Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 4359–4363

TETRAHEDRON: *ASYMMETRY*

A high-yielding low-cost facile synthesis of 2-oxazolidinones chiral auxiliaries

Yikang Wu* and Xin Shen

State Key Laboratory of Bio-organic & Natural Products Chemistry and Shanghai–Hong Kong Joint Laboratory in Chemical Synthesis, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China

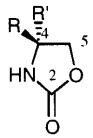
Received 18 September 2000; accepted 10 October 2000

Abstract

The chiral aminol alcohols from reduction of amino acids with $NaBH_4/H_2SO_4$ were directly treated with EtO_2CCl to give the carbamates, which cyclized in the presence of traces of K_2CO_3 at 100–130°C under vacuum to afford chiral 2-oxazolidinones in high yields.

1. Introduction

Chiral 2-oxazolidinones[1] (especially **1**) have been shown to be highly versatile chiral auxiliaries through numerous elegant syntheses[2] by Evans and others. Unfortunately, their broader application in asymmetric synthesis is seriously hampered by the lack of facile, safe, and low-cost access to the chiral auxiliaries themselves. To circumvent this problem, many efforts[3a–m] have been made since the late 1980s.



1a R = ^{i}Pr, R' = H
1b R = Bn, R' = H
1c R = H, R' = Ph
1d R = Ph, R' = H

As already noted by previous investigators, the original Et_2CO_3 procedure[3a] suffered from such draw-backs as the inconvenience and potential hazards associated with borane, tedious work up, and inconsistent results.[3b] The subsequent modifications all aimed at circumventing these problems. For instance, $LiAlH_4$,[3d] $CaBH_4$,[3e] or $LiBH_4$[3f] (formed in situ from $CaCl_2$[3e] or LiI[3f] and $NaBH_4$, with the carboxylic acids being transformed into esters before reduction) were

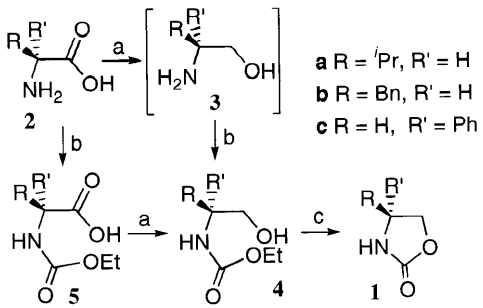
* Corresponding author. E-mail: yikangwu@pub.sioc.ac.cn

0957-4166/00/$ - see front matter
PII: S0957-4166(00)00415-8

employed as reducing agent to replace the borane. Similarly, more reactive (and unfortunately, more expensive) phosgene derivatives such as Cl_3CO_2CCl,[3b,h] $Cl_3CO_2COCCl_3$,[3d] PhO_2CCl,[3c] and BnO_2CCl[3f] were utilized in place of the Et_2CO_3 to ensure a facile ring closure. More recent efforts appear to have already given up the base-catalyzed intramolecular ester exchange ring-closure protocol; some[3m] chose to utilize urea derivatives (prepared at high temperatures not easily accessible using oil baths) with an amino group as leaving group after treatment with nitrite, while others[3g,j,l] attempted to revert the ester exchange mechanism to the less common alkyl–oxygen cleavage ones. Since all these modified procedures, while improving the original one in some way, introduced other undesired factors such as expensive reagents or inconvenient conditions, none of them could serve as a clear-cut solution to the aforementioned problem—the 'bottle-neck' still remains despite all the exhaustive efforts. The long span of time over which all those efforts were made and the large number of research groups involved in such endeavors seem to insinuate that preparing these chiral 2-oxazolidinones in high yields from cheap phosgene derivatives without problems[4] is just impossible.

2. Results and discussion

Now we have found a clear-cut solution (Scheme 1) to the facile access problem. First, we found from the literature a reduction protocol ($NaBH_4/H_2SO_4$) reported by Abiko and Masamune[5] in 1992, which is apparently the cheapest procedure applicable in the present context but has somehow been ignored by previous investigators. Then an alkoxycarbonylation using EtO_2CCl[6] is performed without isolating the amino alcohol, directly affording[7] the rather pure carbamates **4a**,[8] **4b**,[3e,9] and **4c**[3e] in near quantitative yields. More amino alcohols (as shown by the yields of **4a–c**) than previously[5] were thus obtained. Finally, the crude carbamates **4a–c** were heated with K_2CO_3 (0.2–0.5 mol%) at 100–130°C (bath) under aspirator vacuum to afford rather pure **1a–c** (free from any discernible amounts of unreacted starting carbamates or hydrolysis products) in near quantitative yields in 15–120 min (depending on the quantity of added K_2CO_3). The crude oxazolidinones thus obtained could be directly used as chiral auxiliary without any further purification. The overall yields were above 90%. The vacuum proved to be necessary for avoiding hydrolysis, especially when using relatively larger amounts of K_2CO_3. The cyclization of **4a** could be easily achieved even at 100°C, although 120°C was necessary for **4b**,**c** to ensure a fast reaction.



