Probing the Amino-End Reactivity of Sulfonimidamides

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Abstract: The amino terminus of sulfonimidamides was functionalized through a Mitsunobu reaction. The new sulfonimidamides were engaged in oxidative reactions to provide N-heterocycles.

Key words: aminations, diastereoselectivity, iodine, Mitsunobu reaction, sulfur

Sulfonimidamides are chiral analogues of sulfonamides (Figure 1), which have been introduced in the 1960s and 1970s.[1] Since those pioneering reports, sulfonimidamides have been introduced for medicinal chemistry purposes.[2] The more recent development of metal-mediated nitrogen-atom introductions has triggered renewed interest in those molecules.[3] Indeed, their inherent chirality is an appealing feature in the quest for better nitrogen sources.[4]

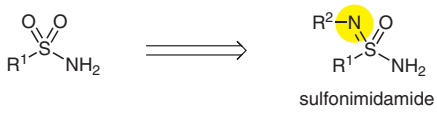
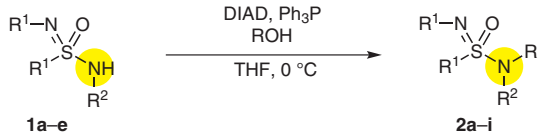


Figure 1

As part of our program devoted to the organic chemistry of sulfur,[5] we have used the stereogenic sulfur atom of sulfonimidamides to build chiral nitrenes for asymmetric aziridinations.[6] The latter are more reactive than their sulfonamide-based equivalents, but led to relatively poor diastereoselectivities. This latter fact was independently confirmed by Dauban and Dodd's group, who demonstrated that double induction (with chiral catalysts) led to consistently high selectivities.[7] Dauban and Dodd elegantly broadened the scope of this enantiocontrolled nitrogen insertion to asymmetric C–H insertions.[8]

Nonetheless, as was expected, the replacement of one oxygen of sulfonamides with a nitrogen substituent led to some changes in reactivity. While some were favorable – such as the enhanced reactivity of sulfonimidamide nitrenes – some were less favorable. For example, it was not possible to obtain nitrenes without electron-withdrawing moieties attached to the unreactive nitrogen. We thus decided to assess the scope of eligible reactions involving the nitrogen terminus of sulfonimidamides. In particular, we were interested in probing the behavior of this nitrogen as a nucleophile and/or radical partner. In this Letter, we report our findings.

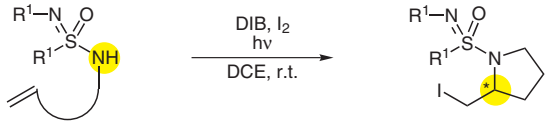
We examined first the Mitsunobu reaction of sulfonimidamides (Scheme 1), in which the nitrogen atom should behave as a nucleophile (Table 1).



Scheme 1

In a typical reaction, sulfonimidamide **1a** was reacted with butenol in the presence of diisopropyl azodicarboxylate (DIAD) and triphenylphosphine in cold THF. Gratifyingly, the substituted sulfonimidamide **2b** was isolated in acceptable yield (56%, Table 1, entry 2), thus showing that the nitrogen was nucleophilic enough to react under Mitsunobu conditions. The yields were generally around 70%, but dropped when a secondary alcohol was used (Table 1, entry 7). The reaction was limited to sulfonimidamides with withdrawing groups attached to the second nitrogen (Table 1, entries 9 and 10). This situation is reminiscent of results in the aziridinations, for which similar electronic effects were observed.[6,7] Finally, N-substituted sulfonimidamides reacted smoothly (Table 1, entry 11). In fact, some of the N,N-disubstituted products were isolated as byproducts during the reactions of **1a**.

With our functionalized sulfonimidamides in hand, we decided to examine whether N-centered radicals could be generated and reacted (Scheme 2, Table 2).



Scheme 2

The suitably substituted sulfonimidamides were oxidized using the (diacetoxyiodo)benzene (DIB)/I_2 system[9] with the aim of generating the corresponding N-centered radicals. The reactions were particularly efficient for monosubstituted olefins (Table 2, entries 1, 2, and 5). Unfortunately, no diastereoselectivity was observed in any of those reactions. Furthermore, all the cyclized compounds included an extra iodine atom.

