N-Amination Using *N*-Methoxycarbonyl-3-phenyloxaziridine. Direct Access to Chiral N_β-Protected α-Hydrazinoacids and Carbazates

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Primary and secondary amines >N–H, including α-aminoacids, can be converted under mild conditions to the corresponding carbazates >N–NH–CO_2Me, on reaction with *N*-methoxycarbonyl-3-phenyloxaziridine **1**.

We report that the new compound *N*-methoxycarbonyl-3-phenyloxaziridine **1** is an exceptionally mild and efficient reagent for the conversion of most primary and secondary amines >N–H to the corresponding carbazates >N–$NHCO_2$Me.

We could prepare oxaziridine **1** in multigram quantities by controlled oxidation† of the *N*-methoxycarbonyl imino derivative **3**[1] using buffered potassium peroxymonosulphate (Oxone) under biphasic conditions[2] ($CHCl_3$–H_2O, Scheme 1); **1** was isolated in 65–70% yield, the main side product being *N*-methoxycarbonyl benzamide **4a**. In contrast, oxidation of **3** with *m*-chloroperbenzoic acid only gave **4a**, although this peracid has been commonly used for the conversion of imines to oxaziridines.[3]

Oxaziridine **1** is a crystalline solid (m.p. 41 °C), which can be stored at −20 °C for several weeks without significant change. Its structure was established by ^{1}H and ^{13}C NMR spectroscopy and elemental (C, H and N) analysis.‡ The alternative isomeric benzamide **4a** and nitrone **4b** structures were ruled

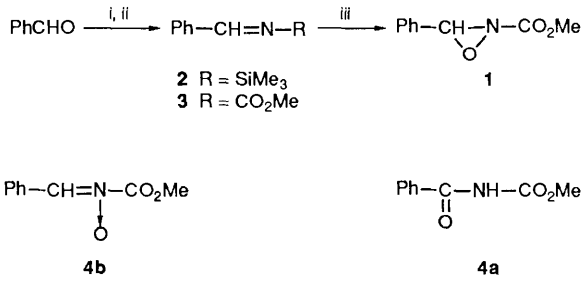
† In a three-necked flask (2 dm^3) immersed in an ice-water bath were placed cold solutions of 4.8 g of **3** in chloroform (135 ml) and 34.22 g of K_2CO_3 in water (267 ml). To this vigorously stirred two-phase mixture was added over 15 min a chilled solution of Oxone (43.46 g) in water (463 ml), the internal temperature being kept at 0–4 °C; the strirring was continued for 45 min at this temperature. The water layer was separated and extracted with dichloromethane (50 ml). The organic layers were combined, washed successively with 5% aqueous $KHSO_4$, 5% aqueous $NaHCO_3$, water, and dried over magnesium sulphate. The solvent was removed *in vacuo* ($T < 30$ °C) and the crude product was chromatographed over 70 g of silica gel (Et_2O–CH_2Cl_2–pentane 1:1:3 then Et_2O–CH_2Cl_2 1:1) to give **1** (3.45 g, 66%, m.p. 41 °C) then **4a** (1.21 g, 23%, m.p. 118 °C, lit.[10] 117–118 °C).

‡ Oxaziridine **1**: ^{1}H NMR ($CDCl_3$, 27 °C, slow *cis*/*trans* equilibrium): the *trans* structure was assigned to the major isomer on the basis of molecular mechanics; δ 3.54 (s, OCH_3, *cis*, 10%) and 3.89 (s, OCH_3, *trans*, 90%); 5.34 (s, PhC*H*, *cis*) and 5.09 (s, PhC*H*, *trans*); 7.43 (m, Ph); ^{13}C NMR ($CDCl_3$, 27 °C, only the major isomer is given): δ 54.9 (OCH_3); 78.15 (benzyl C); 127.9, 128.6, 131.1, 131.8 (Ph); 162.6 (C=O).

