

## Efficient amination of sulfides with a ketomalonate-derived oxaziridine: application to [2,3]-sigmatropic rearrangements of allylic sulfimides†

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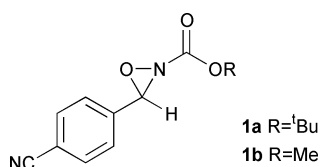
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A novel *N*-Boc-oxaziridine is reported, derived from diethyl ketomalonate, which effects efficient amination of sulfides to sulfimides. The reagent is applied to the [2,3]-sigmatropic rearrangement of allylic sulfimides.

Nitrogen-containing functional groups are widely represented amongst bioactive compounds, making methods for their selective introduction of prime importance in organic synthesis. Electrophilic nitrogen sources offer a valuable strategic alternative to the more traditional nucleophilic reagents.<sup>1</sup> In continuation of our studies on asymmetric heteroatom transfer from small-ring heterocycles (dioxiranes,<sup>2</sup> oxaziridinium salts<sup>3</sup>) we have been attracted to the use of oxaziridines as sources of electrophilic nitrogen.<sup>4,5</sup> The *N*-alkoxycarbonyl oxaziridines **1** pioneered by Collet, Vidal and co-workers<sup>6</sup> are promising in this regard, but their reactions often show low amination efficiency. For example, reaction of **1a** with enolates proceeds in low yield due to competitive aldol reaction with the *p*-cyanobenzaldehyde by-product.<sup>6</sup> Reaction of thioanisole with **1b** affords a mixture of sulfoxide and sulfimide,<sup>6</sup> and we have found that **1a** behaves similarly (*vide infra*). We have started to study the effect of substitution on the oxaziridine carbon on the ratio of oxygen to nitrogen transfer, and report here a novel oxaziridine that effects highly efficient amination of sulfides, leading to sulfimides bearing the synthetically useful *tert*-butoxycarbonyl (Boc) nitrogen protecting group. Additionally, this reagent allows high yielding [2,3]-sigmatropic rearrangement of allylic sulfimides.



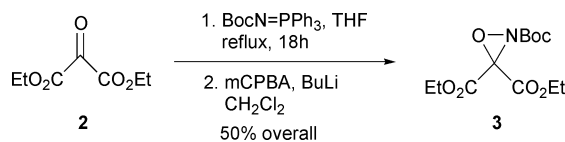
*N*-Alkoxycarbonyloxaziridines are generally prepared by oxidation of the corresponding imines, which in turn are prepared from a carbonyl compound and an *N*-alkoxycarbonyliminophosphorane *via* aza-Wittig reaction.<sup>6</sup> Both imine oxidation and subsequent heteroatom transfer are likely to be facilitated by electron-withdrawing substituents, and compatibility with basic/nucleophilic reaction conditions likely necessitates that the carbonyl compound is not enolisable. We therefore selected commercially available diethyl ketomalonate **2** as a suitable ketone starting material. We were pleased to find that the novel NBoc-protected oxaziridine **3** could be prepared in reasonable overall yield (Scheme 1). Oxaziridine **3** has proved stable to storage at room temperature over several days, or in the freezer (−15 °C) over several weeks.‡

As a test for the ability of **3** to act as a heteroatom transfer reagent, we examined its reaction with thioanisole in comparison to the oxaziridines **1**. Entries 1–3 of Table 1 contain results reported by Collet co-workers,<sup>6</sup> indicating that a mixture of

sulfoxide and sulfimide are obtained, with highest levels of amination (entry 3) being observed at low temperature in a more polar solvent (CH<sub>3</sub>CN). Entries 4 and 5 indicate that the NBoc-analogue **1a** is less effective than **1b** at amination, in line with the idea that steric hindrance at nitrogen plays an important role.<sup>6</sup> Even at −35 °C in CH<sub>3</sub>CN (entry 5), the level of oxidation was significant. Remarkably, however, a very high level of amination was observed for oxaziridine **3**, even in CDCl<sub>3</sub> (entries 6–8). Selectivity was essentially complete at −40 °C. A similar result was observed in several other solvents (CH<sub>2</sub>Cl<sub>2</sub>, ether, THF, MeOH, CH<sub>3</sub>CN, toluene, EtOAc).

