Heteroatom Chemistry
Volume 12, Number 7, 2001

Rapid Communication

Facile Synthesis of a Chiral Auxiliary Bearing the Isocyanide Group

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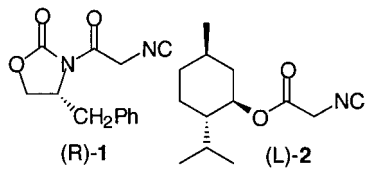
Received 28 February 2001; revised 28 April 2001

ABSTRACT: *The synthesis of a chiral isocyanide possessing the easily cleaved menthoxy group is reported.* © 2001 John Wiley & Sons, Inc. Heteroatom Chem 12:561–562, 2001

INTRODUCTION

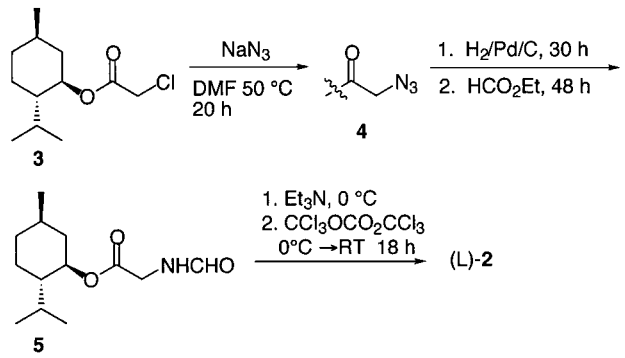
Previously we reported the synthesis of (R)-**1** [1], a chiral auxiliary bearing the isocyanide functionality. However, the synthesis was achieved in six steps and it bears an oxazoline functionality that



requires a two-step procedure for removal [2]. We therefore investigated the synthesis of a chiral isocyanoester bearing the menthoxy group, a chiral auxilliary that has recently emerged [3] as being easily removable. The incorporation of this group into the isocyanide (L)-**2** is shown in Scheme 1. The known compound **3** [prepared by a reported process in which $ClCH_2CO_2H$ was reacted with 1-(R)-menthol in refluxing benzene in the presence of PTSA [4] was allowed to react with sodium azide in DMF. Upon work-up and purification, the azide **4**, that was obtained in 81% yield, was converted to the formamide **5** in a one-pot reaction in which **4** was reduced with hydrogen on Pd/C. The formamide **5**, obtained in 99% yield, was treated with the phosgene equivalent CCl_3COCCl_3 to afford the target isocyanide (L)-**2** in 73% yield and with an overall yield of 59% in three steps. This synthesis offers a more convenient and higher-yield alternative to procedures reported by previous investigators [5].

EXPERIMENTAL SECTION

All reactions were conducted under nitrogen. ^1H and ^{13}C NMR spectra were recorded on a Bruker VRX300 or Bruker DRX400 machine and were calibrated using TMS as an internal standard.



SCHEME 1

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Contract grant sponsor: National Science Foundation.

Preparation of Azide 4

A mixture of 11.6 g (50.0 mmol) of the chloro compound **3**, prepared by a reported procedure [4], and 13.0 g (200 mmol) of sodium azide were weighed under nitrogen into a flask. To this mixture was added 30 ml of DMF followed by connection of the flask to a water condenser. The reaction mixture was then warmed at 50°C for 20 h after which it was cooled to room temperature. The reaction mixture was dissolved in 150 ml of diethyl ether and then the solution was washed with 3×100 ml of water. The organic layer was washed with brine and dried over anhydrous sodium sulfate. Removal of the solvent in vacuo afforded azide **4** which was purified by flash chromatography on silica gel using 20% ethyl acetate in hexane to afford 9.70 g (81% yield) of the pure azide. ^{1}H NMR ($CDCl_3$): δ 2.10–0.68 (aliphatic area, 18 H), 3.81 (s, 2H), 4.77 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 168.0, 76.3, 50.5, 47.0, 40.8, 34.1, 31.5, 26.3, 23.4, 22.8, 16.3. LRMS: Calcd for $C_{12}H_{21}N_3O_2$ 239.32, found *m/e* (M^+) 239.9.

Synthesis of Formamide 5

To 2.00 g (8.83 mmol) of azide **4** dissolved in 10 ml of ethyl formate was added 200 mg of Pd/C. A hydrogen atmosphere was maintained for 30 h followed by stirring at room temperature for an additional 48 h. The reaction mixture was then filtered and excess solvent was removed under reduced pressure to afford 2.00 g (99% yield) of **5** which was found to be essentially pure by both ^{1}H and ^{13}C NMR spectroscopic analysis. ^{1}H NMR ($CDCl_3$): δ 1.98–0.70 (aliphatic area, 18H), 4.05 (d, 2H), 4.76 (m, 1H), 6.09 (bs, 1H), 8.23 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 169.2, 161.3, 76.0, 46.9, 40.8, 40.1, 34.1, 31.4, 26.3, 23.4, 22.0, 20.7, 16.3. LRMS: Calcd for $C_{13}H_{24}NO_3$ 242.34, found *m/e* (MH^+) 242.1.

Synthesis of Isocyanide (L)-2

A small flask was charged with 1.2 g (5.0 mmol) of formate **5** (weighed under nitrogen). To this was added 5 ml of methylene chloride followed by 2.7 ml (20 mmol) of triethylamine. The reaction mixture was cooled to 0°C followed by dropwise addition of 2.0 ml (590 mmol) of $CCl_3OCO_2CCl_3$. The reaction mixture was allowed to warm to room temperature with continuous stirring for 18 h. After the reaction mixture was filtered to remove triethylamine hydrochloride, solvent was removed under reduced pressure and then the crude product was purified by flash chromatography on silica gel using 20% ethyl acetate in hexane to afford 818 mg (73% yield) of the target isocyanide. ^{1}H NMR ($CDCl_3$): δ 0.70–0.80 (overlapping area, 3H), 0.82–1.00 (overlapping area, 7H), 1.09 (m, 2H), 1.51 (m, 2H), 1.70 (m, 2H), 1.83 (m, 2H), 2.01 (m, 1H), 4.21 (s, 2H), 4.80 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 163.5, 161.1, 76.7, 46.9, 40.6, 34.0, 31.4, 26.4, 23.4, 22.0, 20.8, 16.3. LRMS: Calcd for $C_{13}H_{21}NO_2$ 223.32, found *m/e* (M^+) 223.5.

REFERENCES

[1] Tang, J.-S.; Verkade, J. G. J Org Chem 1996, 61, 8750.
[2] Evans, D. A.; Mathre, D. J. J Org Chem 1985, 50, 1830.
[3] (a) Barluenga, J.; Tomás, M.; Lopéz, L. A.; Suárez-Sobrino, A. Synthesis 1997, 967; (b) Barluenga, J.; Suárez-Sobrino, A.; Lopéz, L. A. Aldrichimica Acta 1999, 32, 4.
[4] Pallavicini, M.; Valoti, E.; Villa, L.; Resta, I. Tetrahedron Asymm 1996, 5, 363.
[5] Laangstroem, B.; Stridsberg, B.; Bergson, G. Chim Scr 1978–79, 13, 49.