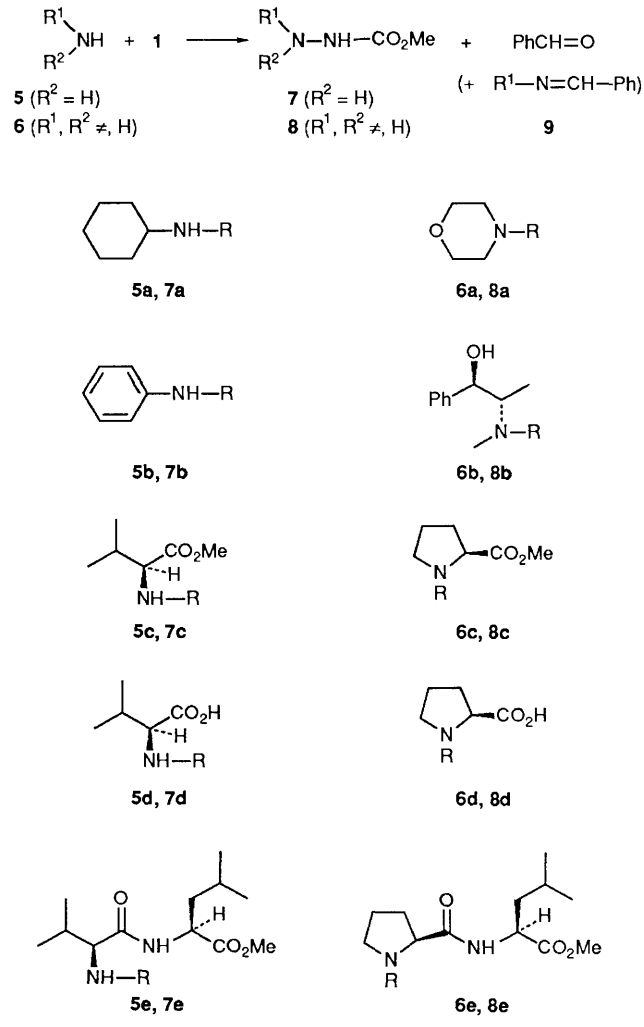
Table 1 Reaction of amines with **1**[a]

Entry	Starting material	Reaction conditions	Product (% yield)	M.p./ °C	7 : 9
1	**5a**	$CHCl_3$, r.t., 40 min	**7a** (80)	63	85 : 15
2	**5b**	Et_2O, r.t., 60 min	**7b** (75)	116	90 : 10
3	**6a**	Et_2O, r.t., 30 min	**8a** (91)	152	
4	**6b**	Et_2O, r.t., 5 h	**8b** (77)[b]	127	
5	**5c**	$CHCl_3$, reflux, 3 h	**7c** (57)[c]	oil	70 : 30
6	**6c**	Et_2O, r.t., 1.5 h	**8c** (60)[d]	oil	
7	**5d**[e]	CH_2Cl_2, 0 °C, 25 min	**7d** (57)[f]	89	85 : 15
8	**6d**[e]	CH_2Cl_2, 0 °C, 25 min	**8d** (85)[g]	76	
9	**5e**	$CHCl_3$, r.t., 4 h	**7e** (25)[h]	94	50 : 50
10	**6e**	Et_2O, r.t., 2 h	**8e** (79)[i]	145	

[a] The amine was allowed to react with 1.1 equiv. of **1**; the indicated yields correspond to isolated, pure products. [b] $[\alpha]_D^{20}$ −16.5° (CH_2Cl_2, *c* 0.9). [c] $[\alpha]_D^{23}$ −40.8 (95% EtOH, *c* 1.1). [d] $[\alpha]_D^{20}$ 78.2° (95% EtOH, *c* 0.69). [e] Benzyltrimethylammonium salt. [f] $[\alpha]_D^{20}$ −36.5° (95% EtOH, *c* 0.99). [g] $[\alpha]_D^{21}$ −61.8° (95% EtOH, *c* 0.5). [h] $[\alpha]_D^{20}$ −110° (CH_2Cl_2, *c* 0.57). [i] $[\alpha]_D^{25}$ −67.2° (CH_2Cl_2, *c* 1).



