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Electrophilic amination of carbanions by *N*-carboxamido oxaziridines

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Abstract

A range of 3-aryl-*N*-carboxamido oxaziridines have been prepared and tested as reagents for electrophilic amination of carbanions. The 3-(2-cyanophenyl)-derivative gave highest yields of amination product, and was used for amination of ketone, ester and amide enolates, as well as sulfone-, phosphonate- and nitrile-stabilized carbanions.

Keywords: amination; oxaziridines; carbanions; amino acids and derivatives; ureas.

The electrophilic amination of nucleophiles is of considerable current interest as it provides a potentially powerful method for the introduction of nitrogen functionality.[1] Methods for efficient asymmetric electrophilic amination would be especially valuable.[2] In this regard, we were attracted to the fascinating observation by Vidal and Collet and co-workers[3–7] that *N*-alkoxycarbonyl oxaziridines (e.g. **1**) transfer nitrogen (rather than oxygen) to various nucleophiles, including ester enolates, resulting in a conceptually simple method for amino acid synthesis (Scheme 1).[4,6] We have initiated a programme aimed at the synthesis and testing of a range of chiral analogues of these oxaziridines as reagents for asymmetric electrophilic amination and among our first targets were *N*-carboxamido oxaziridines **2**. Ultimately, it is intended that the exocyclic nitrogen will be derived from a chiral amine, allowing preparation of diastereomerically pure oxaziridines and investigation of chirality transfer in nucleophile amination. However, an essential initial requirement was the need to establish that *N*-carboxamido oxaziridines were indeed capable of *N*-transfer to carbanions, and to discover the structural features necessary for efficient reaction. An additional stimulus for this study was the realization that the products of enolate amination by **2** — compounds containing an unsymmetrical urea residue α- to a carbonyl function — are of some interest as hydrolytically stable peptidomimetics.[8,9] Here we report the results of our early studies on the reactivity of oxaziridines **2**.

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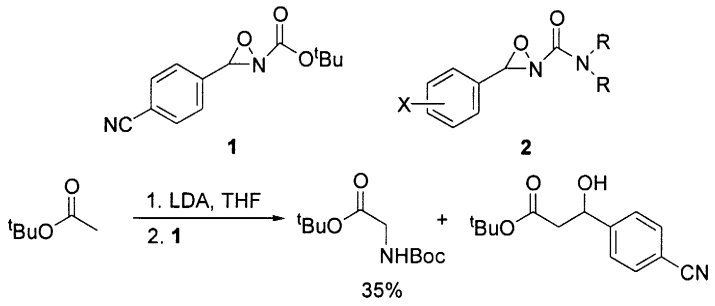
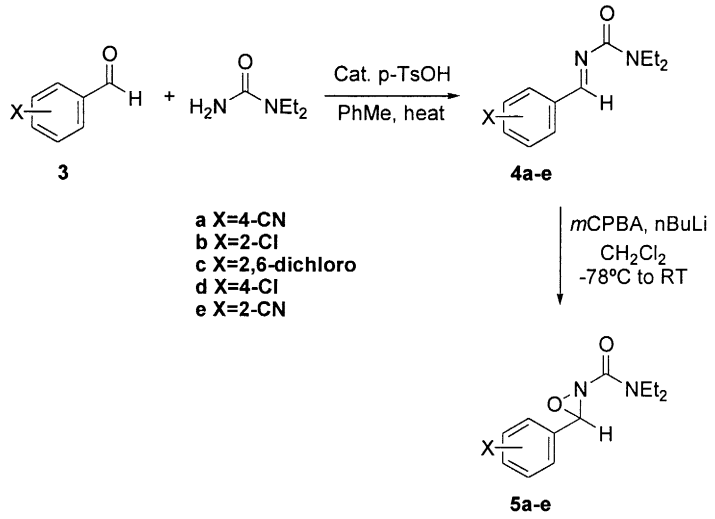


Scheme 1.