The precise factors that lead oxaziridine **3** to afford a higher degree of nitrogen transfer than **1** require further experimental and computational investigation. However, one pertinent feature may be that if **3** were to transfer oxygen, there would be a developing steric interaction between the *N*-alkoxycarbonyl and ester substituents in the transition state leading to the imine co-product. For aldehyde-derived oxaziridine **1**, the corresponding interaction between the NBoc-group and a hydrogen atom would be expected to be considerably less significant, so that oxygen transfer is disfavoured to a lesser degree.

This property was then exploited in the efficient synthesis of a range of sulfimides (Table 2). In all cases, <sup>1</sup>H NMR analysis of the crude reaction mixture indicated very clean reaction, with essentially only the sulfimide product and diethyl ketomalonate being present. Isolated yields were generally good, with the result for dimethyl sulfide (entry 5) affected by the instability of the product sulfimide to chromatography on silica. In contrast to many amination reagents, oxaziridine **3** need not be used in large excess. It is interesting to note that preparation of *N*-alkoxycarbonylsulfimides is rare<sup>7</sup> in comparison to their *N*-sulfonyl counterparts,<sup>8</sup> despite the higher potential utility of the former due to the relative ease of *N*-deprotection. A notable recent contribution came from Bach, who reported the use of BocN<sub>3</sub>/FeCl<sub>2</sub> for sulfide amination.<sup>9</sup> The yields for this



Scheme 1

Table 1 Reaction of oxaziridines **1a**, **1b** and **3** with thioanisole

Entry	Oxaziridine	Solvent	Temp. (°C)	Amination:oxidation <sup>a</sup>
1	<b>1b</b>	CDCl <sub>3</sub>	19	34:66 <sup>b</sup>
2	<b>1b</b>	CDCl <sub>3</sub>	−34	52:48 <sup>b</sup>
3	<b>1b</b>	CH <sub>3</sub> CN	−35	67:33 <sup>b</sup>
4	<b>1a</b>	CDCl <sub>3</sub>	19	27:73
5	<b>1a</b>	CH <sub>3</sub> CN	−35	62:38
6	<b>3</b>	CDCl <sub>3</sub>	10	90:10
7	<b>3</b>	CDCl <sub>3</sub>	0	95:5
8	<b>3</b>	CDCl <sub>3</sub>	−40	>98:2

<sup>a</sup> Measured by integration of the <sup>1</sup>H NMR spectrum of the crude product.

<sup>b</sup> From ref. 6.

† Electronic supplementary information (ESI) available: experimental details and characterisation data. See <http://www.rsc.org/suppdata/cc/b2/b201791a/>

transformation using oxaziridine **3** compare extremely well with those reported by Bach, with the efficient amination of the hindered sulfide **4b** being worthy of note (entry 2, Table 2), since this substrate gave only 6% yield in the Bach system.

A particularly interesting application of sulfide amination is the use of allylic sulfides as substrates, which is followed by rapid [2,3]-sigmatropic rearrangement leading to an allylic amine derivative.<sup>8,10,11</sup> (Table 3). This was studied recently for NBoc sulfimides by Bach using his BocN<sub>3</sub>/FeCl<sub>2</sub> methodology.<sup>11</sup> However, he obtained low yields for substrates bearing groups capable of stabilising radicals (particularly CO<sub>2</sub>R) due to competitive homolytic cleavage of the C–S bond prior to rearrangement, leading to a stabilised allylic radical and thence to several side products. On the assumption that amination by **3** proceeds *via* a concerted, non-radical mechanism, we were optimistic that **3** would provide better yields than Bach's system. Pleasingly, this appears to be the case (Table 3). High yields of the rearrangement product were obtained for several substrates, with preparation of quaternary centres (entry 2) and amino acid derivatives (entry 4) being particularly noteworthy. In all cases, the <sup>1</sup>H NMR spectrum of the crude product from reaction of **3** and the allylic sulfide **6** showed essentially only the desired rearrangement product **7** and diethylketomalonate. The absence of metals in the reaction system is an important potential advantage with regard to product purification.

