Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 1273–1278

TETRAHEDRON: *ASYMMETRY*

New chiral organophosphorus derivatizing agent for the determination of enantiomeric composition of chloro- and bromohydrins by ^{31}P NMR spectroscopy

Sébastien Reymond, Jean Michel Brunel and Gérard Buono*

Ecole Nationale Supérieure de Synthèses, de Procédés et d'Ingénierie Chimiques d'Aix Marseille, UMR CNRS 6516, Faculté de St Jérôme, Av. Escadrille Normandie Niemen, 13397 Marseille, Cedex 20, France

Received 30 December 1999; accepted 11 February 2000

Abstract

The synthesis of a new chiral organophosphorus derivatizing agent prepared from (*S*)-2-anilinomethylpyrrolidine **1** and its successful use in the determination of enantiomeric composition of various halohydrins by ^{31}P NMR spectroscopy is described.

1. Introduction

The steadily growing use of enantiomerically pure materials as chiral building blocks, auxiliaries or chiral ligands in numerous asymmetric syntheses[1] demands fast and accurate methodology for enantiomeric excess determination. Direct chromatographic analyses by GC or HPLC on chiral stationary phases are ideal;[2] however, this approach is still of limited generality and NMR spectroscopy continues to be one of the most important methods to determine the enantiomeric purity of chiral compounds.[3] The utility of chiral derivatizing agents (CDAs) is well documented. Two of the major problems associated with using CDAs are the observation and resolution of appropriate signals in complex NMR spectra and the potential for asymmetric induction during the preparation of the derivatized substrate. ^{31}P NMR spectroscopy provides a very convenient method for determining the enantiomeric excess of chiral phosphorus compounds because the chemical shift dispersion is usually large and spectra are simple, when broad band proton decoupling is applied.[4,5] Thus, several organophosphorus chiral derivatizing agents as well as

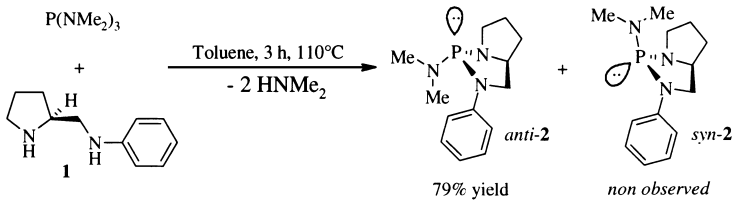
* Corresponding author. Fax: 04-91-02-77-76; e-mail: buono@spi-chim.u-3mrs.fr

0957-4166/00/$ - see front matter
PII: S0957-4166(00)00062-8

achiral reagents for the analysis of chiral diols, amines or alcohols by ^{31}P NMR have been successfully used.[6] Nevertheless, no convenient method for the measurement of the enantiomeric composition of chiral halohydrins has been reported to date.

2. Results and discussion

We wish to report herein the first, simple and very efficient ^{31}P NMR method for the determination of enantiomeric purity of various chiral halohydrins based on the use of (2*R*,5*S*)-2-dimethylamino-3-phenyl-1,3-diazaphosphabicyclo[3.3.0^{1,5}]octane **2** as new chiral derivatizing agent. CDA **2** was easily prepared by the exchange reaction of tris(dimethylamino)phosphine and (*S*)-2-anilinomethylpyrrolidine **1** in refluxing toluene (Scheme 1).



Scheme 1.

After completion of the reaction, CDA **2** was obtained as a single diastereomer in 78% yield after distillation (*anti*-**2**, ^{31}P NMR: $\delta = 116.9$ ppm) and no trace of formation of the other diastereomer *syn*-**2** has been detected during the conversion.[7] Furthermore, the structure of *anti*-**2** has been fully characterized by ^{31}P, ^{1}H and ^{13}C NMR spectroscopy and by X-ray structure analysis of its corresponding borane complex adduct **3**[8] (Fig. 1).

