Sulfur Heterocycles

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Formation of Cyclic Sulfinates and Sulfinamides through Homolytic Substitution at the Sulfur Atom**

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Dedicated to the memory of André Rassat

During the last decade, radical reactions have gained wide acceptance as efficient ways to build complex frameworks under mild conditions.[1] This ability is largely a consequence of the broad array of transformations that these reactions can accommodate. Yet, among all the available radical processes, intramolecular homolytic substitutions[2,3] have remained much less exploited than cyclization reactions, despite their strong synthetic potential. One solution to access these reactions is to use heteroatoms such as oxygen,[4] selenium,[5–7] phosphorus,[8,9] or silicon.[10,11] Sulfur is particularly well-suited, and several reactions have been reported that employ homolytic substitution on this particular atom. A variety of different functions have been introduced (sulfides,[12–14] disulfides,[15] thioesters,[16–18] and sulfoxides;[14,19,20] sulfones seem not to be prone to such processes[14,21]), but so far none in which an additional heteroatom was present in the ring next to the sulfur atom, despite the increased potential offered by the heterocyclic adducts.

Sulfinates[22,23] and sulfinamides[24–26] play pivotal roles in modern asymmetric synthesis as key precursors of chiral molecules. As part of our program devoted to new reactions involving sulfur-based moieties,[27–30] we became interested in the synthesis of cyclic sulfinates and sulfinamides because they are versatile synthetic intermediates,[31,32] and have elicited interest in medicinal chemistry.[33,34] They have also been used in materials science as imaging agents.[35] It thus appeared to us that homolytic substitution would be a unique tool to prepare cyclic sulfinates and sulfinamides through an original strategy. Herein, we report the results we gathered along the way.

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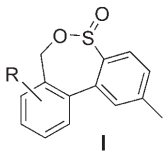
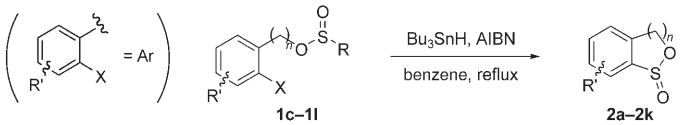
To probe this issue, we initially focused on the readily prepared substrate **1a** (Table 1). Classical tributyltin hydride conditions (Table 1, entry 1) gave an encouraging 62% yield of sultine **2a**, presumably resulting from thiophilic attack by the aryl radical with a concomitant or successive expulsion of the *p*-tolyl radical.[2,36] Besides this homolytic substitution product, the main side product of the reaction was a biarylic adduct (**I**: 11%), which originated from a 7-*endo* cyclization followed by rearomatization. This type of adduct was also obtained in the 5–15% range in other trials (Table 1, entries 2–6).



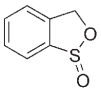
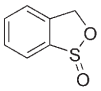
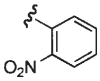
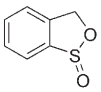
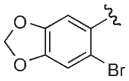
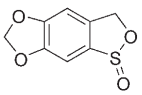
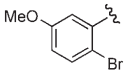
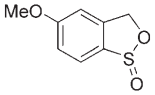
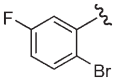
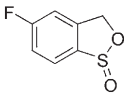
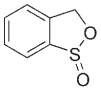
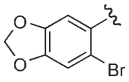
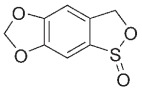
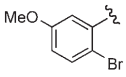
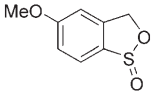
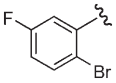
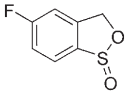
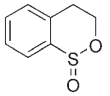
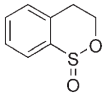
I

We also observed that the homolytic substitution can take place at room temperature, albeit with some erosion of the yield of **2a** (the yields were in the 40% range with the borane/oxygen initiator; the main by-product was the reduced sulfinate isolated in a roughly equimolar amount). Furthermore, TTMSS can replace Bu_3SnH with no significant loss of yield (Table 1, entries 2 and 3). This preliminary synthesis of sultine **2a** drove us to extend the scope of this unprecedented homolytic substitution, and we examined several diversely

Table 1: Synthesis of fused benzosultines.



