfonamide **3**/sulfinamide **4** in method B". [a]Method A (for synthesis of sulfonamide **3a−o**): $Pd(OAc)_2$ (10 mol %), $(t\text{-Bu})_3P{\cdot}HBF_4$ (20 mol %), **2** (2.0 equiv), Bu_3N (1.0 equiv). Method B (for synthesis of sulfinamide **4a−o**): $Pd(OAc)_2$ (10 mol %), PCy_3 (20 mol %), **2** (1.5 equiv), Bu_3N (2.0 equiv). [b]1.0 mmol scale. [c]120 °C. [d]Complex mixture.

sulfinamides **4a−o**, respectively. In general, both products were obtained in moderate to good yields with almost complete selectivity, with the exception of *N*-phenyl substrate **1e**. Bulky substituents on the N atom such as *t*-Bu (**1d**) did not interfere with the reaction. Regardless of the substituents on the benzene ring, the desired products were selectively obtained using either method, although **1j** bearing a nitro group did not tolerate the reaction conditions. While **1n** containing a pyridine moiety failed to produce sulfonamide **3n** due to the formation of byproducts, sulfinamide **4n** could be obtained by method B. The reactions to afford ring-expanded sulfonamide **3o** and sulfinamide **4o** also proceeded, although the yields were low.

To gain insight into the reaction mechanism, the reaction was monitored in detail. When the conditions for the synthesis of sulfonamide **3a** (Table 1, entry 5) were applied, sulfinamide **4a** was formed during the initial stages of the reaction (Figure 2, X =

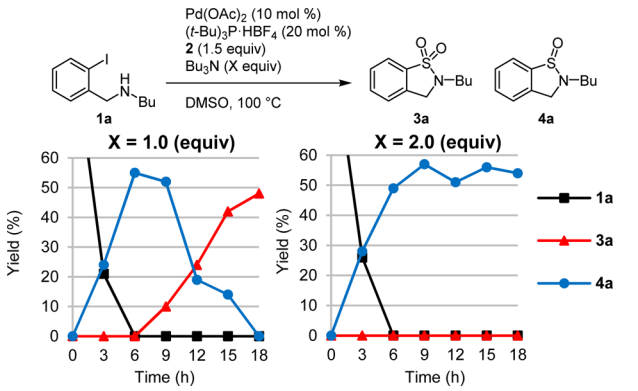


Figure 2. Reaction profile. Yields were determined by isolation of each compound in separate experiments.

1.0). Sulfonamide **3a** was not formed during the accumulation of **4a**. After 6 h, the amount of **4a** decreased, and sulfonamide **3a** formed simultaneously. On the other hand, when the conditions for the synthesis of sulfinamide **4a** (Table 1, entry 7) were applied, **4a** was generated at a rate similar to that of the sulfonamide synthesis, with no decrease in the yield of **4a** (Figure 2, X = 2.0). These results suggest that sulfonamide **3a** was formed

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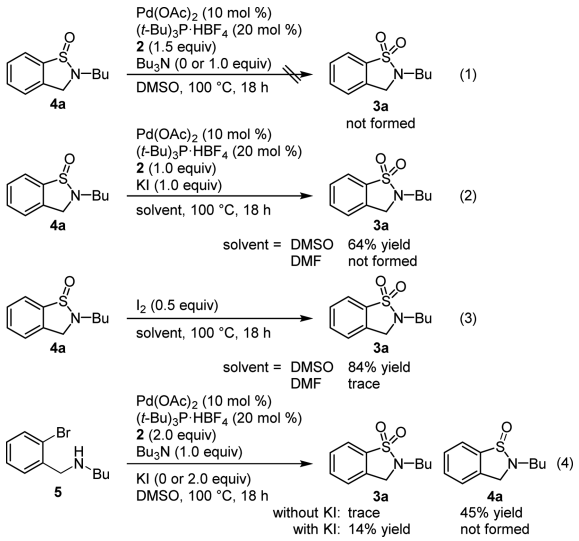
via sulfinamide **4a** and that excess Bu_3N suppressed the formation of sulfonamide **3a**.

To confirm the formation of **3a** from **4a**, the direct conversion of **4a** to **3a** was tested. The formation of **4a** was not observed when the conditions for synthesis of **3a** were applied (Scheme 3, eq 1). Since an iodide ion must be generated during the reaction of **1a** to **3a**, potassium iodide (KI) was added as an iodide source for the conversion of **4a** to **3a**. As expected, **3a** was obtained in 64% yield (Scheme 3, eq 2). Furthermore, when the reaction was carried out in DMF, **4a** was not obtained (Scheme 3, eq 2), suggesting that DMSO served as an oxygen source.[19] In fact, the scent of dimethyl sulfide was noticed upon quenching the reaction. We assumed that molecular iodine (I_2) might be generated in the course of the reaction,[20] and that I_2 would work as an oxidant. To confirm this hypothesis, sulfinamide **4a** and I_2 were mixed in DMSO at 100 °C, giving sulfonamide **3a** in a high yield (Scheme 3, eq 3). Furthermore, conversion of **4a** to **3a** failed when the reaction was performed in DMF (Scheme 3, eq 3), corroborating DMSO as an oxygen source. These mechanistic studies revealed that sulfonamide **3a** was obtained via the formation of sulfinamide **4a**, and that the conversion from **4a** to **3a** requires an iodide source and DMSO as an oxygen source. Larger amounts (1.5 equiv or more) of Bu_3N may quench I_2 that forms in situ, thus suppressing the formation of **3a**. Finally, we tested bromoarene **5** as the substrate and found that KI determined the selectivity between **3a** and **4a** (Scheme 3, eq 4). Notably, **4a** was selectively obtained even in the presence of 1.0 equiv of Bu_3N without KI (the conditions for synthesis of **3a** from iodoarenes). With KI, **3a** was obtained, albeit in lower yield (Scheme 3, eq 4). This result also supports the involvement of iodide ion in the formation of **3a**. The reaction mechanism behind the formation of sulfinamide **4a**, including the possibility of the generation of unstable SO in the reaction system, is under investigation.[21]

Scheme 3. Mechanistic Studies for the Formation of 3a from 4a and Reaction of Bromoarene 5



In conclusion, we have shown for the first time that the Pd-catalyzed selective synthesis of cyclic sulfonamides and sulfinamides could be achieved using $K_2S_2O_5$ as a SO_2 surrogate. The reaction could be conducted in a safe and practical manner, without the use of SO_2 gas or sulfonyl chlorides. Mechanistic studies revealed that sulfinamides were initially formed and could be converted into sulfonamides when 1.0 equiv or less of base was used. Iodide and DMSO played important roles in the formation of sulfonamides from sulfinamides. Although the mechanism behind the formation of sulfinamides requires further investigation, this synthetic method represents an unprecedented approach to the direct introduction of sulfinyl groups into haloarenes using a SO_2 surrogate and will be a powerful tool for the synthesis of cyclic sulfonamides and sulfinamides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00402.

Detailed optimization studies, experimental procedures, and physical and spectral data of newly obtained products (PDF)

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Notes

The authors declare no competing financial interest.

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