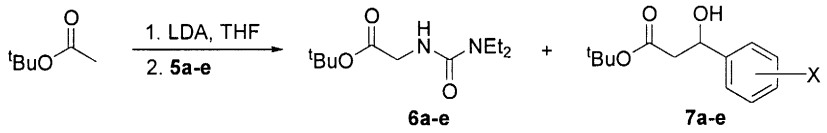
A problem with the *N*-Boc oxaziridine **1** is that enolate amination often proceeds in low yields due to competing aldol reaction with the aldehyde that is released when the oxaziridine transfers nitrogen (Scheme 1).[4,6] In common with Vidal and Collet,[4,6] we reasoned that this aldol side reaction might be suppressed by varying the aldehyde portion, in particular by the incorporation of *ortho*-substitutents on the aromatic ring. The preparation of oxaziridines derived from a range of aromatic aldehydes was therefore our first goal; this was easily accomplished by the sequence shown in Scheme 2. Thus, acid-catalyzed condensation of 1,1-diethylurea with aromatic aldehydes **3a**–**e** provided the imines **4a**–**e** which without purification were oxidized to the oxaziridines **5a**–**e** (50–61% yield from **3**) using mCPBA/BuLi in a slight modification of the procedure described by Vidal and Collet.[5,6,10] Attempted oxidation using Oxone® was far less efficient and resulted in lower yields. The oxaziridines were formed as predominantly a single stereoisomer (presumably *trans*) according to ^{1}H NMR spectroscopy, with small amounts (<8%) of the *cis*-isomer being observed in some cases.



Scheme 2.

With the synthesis of the oxaziridines accomplished, attention was focused on their use in carbanion amination. *tert*-Butyl acetate, amination of the enolate of which using **1** (Scheme 1) has been reported,[4,6] was selected as a suitable test substrate to assess the effect of the aromatic substituents on the ratio of amination to aldol products (Scheme 3). In a typical reaction,[11] a THF solution of the oxaziridine was added to the lithium enolate of the ester in THF at −78°C; reaction was completed upon warming to room temperature. It should be noted that oxaziridines **5** appear to be somewhat less reactive than **1**, which will effect amination at −78°C.[4,6] The results of amination using **5a**–**e** are given in Table 1. Entry 1 shows

the result when using the 3-(4-cyanophenyl)-oxaziridine **5a**, which provided a similar yield of amination product (39% of **6a**) to that obtained using **1**, along with some of the expected aldol product **7a** (20%). Disappointingly, however, *ortho*-substituted chloro analogues **5b** and **5c** (entries 2 and 3) did not react with the enolate, with the starting oxaziridines being recovered (ca. 75%). This lack of reactivity may be due to steric effects since the amination did proceed with the 4-chloro analogue **5d** (entry 4). Entry 5 shows that the oxaziridine **5e**,[10] derived from 2-cyanobenzaldehyde, proved to be the best reagent in this study, giving a 55% yield of the amination product and just 7% of the aldol side-product. When compared to entry 2, where no reaction was observed, the higher reactivity of **5e** may be due to the smaller relative size of the cyano group (A value of CN 0.2 kcal/mol; of Cl, 0.53–0.64 kcal/mol).[12] Thus, the 2-cyano analogue **5e** appears to confirm that *ortho*-substitution is able to slow down the competing aldol reaction, and improve product ratios in favour of electrophilic amination products. To the best of our knowledge, these results represent the first examples of *N*-carboxamido oxaziridines transferring electrophilic nitrogen to enolates.



Scheme 3.

Table 1
Amination of the lithium enolate of *tert*-butylacetate with oxaziridines **5a**–**e**[a]

Entry	Oxaziridine	X	**6**[b]	**7a-e**[b]
1	**5a**	4-CN	39%	20%
2	**5b**	2-Cl	-[c]	-[c]
3	**5c**	2,6-diCl	-[c]	-[c]
4	**5d**	4-Cl	31%	10%
5	**5e**	2-CN	55%	7%

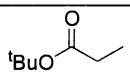
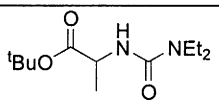
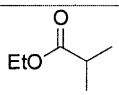
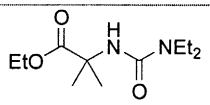
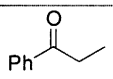
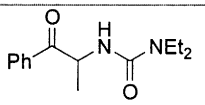
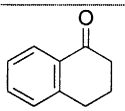
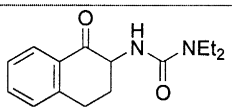
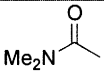
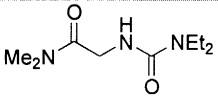
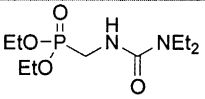
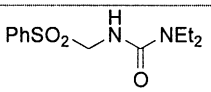
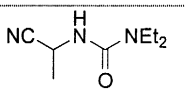
[a] Using 1 eq oxaziridine with respect to enolate; see ref. 11 for a typical procedure. [b] Isolated yields of pure products.

[c] No reaction observed.