Scheme 1. (a) $NaBH_4/H_2SO_4$; (b) EtO_2CCl/Na_2CO_3; (c) cat. K_2CO_3/100–130°C/vacuum

As a key step in the synthesis of 2-oxazolidinones, the cyclization of **4** deserves a few more comments here. Although the inconsistent[3b] results with the Evans' procedure and the difficulty[10] with McKillop's procedure[3e] are generally believed to be associated with the poor leaving ability of the ethoxyl in **4**, the conformational factors may also contribute to a certain extent. For instance, in Hintermann and Seebach's[3i] carbamates the most stable conformer is the one shown by **A** in Fig. 1 regardless of the size of R. Since the cyclization requires the OH *syn* (most easily attainable from the *gauche* conformers) to the $NHCO_2Et$, these carbamates are expected to undergo easier cyclizations than[11] **1b** (where the *gauche* conformer **B** is hardly more stable than the *anti* one **C**, Fig. 1). Replacement of the benzyl with a bulkier isopropyl (which is also bulkier than $NHCO_2Et$) renders **D** the most stable one. This explains why **1a** cyclized at a much faster rate than **1b** at lower temperatures under otherwise the same conditions.

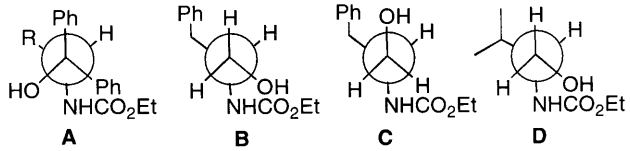


Figure 1. The Newman projections of C-4 and C-5 of the conformers of some carbamates

As shown in Fig. 2, cyclization of the carbamates relies on an alkoxide cycle: The ethoxide formed in the ring closure must generate an alkoxide of the starting carbamate to sustain the reaction. The solvent-free conditions disclosed here no doubt provide a maximal probability for the ethoxides to encounter starting carbamates and therefore make the ring closure much easier than in solutions as in the previous procedures. However, it is noteworthy that, even under such most favorable conditions, the cyclization was completely quenched if the boron-derived impurities from the reduction was not thoroughly removed (presumably due to annihilation of the ethoxides by the boric acids, which extinguishes the alkoxide cycle). It appears that complete hydrolysis of the boron esters derived from $NaBH_4$ and clean isolation of the carbamates **4** through aqueous work up are prerequisites for a successful cyclization and a priori for obtaining reproducible results using earlier conditions. It should be noted that the solvent-free cyclization at easily accessible temperatures disclosed here might also be applicable to the cyclization of similar carbamates, including those[12] not related to the auxiliary chemistry.

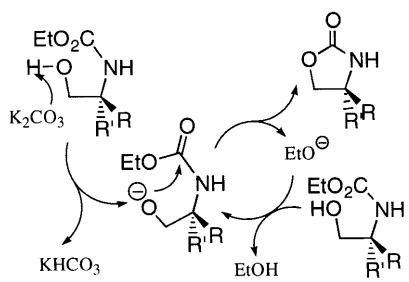


Figure 2. The initial deprotonation by K_2CO_3 and the subsequent catalytic cycle of the alkoxides

In brief, we have developed a long awaited high-yielding low-cost simple route to the 2-oxazolidinones **1** using a one-pot $NaBH_4/H_2SO_4$ reduction and EtO_2CCl alkoxycarbonylation,

followed by a solvent-free cyclization. The cost for preparing **1** is thus reduced. The reaction conditions are mild and easily accessible in both laboratory and industry, and the set-ups as well as the operations are very simple; the preparation of these auxiliaries is thus no longer a costly and/or tedious task demanding much experience and great care.

