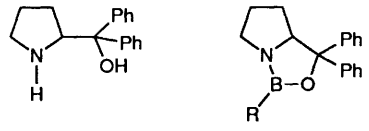
A New Route to Oxazolidinones

Dominique Delaunay and Maurice Le Corre*
Laboratoire de Synthèse Organique, Associé au CNRS, Université de Rennes I, Avenue du Général Leclerc 35042 Rennes Cedex, France

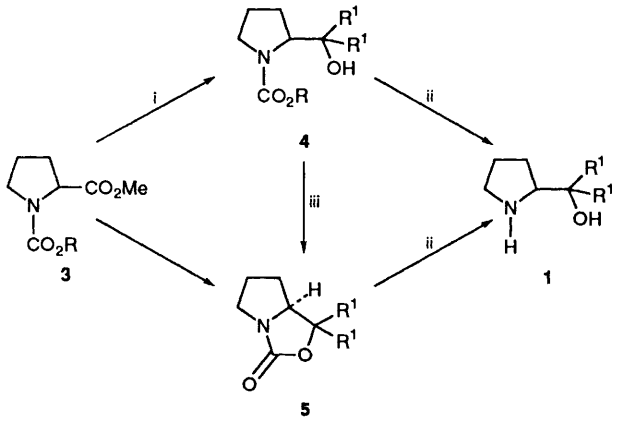
The oxazolidinones **5** and **7** have been prepared by coupling Grignard reagents with *N*-alkoxycarbonyl-α-amino esters. Hydrolysis of oxazolidinones **5** afforded β-amino alcohols with good yield and enantiomeric excess.

A recent paper concerning the reactivity of *N*-alkoxycarbonylproline methyl ester [1] has prompted us to report the results of our research in this area. Diphenyl(pyrrolidin-2-yl)methanol **1a** is an important precursor of the diphenyloxazaborolidine **2** and several routes to this alcohol have been reported.[2a–h]



1a **2**

From *N*-alkoxycarbonylproline methyl ester **3**, the synthesis of **1a** can be realized in two steps: (i) preparation of the alcohol **4** and (ii) deprotection of the carbamate group (Scheme 1). The



Scheme 1 *Reagents and conditions:* i, R^1MgBr; ii, KOH, heat; iii, KOH, room temp.

method for the final step is dependent on the nature of R (benzyl [2a,h] or ethyl [1]).

Oxazolidinone **5** has been suggested as an intermediate in the synthesis of alcohol **1** [1] but has not yet been isolated. Oxazolidinones are usually produced from β-amino alcohols or from epoxides by treatment with various amino compounds.[3] Oxazolidinones can also be prepared from *N*-Boc derivatives of β-amino alcohols by an intramolecular attack of a toluene-*p*-sulfonate intermediate.[4]

Our studies on the reactivity of alcohols **4** revealed that hydrolysis can be stopped at the oxazolidinones **5**. Indeed, hydrolysis of **4**, achieved at room temperature, provided 70–95% yield of **5** (Table 1).

Because there is no report describing the formation of such oxazolidinones, we thought that the cyclization was dependent on the nature of R. Therefore, we studied the influence of R on the formation of oxazolidinones. As shown in Table 1 (entries a, e, f), when the R group was changed (methyl, ethyl or benzyl), the cyclization still occurred and yields were not affected.

Table 1 Preparation of oxazolidinones **5** by cyclization of **4**

Entry	R	R^1	Yield[a] (%)
a	Me	Ph	92
b	Me	Et	75
c	Me	Bu	70
d	Me	2-Naphthyl	80
e	Et	Ph	94
f	CH_2Ph	Ph	93

[a] Isolated yield calculated from **4**.

Table 2 Preparation of oxazolidinones by addition of R^1MgBr to *N*-methoxycarbonylproline methyl ester **3** (R = Me)

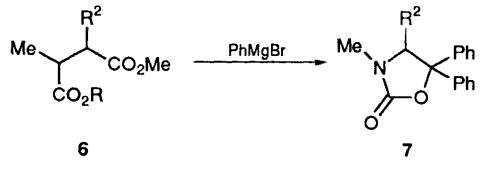
Entry	R^1	Yield[a] (%)
a	Ph	60
b	Et	70
c	Bu	41
d	2-Naphthyl	72

[a] Isolated yield calculated from **3**.