1c–1l **2a–2k**

Entry	**1**, *n*	Ar	R	Product		Yield [%]
1	**1a**, 1		*p*Tol		**2a**	62
2	**1b**, 1		*p*Tol		**2a**	58[a]
3	**1c**, 1				**2a**	56 (65[a])
4	**1d**, 1		*p*Tol		**2d**	69
5	**1e**, 1		*p*Tol		**2e**	70
6	**1f**, 1		*p*Tol		**2f**	73
7	**1g**, 1		*t*Bu		**2a**	97
8	**1h**, 1		*t*Bu		**2d**	100
9	**1i**, 1		*t*Bu		**2e**	100 (73[b])
10	**1j**, 1		*t*Bu		**2f**	95 (86[b,c])
11	**1k**, 2		*p*Tol		**2k**	45[d]
12	**1l**, 2		*t*Bu		**2k**	89[e] (64[b])

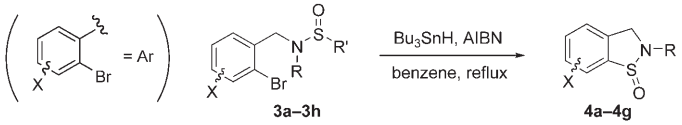
[a] Bu_3SnH was replaced by TTMSS. [b] Conditions: AIBN, Bu_3SnCl (10 mol%), $NaBH_4$ (2 equiv), *t*BuOH, Δ. [c] NMR yield, calculated by using 1,3,5-trimethoxybenzene as an internal standard. [d] Reduced material (48%) was also isolated. [e] Reduced material (5%) was also isolated. TTMSS = tris(trimethylsilyl)silane; AIBN = azobisisobutyronitrile; *p*Tol = *p*-tolyl.

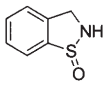
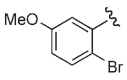
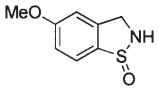
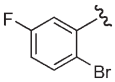
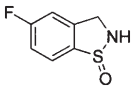
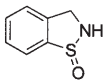
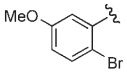
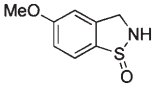
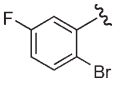
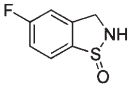
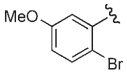
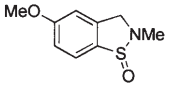
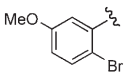
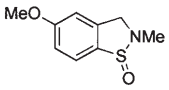
substituted aromatic precursors **1c**–**1l**. Entries 4–6 in Table 1 nicely illustrate the variety of the aromatic substitution pattern compatible with this reaction, including piperonal derivative **1d** and fluorine derivative **1f**. Introduction of a nitro group on the leaving aromatic moiety did not lead to an increase in the yield (Table 1, entry 3). To suppress the biarylic side product, we intended to introduce a new nonaromatic R group with a higher leaving homolytic ability. A *tert*-butyl group appeared to be the logical choice, as *tert*-butyl sulfur species are highly accessible from *tert*-butyldisulfide, and the expulsion of a more stable tertiary radical should be rendered easier. This proved to be the case, as shown with precursors **1g**–**1j**, which yielded essentially quantitative yields of the corresponding sultines **2a** and **2d**–**2f** (Table 1, entries 7–10). Again, use of the borane/oxygen initiator resulted in some formation of reduced material (9%), but the reaction still yielded 90% of **2a** at room temperature. Sultines with a six-membered ring are equally accessible by this method (precursors **1k** and **1l**). In that case, a net-yield increase was observed when using a *tert*-butyl precursor (compare Table 1, entries 11 and 12), and no biarylic by-product was isolated when starting from **1k**. Finally, the fact that catalytic tin hydride (only 10 mol%) conditions could be used is also worthy of note (Table 1, entries 9, 10, and 12).

We then extended this reaction to sulfinamides. It was interesting to verify whether a similar pathway could be followed, because of the different electronic and steric environment. Gratifyingly, cyclic sulfinamides **4** could be obtained. Functionalization on the aromatic moiety was also tolerated (Table 2, entries 1–6). In the case of precursors **3a**–**3c**, the corresponding biaryl products were again detected in a 10–20% yield (based on NMR spectroscopy), but could not be isolated as a result of degradation in the purification process by column chromatography. Logically, this competitive process was eliminated with precursors **3d** and **3e**, and improved yields were observed. However, the introduction of a methyl group on the nitrogen atom proved to be detrimental for both **3g** and **3h**, and lower yields of **4** were obtained. We suspect that the methyl group suffers from 1,5-intramolecular hydrogen abstraction by the highly reactive aryl radical. The resulting stabilized α-amino radical would then undergo fragmentation to give untractable material.

We then examined the case of alkyl radicals (Table 3). The reaction of tolylsulfinates only afforded reduced material, as also reported by Studer et al.[37] Presumably, the expulsion of a high-energy aryl radical would be disfavored and this energetic gap would account for the lack of cyclization. Nonetheless, the *tert*-butyl sulfinates worked well. When Bu_3SnH was used (conditions A), we faced problems during the purification step (Table 3, entries 1, 3, 5, 7, and 9). The sultines were soluble in hexane, and therefore the CH_3CN/hexane separation method could not be used any more. All

Table 2: Synthesis of cyclic sulfinamides.