Scheme 1 *Reagents and conditions*: i, LiBu, $HN(SiMe_3)_2$, hexane, 0 °C, 0.25 h, distillation (83%); ii, $ClCO_2Me$, $CHCl_3$, reflux, 1 h, distillation (80%); iii, Oxone, K_2CO_3, $CHCl_3$–H_2O, 0–4 °C, 1 h (65–70%)



(**5**, **6** R = H; **7**, **8** R = $NHCO_2Me$)

Scheme 2

out by the obtention of **1** in optically active form (see below). In solution ($CDCl_3$), **1** was found to be a mixture of slowly interconverting *trans*- and *cis*-isomers in a ratio of 9 : 1, with a *cis* to *trans* inversion barrier $\Delta G^{\ddagger}$ *ca.* 16 kcal mol^{-1} (by ^1H NMR).

The most striking property of **1** is its ability to transfer its $-NCO_2Me$ group, rather than its oxygen,[4] to a variety of primary and secondary amines (Scheme 2 and Table 1).§ Simple primary amines such as cyclohexylamine **5a** and aniline **5b** (entries 1 and 2) were converted to their carbazates **7a** and **7b**, respectively, in less than 1 h at room temperature; since benzaldehyde is liberated during the transfer a minor side reaction is the formation of the imine **9** between the latter and the starting amine. Diethyl ether, chloroform or dichloromethane could be employed as the solvent for the reaction; diethyl ether, however, was generally preferred because the desired carbazates were often insoluble in this solvent and could be isolated by simple filtration.

With the secondary amines, no imine formation can occur, and the reaction proceeded quite well (entries 3 and 4). The transfer, however, was much faster with morpholine **6a**, than with (−)-ephedrine **6b**, probably owing to steric hindrance. In the latter case, the reaction was attended by a kinetic resolution of **1**; when 1.9 equiv. of the racemic oxaziridine was used, the excess reagent, recovered at the end of the reaction, showed $[\alpha]_D^{20}$ +15° ($CHCl_3$, 0.6), enantiomeric excess *ca.* 10% [by NMR in the presence of *R*-(−)-2,2,2-trifluoro-1-(9-anthryl) ethanol as the chiral shift reagent].

In connection with our current work on α-hydrazinoacids and hydrazinopeptides,[5,6] we examined the ability of **1** to transfer its $-NCO_2Me$ group to α-aminoacid and dipeptide derivatives (entries 5–10). Both *S*-valine–OMe and *S*-proline-OMe (**5c** and **6c**) gave the desired carbazates (**7c** and **8c**, respectively) in essentially the same yield; however, the valine ester proved to be much less reactive and in this case the transfer was better effected in refluxing $CHCl_3$. With the analogous dipeptide esters Val-Leu-OMe **5e** and Pro-Leu-OMe **6e**, the reaction followed the same trend, the nitrogen transfer being much faster to the terminal proline (**6e**–**8e**) than to the terminal valine (**5e**–**7e**). Finally, we found that the free amino acids valine **5d** and proline **6d**, in the form of their benzyltrimethylammonium salts, reacted with **1** within a few minutes at 0 °C in CH_2Cl_2 to give the corresponding carbazates **7d** and **8d**, respectively. The structure of **8d** was confirmed by X-ray crystallography.[6] This reaction is particularly useful for the synthesis of hydrazinoproline, for which no good method was available so far.[5a,7]

The transfer of NR groups (NH, NMe, NCl) from certain oxaziridines to amines has already been observed, and a few applications of these reagents to the synthesis of hydrazine derivatives have been reported.[8,9] By comparison, the use of oxaziridine **1** offers several advantages: (*i*) the reagent is a pure, easy to handle, crystalline solid; (*ii*) the reaction takes

§ Carbazates **7a** and **7b** showed m.p.s in agreement with literature.[11,12] New carbazates **7c–e** and **8a–e** exhibited ^1H, ^{13}C NMR and FTIR spectra in accord with assigned structures and gave satisfactory results in elemental (C, H and N) analyses.

place under mild conditions to give, in general, the desired carbazates in fair to excellent yields; (*iii*) the N–$NHCO_2Me$ group can be hydrolysed back to the hydrazine by different methods, *e.g.* by reaction with BBr_3; (*iv*) optically active amines are converted to optically active hydrazines of the same configuration without loss of optical activity. Application of this methodology to the synthesis of L or D N_β-protected α-hydrazinoacids and hydrazinopeptides is underway.

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