Using these results, we envisaged a more practical access to oxazolidinones, based on the cyclization of the key intermediate alcohol, formed during the Grignard reaction. In fact the cyclization occurred when the reaction was performed at reflux in THF.

Using these conditions, we prepared a series of oxazolidinones from *N*-methoxycarbonylproline methyl ester **3** (R = Me) in good yields (Table 2).

In the course of our investigations on the preparation of oxazolidinones, we applied the same treatment to some other acyclic carbamates **6** (Scheme 2). We observed that the success



6 **7**

Scheme 2

of the reaction is very dependent on the nature of R^2. When R^2 = Ph no cyclization occurs and when R^2 = benzyl or H, yields of **7** are 30 and 60%, respectively.

Oxazolidinones **5a–d** were synthesized from (*S*)-proline and so it was of interest to check their optical purity. This was determined by comparing the specific rotation of **1a** produced from **5a** with the specific rotation of the pure amino alcohol reported in the literature.[2d] We observed that oxazolidinone **5a** directly obtained from **3** is not optically pure. Presumably, racemization occurred at the phenyl ketone intermediate stage. However, oxazolidinone **5a** prepared by the two-step sequence,

i.e. preparation of the carbamate alcohol and subsequent cyclization at room temperature, afforded the amino alcohol with more than 99% optical purity.

In conclusion, this two-step sequence reaction is an efficient way to prepare oxazolidinones.

Experimental

Melting points were determined on a Richter apparatus. Thin-layer chromatography (TLC) was carried out on Merck precoated 0.2 mm thick plates of silica gel 60 F_{254}. Column chromatography was performed on Merck silica gel 60, 70–230 mesh. Optical rotations were measured on a Perkin-Elmer 241-MC polarimeter at room temperature and are given in units of 10^{-1} deg cm^2 g^{-1}. ^{1}H NMR spectra were recorded at 300 MHz. *J* Values are given in Hz. ^{13}C NMR spectra were recorded at 75.5 MHz. Anhydrous THF was distilled from sodium benzophenone ketyl prior to use. Grignard reagents were obtained from the corresponding alkyl or aryl bromide in THF. Reactions were carried out under an atmosphere of dry N_2. *N*-alkoxycarbonyl-α-amino esters **3** and **6**,[5,1] *N*-alkoxycarbonyl-*N*-methylamino acids[6] and diphenylmethanols **4**[1] were prepared according to the established procedures.

Synthesis of Oxazolidinones **5** *from Carbamates* **4**.—A solution of the appropriate diphenylmethanol **4** (4.0 mmol) and KOH–MeOH (2 mol dm^{-3}; 20 cm^3) was stirred for 2 h at room temperature. The methanol was evaporated under reduced pressure and then water (20 cm^3) was added. The mixture was extracted with dichloromethane (3 × 60 cm^3). The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent was evaporated to afford oxazolidinone **5**.

7,7-*Diphenyl*-4,5,6,6a-*tetrahydro*-1H,3H-*pyrrolo*[1,2-c]-*oxazol*-2-*one* **5a** (R^1 = *Ph*). 1.03 g (92%), m.p. 147–148 °C (EtOH); δ_H 1.11 (m, 1 H), 1.71 (m, 1 H), 1.90 (m, 2 H), 3.24 (m, 1 H, CHN), 3.71 (m, 1 H, CHN), 4.54 (dd, 1 H, *J* 5.39, 10.51, CH), 7.25–7.39 (m, 6 H, Ar) and 7.50–7.53 (m, 4 H, Ar); δ_C 24.89, 29.01, 46.03, 69.24, 85.26, 125.48, 125.96, 127.69, 128.30, 128.33, 128.57, 140.28, 143.30 and 160.45. $[\alpha]_{589}^{24}$ −241.6 (*c* 0.238 in MeOH) (Found: C, 77.25; H, 5.9; N, 4.9. Calc. for $C_{18}H_{17}NO_2$: C, 77.39; H, 6.14; N, 5.01%).