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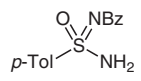
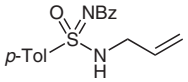
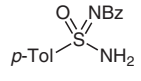
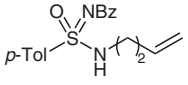
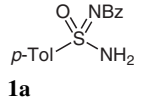
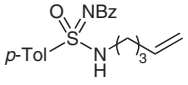
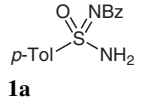
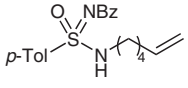
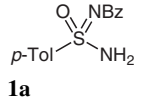
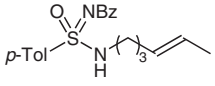
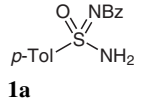
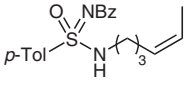
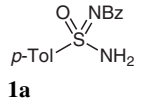
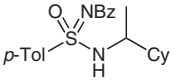
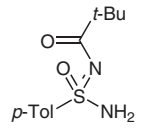
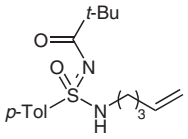
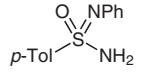
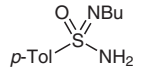
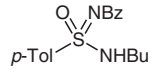
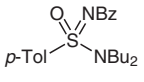
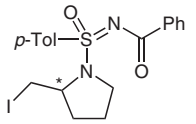
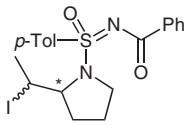
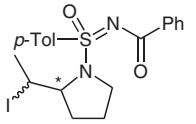
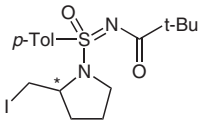
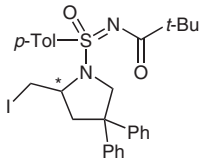
Table 1 Mitsunobu Reactions of Sulfonimidamides

Entry	Starting material	Product	Yield (%)
1	 **1a**	 **2a**	43
2	 **1a**	 **2b**	56
3	 **1a**	 **2c**	68
4	 **1a**	 **2d**	76
5	 **1a**	 **2e**	75
6	 **1a**	 **2f**	69
7	 **1a**	 **2g**	20
8	 **1b**	 **2h**	60
9	 **1c**	Degradation	–
10	 **1d**	Degradation	–
11	 **1e**	 **2i**	100

We wondered whether the reaction followed a radical pathway, or an alternative electrophilic iodocyclization.[10] In order to ascertain the exact mechanism, we ran several control experiments with sulfonimidamides **2c** and **2j** (Table 3).

The optimal yields were obtained when iodine and DIB were present, and when the reaction was irradiated. Removal of iodine was fatal to the reactivity (Table 3, entry 2). When either DIB or light was omitted, the conversions were much poorer, and starting material was recovered (Table 3, entries 3 and 5). Those reactions hint at a radical mechanism featuring homolytic cleavage of an N–I bond

Table 2 Iodine-Mediated Cyclizations of Sulfonimidamides

Entry	Starting material	Product	Yield (%)	ds
1	**2c**	 **3a**	85	60:40
2	**2e**	 **3b**	48	–[a]
3	**2f**	 **3b**	54	–[a]
4	**2h**	 **3c**	79	50:50
5	**2j**	 **3d**	92	50:50

[a] A mixture of all possible diastereomers was isolated.

presumably generated through oxidation of the sulfonimidamide by the hypervalent iodine derivative. The nitrene chemistry of sulfonimidamides tells us that such an outcome is possible.

On the other hand, when only iodine was added to the solution, the same products were obtained, albeit in low yield (Table 3, entry 4). In this case, the products can only arise from an ionic reaction. Overall, we cannot definitely discard one of the two mechanisms, which may coexist. That said, because the reactions were faster upon irradiation, a dominant radical pathway seems the most likely.

In conclusion, we have extended the number of reactions compatible with sulfonimidamide moieties. The stereochemical outcomes of those processes were rather disappointing. Work to increase the chiral transfer from sulfur as well as identify other transformations applicable to sulfonimidamides is pursued in our laboratory and we will report on this in due course.

General Procedure for the Mitsunobu Reaction

Triphenylphosphine (1.5 equiv) and the alcohol (2 equiv) were added to a solution of sulfonimidamide (1 equiv) in THF at 0 °C. Diisopropyl azodicarboxylate (1.4 equiv) was then added dropwise, and the reaction mixture was slowly warmed to r.t. and left overnight.