Entry	Precursor	Ar	R	R′	Product		Yield [%]
1	**3a**		H	*p*Tol		**4a**	58
2	**3b**		H	*p*Tol		**4b**	66
3	**3c**		H	*p*Tol		**4c**	63
4	**3d**		H	*t*Bu		**4a**	85
5	**3e**		H	*t*Bu		**4b**	86
6	**3f**		H	*t*Bu		**4c**	85 (80[a])
7	**3g**		Me	*p*Tol		**4g**	36
8	**3h**		Me	*t*Bu		**4g**	31

[a] Conditions: AIBN, Bu_3SnCl (10 mol%), $NaBH_4$ (2 equiv), *t*BuOH, Δ.

Table 3: Cyclic sulfinates from an alkyl radical.

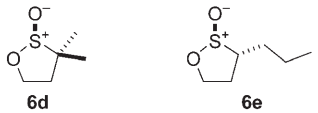
Entry	Precursor	R^1	R^2	Conditions[a]	Product, yield [%]	*trans*/*cis*
1	**5a**	H	H	A	**6a**, 85	–
2	**5a**	H	H	B	**6a**, 65	–
3	**5b**	Me	H	A	**6b**, 60	66:34
4	**5b**	Me	H	B	**6b**, 69	63:37
5	**5c**	*t*Bu	H	A	**6c**, 85	100:0[b]
6	**5c**	*t*Bu	H	B	**6c**, 84	100:0
7	**5d**	Me	Me	A	**6d**, 70	–
8	**5d**	Me	Me	B	**6d**, 63	–
9	**5e**	*n*Pr	H	A	**6e**, 85	69:31
10	**5e**	*n*Pr	H	B[c]	**6e**, 99	63:37

[a] Conditions A: Bu_3SnH, AIBN (10 mol%), benzene, Δ; B: TTMSS, V-501 (25 mol%), benzene, Δ. [b] The product could not be separated from AIBN by-products. The yield was calculated relative to 1,3,5-trimethoxybenzene as internal standard. [c] AIBN was used.

the other methods we tried led to the loss of the products. The yields reported indicate the calculated amount of desired product present in the isolated mixture. Tin by-products (usually 10–30 mol%) were also present. Moreover, some of the products could not be separated from the AIBN residues. We thus changed to TTMSS as mediator and V-501 (azobis-4-cyanovaleric acid) as initiator (conditions B), because we anticipated that separation from the by-products could be achieved readily, either upon aqueous workup or by filtration on silica. This change proved rewarding, as the sultines were obtained in similar yields with no traces of either mediator or initiator residues (Table 3, entries 2, 4, 6, 8, 10).

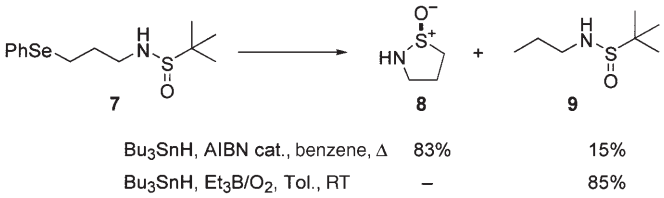
When a prochiral radical was cyclized, the *trans* diastereomers were favored (Table 3, entries 3–6, 9, 10), as evidenced by comparison with known products.[38] The selectivity depends on the size of the substituents. Methyl and propyl groups typically gave a 2:1 selectivity, while the bulky *tert*-butyl group led to the formation of a single diastereomer, which we assumed to be a *trans* isomer by analogy with the methyl case.

Noticeably, the method still worked smoothly with an incoming tertiary radical, that is, with no positive bond-energy balance. Cyclization of **5d** thus delivered sultine **6d**, which is a component of cat's urine (Table 3, entries 7 and 8).[39] Interestingly, sultine-based natural products are not abundant. Yet, both **6d** and **6e** have olfactory or flavor properties,



and small substituent variations seem to lead to strong modifications of the former. For example, cyclization of substrate **5e** quantitatively gave sultine **6e**, which is present in the volatile compounds of yellow passion-fruit extracts.[39] The method we have devised is ideally suited to the preparation of analogues.

We finally examined the cyclization of alkyl sulfinamide **7** (Scheme 1). The reaction still worked and cyclic sulfinamide **8** could be isolated in good yield (83%). However, some reduced material was also obtained. As was expected from



Scheme 1. Cyclization of alkyl sulfinamide **7**.

the previous experiments, lowering the temperature gave only reduced product **9**. This finding represents a noticeable difference compared with the benzofused sultine case, and shows that the formation of cyclic alkyl sulfinamides is a slower process.

In conclusion, we have devised an efficient, general access procedure for cyclic sulfinates and sulfinamides based on homolytic substitution at the sulfur atom. Both purely alkyl and benzofused families of compounds could be accessed. The cyclization of a prochiral radical proceeded with varied stereochemical outcomes, which depended on the size of the incoming radical. Biologically active sultines were quickly prepared by this method, which opens the way to the synthesis of a vast library of analogues. We are currently assessing the process at the stereogenic sulfur atom, with a view to preparing enantiopure sultines and cyclic sulfinamides. Progress along this route will be presented in due course.

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