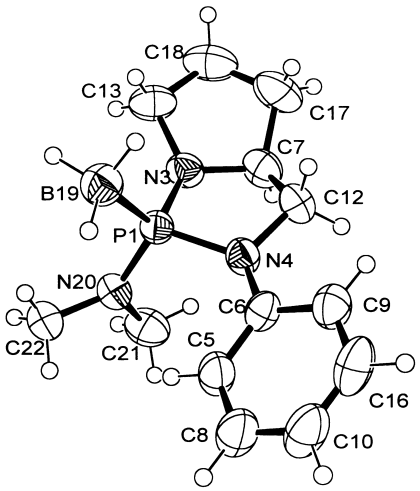
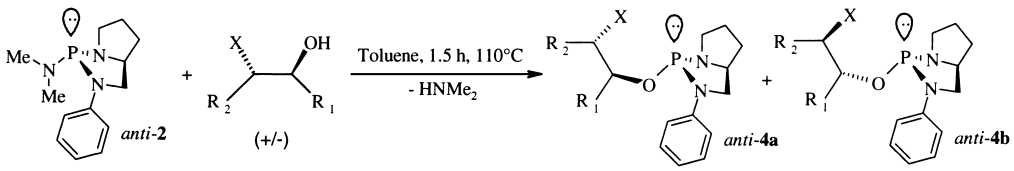
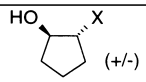
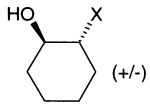
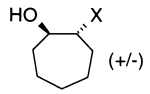
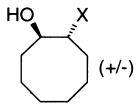
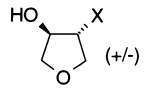
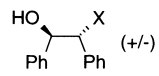
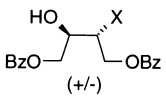
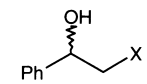
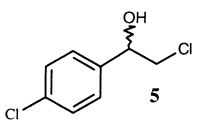


Figure 1.



Scheme 2.

Table 1

Entry	Halohydrins	X	^{31}P NMR Chemical shifts of diastereomeric derivatives *anti*-**4a** and *anti*-**4b**		Δδ (ppm)
1		Cl	122.0	120.0	2.0
		Br	119.8	118.0	1.8
2		Cl	129.7	121.7	8.0
		Br	127.2	120.4	6.8
3		Cl	127.0	121.2	5.8
		Br	127.3	120.5	6.8
4		Cl	131.6	119.5	12.1
		Br	132.3	119.4	12.9
5		Cl	121.6	121.4	0.2
		Br	121.7	121.3	0.4
6		Cl	120.2	118.8	1.4
		Br	121.6	118.6	3.0
7		Cl	125.1	123.4	1.7
		Br	124.8	123.3	1.5
8		Cl	120.6	120.3	0.3
		Br	121.1	119.5	1.6
9[10]			121.4	120.0	1.4

CDA *anti*-**2** is stable for weeks under inert atmosphere and not sensitive to moisture. For easy handling, CDA *anti*-**2** was stored as 0.5 M solution in toluene under argon and taken by syringe when needed. The reaction between *anti*-**2** and a racemic halohydrin was performed for 1.5 h in refluxing toluene (Scheme 2).

In all cases, the reaction is quantitative and leads to the exclusive synthesis of diastereomeric compounds *anti*-**4a** and *anti*-**4b** without formation of any byproducts. Analysis of the crude mixture of diastereomeric derivatives *anti*-**4a** and *anti*-**4b** was performed by ^{31}P NMR spectroscopy in $CDCl_3$ and the results obtained with several halohydrins are summarized in Table 1. The enantiomeric purity can be accurately measured by integration of the signals of the diastereomeric phosphorus compounds and no kinetic resolution has been observed. Thus integration of the racemic mixtures always corresponds to 50:50 (±2).[9]

The diastereomeric pairs of derivatives exhibit typical NMR shift differences between 0.2 and 12.9 ppm. It is worth mentioning that the presence of a lone pair of electrons on phosphorus tends to increase the chemical shift difference. Reagent *anti*-**2** shows excellent reactivity toward chlorohydrin and bromohydrin and in all these cases the enantiomeric purity can be accurately measured. Moreover, it should be noted that CDA *anti*-**2** can be used in slight excess, since its chemical shift does not interfere with those of *anti*-**4a** and *anti*-**4b**. On the other hand, attempts to determine the enantiomeric purity of various iodohydrins failed due to the high reactivity and instability of these compounds, which lead only to the formation of numerous unidentified byproducts.