Table 3 Control Experiments

Entry	Starting material	Conditions	Product, yield (%)	Observation
1	**2c**	DIB, I_2, hν, 1 h	**3a**, 85	–
2	**2c**	DIB, hν, 1.5 h	–	Recovered starting material
3	**2c**	I_2, hν, 1 h	**3a**, 32	Starting material (44%)
4	**2c**	I_2, 1h	**3a**, 33	Starting material (47%)
5	**2c**	DIB, 1 h	–	Starting material (50%) + degradation
6	**2j**	DIB, I_2, hν, 1 h	**3d**, 92	–
7	**2j**	DIB, I_2, 1 h	**3d**, 70	Some starting material

After concentration in vacuo, the crude mixture was purified by flash chromatography.

Compound 2c
Colorless oil. IR (diamond): 3066, 2924, 1604 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.64 (quin, *J* = 7.0 Hz, 2 H, CH_2CH_2N), 2.07 (q, *J* = 7.0 Hz, 2 H, CH_2CH=), 2.41 (s, 3 H, Ar*Me*), 2.88–2.93 (m, 1 H, C*H*HN), 3.10–3.15 (m, 1 H, CH*H*N), 4.94–5.01 (m, 2 H, $=CH_2$), 5.65–5.75 (m, 1 H, =CH), 7.30–7.49 (m, 6 H, Ph + NH), 7.87 (d, *J* = 8.1 Hz, 2 H, Tol), 8.13 (d, *J* = 8.1 Hz, 2 H, Tol). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5 (Ar*Me*), 28.7 (CH_2CH_2), 30.5 (CH_2CH_2), 41.2 (CH_2N), 115.6 ($=CH_2$), 127.2 (CH arom.), 127.9 (CH arom.), 129.4 (CH arom.), 129.8 (CH arom.), 132.1 (CH arom.), 135.6 (C arom.), 136.2 (C arom.), 136.9 (CH arom.), 144.2 (CS), 172.9 (C=O). HRMS: *m/z* calcd for $C_{19}H_{23}N_2O_2S$ [MH^+]: 343.1480; found: 343.1496. Anal. Calcd (%) for $C_{19}H_{22}N_2O_2S$ (342.46 g·mol^{-1}): C, 66.64; H, 6.48; N, 8.18. Found: C, 66.44; H, 6.58; N, 8.19.

General Procedure for the DIB-Mediated Cyclizations
(Diacetoxyiodo)benzene (3 equiv) and I_2 (1.2 equiv) were added to a solution of sulfonimidamide in 1,2-dichloroethane. The mixture was irradiated at r.t. with a tungsten lamp (300 W) for 1 h under an argon atmosphere. After completion, the mixture was poured into sat. aq $Na_2S_2O_3$ and then extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4. After concentration in vacuo, the crude mixture was purified by flash chromatography.

Compound 3a
Two diastereomers, colorless oils.

Diastereomer 1: IR (diamond): 3063, 2924, 1718, 1631 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.77–1.82 (m, 1 H, NCH_2CHH), 1.91–2.04 (m, 2 H, NCH_2CHH + CHC*H*H), 2.11–2.16 (m, 1 H, CHCH*H*), 2.43 (s, 3 H, Ar*Me*), 3.11–3.19 (m, 2 H, NCH_2), 3.43 (B of ABX, *J* = 9.4, 9.4 Hz, 1 H, C*H*HI), 3.70 (B of ABX, *J* = 9.4, 2.5 Hz, 1 H, CH*H*I), 4.58–4.62 (m, 1 H, CHN), 7.35–7.55 (m, 5 H, Ph), 7.96 (d, *J* = 8.1 Hz, 2 H, Tol), 8.16 (d, *J* = 8.1 Hz, 2 H, Tol). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.4 (CH_2I), 21.6 (Ar*Me*), 24.3 (CH_2CH_2), 31.4 (CH_2CH_2), 48.8 (CH_2N), 61.9 (CHN), 127.8 (CH arom.), 128.0 (CH arom.), 129.4 (CH arom.), 130.0 (CH arom.), 132.1 (CH arom.), 135.2 (C arom.), 135.7 (C arom.), 144.4 (CS), 172.8 (C=O). HRMS: *m/z* calcd for $C_{19}H_{22}N_2O_2SI$ [MH^+]: 469.0447; found: 469.0461. Anal. Calcd (%) for $C_{19}H_{21}N_2O_2SI$ (468.35 g·mol^{-1}): C, 48.72; H, 4.52; N, 5.98. Found: C, 49.04; H, 4.51; N, 5.71.

Diastereomer 2 has similar signals. Full characterization will be reported in a forthcoming full paper.

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