In summary, we have reported the first example of the use of a ketomalonate-derived *N*-alkoxycarbonyloxaziridine in electrophilic amination. Oxaziridine **3** effects highly efficient amination of sulfides, and in the case of allylic sulfides provides useful allylic amine derivatives bearing the synthetically

versatile NBoc protecting group. Investigation of the stereochemical aspects of this rearrangement process, including the design and synthesis of chiral analogues of **3**, are currently under investigation along with the reaction of **3** with other nucleophiles.

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## Notes and references

‡ Experimental procedures and characterisation data are provided in the ESI.†

Data for **3**: colourless oil,  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  2986, 1777, 1765, 1373, 1244, 1151, 1071, 845;  $\delta_{\text{H}}$  (250 MHz, CDCl<sub>3</sub>) 4.41–4.31 (4H, m), 1.52 (9H, s), 1.37–1.31 (6H, m);  $\delta_{\text{C}}$  (62.5 MHz, CDCl<sub>3</sub>) 162.2, 161.7, 156.2, 86.5, 75.8, 63.9, 63.2, 27.6, 13.8;  $m/z$  (CI) 307 (MNH<sub>4</sub><sup>+</sup>, 90%); Found: MNH<sub>4</sub><sup>+</sup>, 307.1517. C<sub>12</sub>H<sub>23</sub>N<sub>2</sub>O<sub>7</sub> requires M, 307.1505.

Typical amination procedure (Tables 2 and 3): To a stirred solution of oxaziridine **3** (250 mg, 0.86 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 ml) at –40 °C was added dropwise a solution of sulfide (0.82 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 ml). The resulting solution was allowed to warm to rt over 30 mins and then the solvent was removed under reduced pressure. Chromatography yielded the required product.

Table 2 Reaction of sulfides **4** with oxaziridine **3**

$\text{R}^1-\text{S}-\text{R}^2 \xrightarrow[\text{-40}^\circ\text{C}]{\text{CH}_2\text{Cl}_2, 1.05 \text{ eq. } \mathbf{3}} \text{R}^1-\text{S}(\text{NBoc})-\text{R}^2$				
Entry	Substrate	R <sup>1</sup>	R <sup>2</sup>	Yield of <b>5</b> (%) <sup>a</sup>
1	<b>4a</b>	Ph	Me	97
2	<b>4b</b>	<sup>t</sup> Bu	Me	75
3	<b>4c</b>	Ph	Bn	77
4	<b>4d</b>	Bn	Et	75
5	<b>4e</b>	Me	Me	49 <sup>b</sup>

<sup>a</sup> Isolated yield after chromatography on silica. <sup>b</sup> Product unstable to chromatography.

Table 3 Conversion of allylic sulfides **6** to allylic amines **7**

$\text{PhS}-\text{CH}_2-\text{CH}=\text{CH}-\text{R}^1 \xrightarrow[\text{-40}^\circ\text{C}]{\text{CH}_2\text{Cl}_2, 1.05 \text{ eq. } \mathbf{3}} \text{PhS}-\text{CH}(\text{NBoc})-\text{CH}_2-\text{CH}=\text{CH}-\text{R}^1$				
Entry	Substrate	R <sup>1</sup>	R <sup>2</sup>	Yield of <b>7</b> (%) <sup>a</sup>
1	<b>6a</b>	H	Me	94
2	<b>6b</b>	Me	Me	93
3	<b>6c</b>	H	Ph	73
4	<b>6d</b>	H	CO <sub>2</sub> Me	85

<sup>a</sup> Isolated yield after chromatography.

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