7,7-*Diethyl*-4,5,6,6a-*tetrahydro*-1H,3H-*pyrrolo*[1,2-c]*oxazol*-2-*one* **5b** (R^1 = *Et*). 0.55 g (75%), obtained as an oil; δ_H 0.79 (2 × t, 6 H), 1.43 (m, 1 H), 1.74 (m, 6 H), 1.91 (m, 1 H), 2.99 (m, 1 H, CHN) and 3.38 (m, 2 H, CHN, CH); δ_C 7.20, 8.11, 25.55, 26.02, 26.11, 29.99, 44.90, 67.21, 84.64 and 160.00 (Found: C, 65.2; H, 9.3; N, 7.3. Calc. for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64%).

7,7-*Dibutyl*-4,5,6,6a-*tetrahydro*-1H,3H-*pyrrolo*[1,2-c]*oxazol*-2-*one* **5c** (R^1 = *Bu*). 0.67 g (70%), obtained as an oil; δ_H 0.82 (2 × t, 6 H), 1.19 (m, 8 H), 1.47 (m, 2 H), 1.67 (m, 5 H), 1.79 (m, 1 H), 3.06 (m, 1 H, CHN) and 3.46 (m, 2 H, CHN, CH); δ_C 13.89, 13.96, 22.95, 23.03, 25.05, 25.59, 25.96, 26.23, 33.58, 37.86, 44.99, 67.84, 84.17 and 160.00 (Found: C, 70.0; H, 10.45; N, 5.7. Calc. for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85%).

7,7-*Di*(2-*naphthyl*)-4,5,6,6a-*tetrahydro*-1H,3H-*pyrrolo*-[1,2-c]*oxazol*-2-*one* **5d** (R^1 = 2-*naphthyl*). 1.21 g (80%), m.p. 78–80 °C (EtOH); δ_H 1.20 (m, 1 H), 1.86 (m, 3 H), 3.31 (m, 1 H, CHN), 3.77 (m, 1 H, CHN), 4.79 (dd, 1 H, *J* 5.40, 10.56, CH) and 7.31–8.12 (m, 14 H); δ_C 25.05, 29.17, 46.16, 68.75, 86.24, 123.83–124.90, 126.57–128.74, 132.62–133.05, 137.47, 140.14 and 160.52 (Found: C, 82.0; H, 5.2; N, 3.4. Calc. for $C_{26}H_{21}NO_2$: C, 82.29; H, 5.58; N, 3.69%).

Direct Synthesis of Oxazolidinones **5** *from Esters* **3**.—A solution of ester **3** (R = Me) (5.3 mmol) in dry THF (10 cm^3) was added to a solution of R^1MgBr (18.5 mmol). The reaction mixture was stirred at reflux for 1 h and then poured with stirring into crushed ice (23 g) and ammonium chloride (5.5 g) in water (8 cm^3). The resulting mixture was extracted with dichloromethane (3 × 50 cm^3). The combined organic layers were dried over anhydrous Na_2SO_4 and then the solvent was removed under reduced pressure to obtain crude product **5** which was further purified by column chromatography. **5a**: 0.88 g (60%) (cyclohexane–ethyl acetate, 7:3); **5b**: 0.68 g (70%) (cyclohexane–ethyl acetate, 1:1); **5c**: 0.52 g (41%) (cyclohexane–ethyl acetate, 7:3); **5d**: 1.45 g (72%) (cyclohexane–diethyl ether, 1:1).

Synthesis of Oxazolidinones **7**.—Oxazolidinones **7** were obtained in a similar manner as above starting from the carbamate **6** (5.3 mmol) and PhMgBr (18.5 mmol). The reaction mixture was refluxed for 8 h for the preparation of **7a** and 3 h for the preparation of **7b**.

3-*Methyl*-5,5-*diphenyloxazolidin*-2-*one* **7a** (R^2 = *H*). 0.80 g (60%), m.p. 142–145 °C (cyclohexane–diethyl ether, 3:7); δ_H 2.88 (s, 3 H, CH_3), 4.11 (s, 2 H, CH_2) and 7.25–7.41 (m, 10 H, Ar); δ_C 31.13, 59.72, 82.77, 125.44, 128.19, 128.66, 142.76 and 157.44 (Found: C, 75.5; H, 5.9; N, 5.3. Calc. for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53%).