3. Conclusion

In conclusion, this procedure proved to be very efficient for an easy determination of the enantiomeric purity of various chiral halohydrins. Studies are now in progress to extend this methodology to the measurement of the enantiomeric purity of chiral azido alcohols and cyanohydrins.

4. Experimental

^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on Bruker AC100 and AC200 spectrometers in $CDCl_3$ as solvent. The chemical shifts (ppm) were determined relative to Me_4Si (^{1}H and ^{13}C) and 85% H_3PO_4 (^{31}P). Toluene was distilled from sodium/benzophenone ketyl immediately prior to use. (*S*)-2-Anilinomethyl pyrrolidine **1** was prepared according to the procedure previously reported in the literature.[11]

4.1. General procedure for the determination of the enantiomeric composition of chiral halohydrins

To a 25 mL two-necked round-bottomed flask under argon atmosphere containing 30 mL of dry toluene were dropped (*S*)-anilinomethylpyrrolidine **1** (2.64 g, 15 mmole) and tris(dimethylamino)-phosphine (2.44 g, 15 mmole). The solution was heated to reflux and monitored by ^{31}P NMR spectroscopy. After 3 h, 1 mL of this 0.5 M solution was introduced into a small round-bottomed flask under argon and 1 equivalent of the desired racemic chlorohydrins was added. This mixture was refluxed for 1.5 h and then the solvent removed under vacuum. The residue was transferred under argon into a 5 mm NMR tube along with 100 μL of $CDCl_3$ and the ^{31}P NMR spectrum was recorded at 40.539 MHz.

A sample of the crude derivatizing reagent *anti*-**2** was subjected to fractional distillation under reduced pressure for analysis: bp 148°C/5×10^{-3} mbar; $[\alpha]_D^{20} = -350.7$ ($c = 1.13$, CH_2Cl_2); ^{31}P NMR δ 117.9; ^{1}H NMR δ 1.55–1.90 (m, 3H), 1.93–2.12 (m, 1H), 2.63 (s, 3H), 2.67 (s, 3H), 3.05–3.30 (m, 2H), 3.42–3.60 (m, 1H), 3.79 (t, $J = 7.0$ Hz, 1H), 4.10–4.22 (m, 1H), 6.75–6.95 (m, 3H), 7.25 (t, $J = 7.2$ Hz, 2H); ^{13}C NMR δ 25.4 (d, $J = 4.1$ Hz), 32.3, 36.7, 37.0, 50.4 (d, $J = 40.6$ Hz), 54.4 (d, $J = 4.7$ Hz), 62.3 (d, $J = 7.3$ Hz), 114.4 (d, $J = 11.6$ Hz), 117.5, 128.9, 146.5 (d, $J = 14.4$ Hz).