3. Experimental

A typical procedure[13] is as follows: (*S*)-(−)-4-Benzyl-2-oxazolidinone **1b**. L-Phenylalanine (33.00 g, 200 mmol) was reduced following (but skipping the addition of MeOH) the literature procedure[5] up to 'adding 5N NaOH (200 mL used for this work) and heating for 3 h'. The mixture was cooled to rt with stirring before introducing H_2O (150 mL) and $NaHCO_3$ (84.00 g, 1.00 mol), followed by $ClCO_2Et$ (21 mL, 210 mmol, cooling with 5°C bath). After stirring at rt for another 1.5 h the mixture was extracted with EtOAc (100 mL×4). The combined organic phases were washed with H_2O (50 mL) and brine (50 mL), dried over $MgSO_4$. Removal of the solvent gave rather pure **4b** as a white solid (44.26 g, 198 mmol). Powered K_2CO_3 (140 mg, 1.01 mol) was added and the mixture was heated (125–130°C, bath) with magnetic stirring under aspirator vacuum (ca. 40 mmHg) until the gas evolving stopped. After cooling down to rt a white solid (>98% yield for the essentially pure **1b**, ee >99% by chiral HPLC) was obtained. Recrystallization (1:1 EtOAc/hexanes) gave pure **1b** in two crops (30.91 g, 87% from L-phenylalanine; chromatography of the mother liquor raised the overall yield to 95% yield) as white long prisms: mp 90–91°C; $[\alpha]^{30}$ −62 (*c* 1.0, $CHCl_3$) [lit.[14] $[\alpha]^{20}$ −63 (*c* 1, $CHCl_3$)]; ee >99% (HPLC on Chiralcel OC column eluting with 7:3 ^{n}hexane/^{i}propanol at 0.6 mL/min and detection at 211 nm).[3b]

(*S*)-(−)-4-Isopropyl-2-oxazolidinone **1a**. White needles, 83.9% (from L-valine) by recrystallization (1:7 EtOAc/hexanes, in two crops) or 91% by chromatography; mp 71.5–73°C; $[\alpha]^{30}$ −17 (*c* 6.0, EtOH) [lit.[14] $[\alpha]^{20}$ −18 (*c* 6, EtOH)].

(*R*)-(−)-4-Phenyl-2-oxazolidinone **1c**. White needles, 82% (from D-phenylglycine) by recrystallization (2:1 EtOAc/hexanes, in two crops) or 91% by chromatography; mp 132–134°C; $[\alpha]^{30}$ −50 (*c* 2.0, $CHCl_3$) [lit.[14] $[\alpha]^{25}$ −48 (*c* 2, $CHCl_3$)]; ee >99%.

Acknowledgements

This work was supported by the Chinese Academy of Sciences (CAS 'Knowledge Innovation' Project), the Life Science Special Fund of CAS Supported by the Ministry of Finance (Stz 98-3-03), the Major State Basic Research Development Program (G2000077502), the Ministry of Science and Technology of China (970211006-06), and the National Natural Science Foundation of China (29832020).

References

1. (a) Evans, D. A.; Bartoli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129. (b) For a review, see: Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835–875.