4-*Benzyl*-3-*methyl*-5,5-*diphenyloxazolidin*-2-*one* **7b**. (R^2 = CH_2Ph). 0.54 g (30%), m.p. 170–172 °C (cyclohexane–ethyl acetate, 8:2); δ_H 2.54 (s, 3 H, CH_3), 2.49–2.70 (m, 2 H, *J* 4.90 and 8.61, 14.37, CH_2), 4.64 (dd, 1 H, *J* 4.92, 8.60, CH) and 6.99–7.52 (m, 15 H, Ar); δ_C 31.25, 38.34, 67.14, 87.10, 126.02–128.92, 137.20–142.80 and 156.98 (Found: C, 80.1; H, 6.1; N, 4.0. Calc. for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08%).

Synthesis of Diphenyl(*pyrrolidin*-2-*yl*)*methanol* **1a** *from Oxazolidinone* **5a**.—A suspension of oxazolidinone **5a** (obtained from diphenylmethanol **4**) (3.6 mmol) and KOH–MeOH 5 mol dm^{-3}; 7 cm^3) was refluxed for 4 h. The methanol was evaporated and water (10 cm^3) was added to the residue. The mixture was extracted with dichloromethane (3 × 30 cm^3) and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was evaporated to give the title compound **1a** (0.9 g, 99%). An analytical sample was prepared by recrystallization from hexane, m.p. 79–80 °C [lit.,[2b] m.p. 76.5–77.5 °C (H_2O–MeOH); lit.,[2d] m.p. 79–79.5 °C (hexane)]; δ_H 1.70 (m, 4 H), 2.96 (m, 2 H, CH_2N), 3.61 (br, 2 H, NH, OH), 4.30 (t, 1 H, *J* 7.47, CH), 7.23–7.40 (m, 6 H, Ar) and 7.60–7.69 (m, 4 H, Ar); δ_C 25.56, 26.35, 46.83, 64.54, 77.17, 125.58–128.81, 145.45 and 148.15; $[\alpha]_{589}^{24}$ −53.8 (*c* 0.264 in MeOH) {lit.,[2d] $[\alpha]_{589}^{24}$ −54.3 (*c* 0.261 in MeOH)}.

References

1 J. V. B. Kanth and M. Periasamy, *Tetrahedron*, 1993, **49**, 5127.

2 (*a*) E. J. Corey, R. K. Bakshi and S. Shibata, *J. Am. Chem. Soc.*, 1987, **109**, 5551; (*b*) E. J. Corey, S. Shibata and R. K. Bakshi, *J. Org. Chem.*, 1988, **53**, 2861; (*c*) E. J. Corey, R. K. Bakshi, S. Shibata, C. P. Chen and V. K. Singh, *J. Am. Chem. Soc.*, 1987, **109**, 7925; (*d*) D. J. Mathre, T. K. Jones, L. C. Xavier, T. J. Blacklock, R. A. Reamer, J. J. Mohan, E. T. T. Jones, K. Hoogsteen, M. W. Baum and E. J. J. Grabowski, *J. Org. Chem.*, 1991, **56**, 751; (*e*) D. Enders, H. Kipphardt, P. Gerdes, L. J. Breña-Valle and V. Bhushan, *Bull. Soc. Chim. Belg.*, 1988, **97**, 691; (*f*) D. Seebach, D. Enders and B. Renger, *Chem. Ber.*, 1977, **110**, 1852; (*g*) Roussel-Uclaf, French Patent FR 3638M, 1965; (*h*) U. Kraatz, German Patent DE 3609152A1, 1987.

3 V. A. Pankratov, T. M. Frenkel' and A. M. Fainleib, *Russ. Chem. Rev.*, 1983, **52**, 576.

4 C. Agami, F. Couty, L. Hamon and O. Venier, *Tetrahedron Lett.*, 1993, **34**, 4509.

5 T. F. Buckley, III and H. Rapoport, *J. Am. Chem. Soc.*, 1981, **103**, 6157.

6 S. T. Cheung and N. L. Benoiton, *Can. J. Chem.*, 1977, **55**, 916.

Paper 4/03505D
Received 10*th June* 1994
Accepted 8*th July* 1994