After highlighting the 3-(2-cyanophenyl)-oxaziridine **5e** as the most effective aminating reagent in our test reaction, a study was undertaken to extend the scope of this reagent and confirm its utility in electrophilic amination of a variety of carbanions (Table 2). More highly-substituted ester enolates were aminated in good yield (entries 1 and 2); entry 2 is particularly interesting since it generates an α,α-disubstituted peptidomimetic.[8,9] We were pleased to find that ketone enolates (acyclic and cyclic, entries 3 and 4) and amide enolates (entry 5) were also aminated in good yield. In addition, phosphonate and sulfone carbanions were aminated, providing a novel and direct route to the corresponding α-amino compounds (entries 6 and 7). The amination of an α-cyanocarbanion was also demonstrated (entry 8).

In summary, a range of new *N*-carboxamido oxaziridines have been prepared and shown to be effective in the electrophilic amination of a range of carbon nucleophiles. Importantly, use of a 2-cyano-substituted aromatic moiety results in improved product ratios in favour of electrophilic amination over aldol reaction. Work is underway to prepare and test chiral *N*-carboxamido oxaziridines for use in asymmetric electrophilic amination.

Table 2
Carbanion amination using oxaziridine **5e**[a]

Entry	Substrate	Product	Yield[b]
1			55%
2			53%
3			60%
4			59%
5			51%
6			51%
7	$PhSO_2CH_3$		43%
8			56%

[a] Using 1 eq oxaziridine with respect to enolate; see ref. 11 for a typical procedure. [b] Isolated yields of pure products.

Acknowledgements

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10. The procedure of Ref. 6 was employed using anhydrous mCPBA (1.6 equiv.) and *n*BuLi (1.5 equiv.), except that after addition of the imine, the reaction was stirred at −78°C for 3 h, then brought to rt over 90 min before quenching and work-up. This was found to reduce the amount of isomeric amide formed as by-product. Data for **5e**: white solid (1.16 g, 61%); mp 41°C; ν_{max} ($CHCl_3$ solution)/cm^{-1} 2972, 2937, 2361, 2228, 1698, 1601, 1430, 1271; δ_H (400 MHz, $CDCl_3$) 7.75–7.55 (4H, m), 5.62 (1H, s), 3.70–3.53 (2H, m), 3.47–3.38 (2H, m), 1.23 (3H, t, *J* 7.1 Hz), 1.21 (3H, t, *J* 7.1 Hz); δ_C (67 MHz, $CDCl_3$) 160.0 (C), 136.4 (C), 133.2 (CH), 133.1 (CH), 130.7 (CH), 128.4 (CH), 116.3 (C), 112.7 (C), 74.8 (CH), 42.1 (CH_2), 42.0 (CH_2), 14.4 (CH_3), 12.6 (CH_3); MS (EI+) *m/z* 245 (M^+, 3.48%); HRMS observed 245.1174, $C_{13}H_{15}N_3O_2$ requires 245.1164. Anal. calcd for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.46; H, 6.23; N, 16.99.
11. Typical procedure for enolate/carbanion aminations: to diisopropylamine (77 μl, 0.55 mmol, 1.1 equiv.) in THF (850 μl) at 0°C under nitrogen was added *n*BuLi (2.5 M, 211 μl, 0.53 mmol, 1.05 equiv.). The resulting mixture was stirred for 30 min, then cooled to −78°C. A solution of *tert*-butyl acetate (67 μl, 0.50 mmol) in THF (850 μl) was slowly added, and the resulting mixture stirred at −78°C for 1 h. A solution of oxaziridine **5e** (123 mg, 0.50 mmol) in THF (850 μl) was then added in a single portion, and the reaction stirred for 3 h at −78°C before being allowed to reach rt over a period of 90 min. The reaction was quenched by the addition of saturated sodium bicarbonate solution, and diluted with CH_2Cl_2. The layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution, then saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The crude product was purified by flash column chromatography to yield aminated product **6e** (63.5 mg, 55%) and aldol side product **7e** (8.7 mg, 7%). Data for **6e**: ν_{max} ($CHCl_3$ solution)/cm^{-1} 3168, 2927, 2855, 1721, 1614, 1467, 1452, 1215, 1075; δ_H (400 MHz, $CDCl_3$) 4.82 (1H, s), 3.94 (2H, d, *J* 4.9 Hz), 3.29 (4H, q, *J* 7.1 Hz), 1.48 (9H, s), 1.17 (6H, t, *J* 7.1 Hz); δ_C (67 MHz, $CDCl_3$) 170.5 (C), 156.8 (C), 81.7 (C), 43.2 (CH_2), 41.2 (2×CH_2), 27.9 (3×CH_3), 13.7 (2×CH_3); MS (EI+) *m/z* 231 (M^+H, 20.5%), 175 (M-*t*Bu, 60.4%); HRMS observed 231.1712, $C_{11}H_{23}N_2O_3$ requires 231.1708.
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