2. See, for example: (a) Evans, D. A.; Kim, A. S.; Metternich, R.; Novack, V. J. *J. Am. Chem. Soc.* **1998**, *120*, 5921–5942. (b) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434–9453. (c) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653–5660. (d) Nicolaou, K. C.; Gaulfield, T.; Kataoka, H.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 7910–7912.
3. (a) Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 77–82. (b) Pridgen, L. N.; Prol Jr., J. *J. Org. Chem.* **1989**, *54*, 3231–3233. (c) Wuts, P. G. M.; Pruitt, L. E. *Synthesis* **1989**, 622–623; (d) Correa, A.; Denis, J.-N.; Greene, A. E. *Synth. Commun.* **1991**, *21*, 1–9. (e) Lewis, N.; McKillop, A.; Taylor, R. J. K.; Watson, R. J. *Synth. Commun.* **1995**, *25*, 561–568. (f) Sudharshan, M.; Hultin, P. G. *Synlett* **1997**, 171–172. (g) Matsunaga, H.; Ishizuka, T.; Kunieda, T. *Tetrahedron* **1997**, *53*, 1275–1294. (h) Bull, S. D.; Davis, S. G.; Jones, S.; Polywka, M. E. C.; Prasad, R. S.; Sanganee, H. J. *Synlett* **1998**, 519–521. (i) Hintermann, T.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 2093–2126. (j) Feroci, M.; Inesi, A.; Mucciante, V.; Rossi, L. *Tetrahedron Lett.* **1999**, *40*, 6059–6060. (k) Sugiyama, S.; Watanabe, S.; Ishii, K. *Tetrahedron Lett.* **1999**, *40*, 7489–7492. (l) Kim, T. H.; Lee, G.-J. *Tetrahedron Lett.* **2000**, *41*, 1505–1508. (m) Suzuki, M.; Yamazaki, T.; Ohta, H.; Shima, K.; Ohi, K.; Nishiyama, S.; Sugai, T. *Synlett* **2000**, 189–192. (n) Knölker, H.-J.; Braxmeier, T. *Tetrahedron Lett.* **1998**, *39*, 9407–9410. (o) Nicolás, E.; Russell, K. C.; Hruby, V. J. *J. Org. Chem.* **1993**, *58*, 766–770.
4. We have also tried many bases such as DBU, DMAP, NEt_3, NaOH, or run the reaction under acidic conditions (*p*TsOH, conc. H_2SO_4, or $SOCl_2$), but none of these experiments gave acceptable results. Using $^iPrO_2CCl$ as alkoxycarbonylating agent instead of $(Boc)_2O$ under otherwise the same conditions as in Ref. 3(o) also failed to give any 2-oxazolidinones.
5. Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 5517–5518.
6. MeO_2CCl works in exactly the same way except for giving methanol instead of ethanol at the cyclization step.
7. The carbamates are also accessible by e.g., reducing **5a** (Ref. 15) and **5b** (Ref. 16) with $NaBH_4/H_2SO_4$ (Ref. 5). However, the products thus obtained often contain some over-reduction products.
8. Duddu, R.; Eckhardt, M.; Furlong, M.; Knoess, H. P.; Berger, S.; Knochel, P. *Tetrahedron* **1994**, *50*, 2415–2432.
9. Kozikowski, A. P.; Ma, D.-W. (Georgetown University, USA). PCT Int. Appl. WO 9743268 A1 20 Nov 1997; *Chem. Abstr.* **1998**, *128*, 3885.
10. We failed to obtain any oxazolidinones in refluxing toluene in the presence of K_2CO_3 (Ref. 3e).
11. This explains why NaOH in MeOH worked nicely on Hintermann and Seebach's (Ref. 3i) carbamates but led to formation of substantial amounts of hydrolysis product apart from **1b**.
12. For instance, Dufour, M.-N.; Jouin, P.; Poncet, J.; Pantaloni, A.; Castro, B. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1895–1899.
13. The spectroscopic data of the products are well consistent with the published ones; those not reported, not found in the easily accessible journals, not detailed, or mis-assigned data are listed below. Data for **4a**: $[\alpha]^{29}$ −28.6 (*c* 0.85, $CHCl_3$). Data for **4b**: mp 64.5–66.0°C; $[\alpha]^{20}$ −23.1 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 7.47–7.33 (m, 5H; aromat.), 5.03 (br s, 1H; N**H**), 4.22 (q, $J=7.1$ Hz, 2H; C$\mathbf{H}_2$Me), 4.05 (br s, 1H; **H**C–NCO_2Et), 3.82 (br dd, $J=3.3$, 11 Hz, 1H; C$\mathbf{H}_2$OH), 3.72 (br dd, $J=5.2$, 11 Hz, 1H; C$\mathbf{H}_2$OH), 3.00 (br s, 1H; benzylic), 2.98 (br s, 1H; benzylic), 2.69 (vbr s, 1H; O**H**), 1.35 (t, $J=7.1$ Hz, 3H; C$\mathbf{H_3}$). Data for **4c**: Mp 80–82°C; $[\alpha]^{29}$ −44.6 (*c* 0.98, $CHCl_3$). Data for **1b**: ^1H NMR (300 MHz, $CDCl_3$) 7.38–7.29 (m, 3H; aromat.), 7.17–7.21 (m, 2H; aromat.), 5.51 (br s, 1H; NH), 4.47 (br t, $J=8.2$ Hz, 1H; H-5), 4.17 (br dd, $J=5.5$, 8.2 Hz, 1H; H-5), 4.09 (br sextet, 1H; H-4), 2.90 (br s, 1H; benzylic), 2.88 (br s, 1H; benzylic).
14. Aldrich Catalog (for year 1998–1999) Handbook of Fine Chemicals.
15. Langer, K.; Mattay, J. *J. Org. Chem.* **1995**, *60*, 7256–7266.
16. Cups, T.; Boutin, R. H.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 3972–3979.