References

1. For example: (a) Martens, J. In *Topics in Current Chemistry*; Springer-Verlag: Berlin, 1984; Vol. 125, p. 165. (b) Seebach, D.; Inwinkelried, R.; Weber, T. In *Enantiomerically Pure Compound Syntheses with C-Bond Formation via Acetals and Enamines*, *Modern Synthetic Methods*; Springer-Verlag: Berlin, 1986; pp. 125–129. (c) Decker, M. *Handbook of Chiral Chemicals*; Ager, D. J., Ed.; Marcel Dekker: New York, 1999.
2. (a) Schurig, V. *J. Chromatogr. A* **1994**, *666*, 111. (b) *Chromatographic Separations Based on Molecular Recognition*; Jinno, K., Ed.; Wiley-VCH: New York, 1997.
3. For a review of NMR methods, see: Parker, D. *Chem. Rev.* **1991**, *91*, 1441.
4. Verkade, J. G.; Quin, L. D. In *Phosphorus 31 NMR Spectroscopy in Stereochemical Analysis: Organic Compounds and Metal Complexes*; VCH publishers, Inc.: Deerfield Beach, Florida, 1987; Vol. 8.
5. Hulst, R.; Kellog, R. M.; Feringa, B. L. *Rec. Trav. Chim. Pays-Bas* **1995**, *114*, 115.
6. (a) Anderson, R. C.; Shapiro, M. J. *J. Org. Chem.* **1984**, *49*, 1304. (b) Kato, N. *J. Am. Chem. Soc.* **1990**, *112*, 254. (c) Johnson, C. R.; Elliot, R. C.; Penning, T. D. *J. Am. Chem. Soc.* **1984**, *106*, 5019. (d) Feringa, B. L.; Smaardijk, A.; Wynberg, H. *J. Am. Chem. Soc.* **1985**, *107*, 4798. (e) Feringa, B. L.; Strijtveen, B.; Kellog, R. M. *J. Org. Chem.* **1989**, *51*, 5484. (f) Alexakis, A.; Mutti, S.; Normant, J. F.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 437. (g) Alexakis, A.; Mutti, S.; Mangeney, P. *J. Org. Chem.* **1992**, *57*, 1224. (h) Brunel, J. M.; Pardigon, O.; Maffei, M.; Buono, G. *Tetrahedron: Asymmetry* **1992**, *3*, 1243. (i) Brunel, J. M.; Faure, B. *Tetrahedron: Asymmetry* **1995**, *6*, 2353. (j) Garner, C. M.; McWhorter, C.; Goerke, A. R. *Tetrahedron Lett.* **1997**, *38*, 7717. (k) Oshikawa, T.; Kumagai, S.; Kobayashi, J.; Yamashita, M.; Seo, K. *J. Chem. Soc., Chem. Commun.* **1995**, 435. (l) Hulst, R.; Zijlstra, R. W. J.; Feringa, B. L.; de Vries, N. K.; Hoeve, W. T.; Wynberg, H. *Tetrahedron Lett.* **1993**, *34*, 1339. (m) de Parrodi, C. A.; Moreno, G. E.; Quintero, L.; Juaristi, E. *Tetrahedron: Asymmetry* **1998**, *9*, 2093.
7. The notations of the *syn* and *anti* diastereomers are according to the methylene substituent of the pyrrolidine ring with respect to the dimethylamino group. If they are on the same side of the five-membered phosphorus-containing ring, we call it a *syn* diastereomer; otherwise, it is an *anti* diastereomer. *syn* (unlike) = (2*S*,5*S*)-2-dimethylamino-3-phenyl-1,3-diazaphosphabicyclo[3.3.0^{1,5}]octane and *anti* (like) = (2*R*,5*S*)-2-dimethylamino-3-phenyl-1,3-diazaphosphabicyclo[3.3.0^{1,5}]octane. (a) Cros, P.; Buono, G.;Peiffer, G.; Denis, D.; Mortreux, A.; Petit, F. *New J. Chem.* **1987**, *11*, 573. (b) Brunel, J. M.; Chiodi, O.; Faure, B.; Fotiadu, F.; Buono, G. *J. Organomet. Chem.* **1997**, *529*, 285.
8. X-Ray structure analysis of **3**: a plate white monocrystal of $C_{13}H_{23}B_1N_3P$, obtained by recrystallization in ethyl acetate, with approximate dimensions 0.2×0.2×0.2 mm was mounted on a glass capillary. All the measurements were made on a Rigaku diffractometer with Mo-Kα radiation. Cell constants and the orientation matrix for data collection were obtained from a least square refinement using setting angles of 30 reflections in the range $\theta = 1$–25°, which corresponded to a monoclinic cell with dimensions: $a = 7.9186(2)$, $b = 9.6315(3)$, $c = 19.5340(7)$ Å. For $Z = 5$ and $M = 263.13$, $\rho_{meas} = 1.25$ g cm^{-3}. The space group was determined to be $P2_12_12_1$ from the systemic absences. A total of 1503 reflections were collected at T = 298 K. The standards were measured after every 158 reflections. Selected bond distances (Å): P1–N3, 1.648(1); P1–N4, 1.691(1); P1–N20, 1.632(1); P1–B19, 1.912(1); N3–C7, 1.479(2); N3–C13, 1.471(2); N4–C6, 1.418(2). Selected bond angles (°): N3–P1–N4, 92.5(1); N3–P1–N20, 109.4(1); N4–P1–N20, 108.1(1); P1–N3–C7, 114.7(1); P1–N3–C13, 125.5(1); C7–N3–C13, 111.6(1); P1–N4–C12, 111.9(1); P1–N4–C6, 123.9(1); C6–N4–C12, 119.8(1); P1–N20–C22, 124.5(1); P1–N20–C21, 121.2(1). CCDC 139376.
9. It is noteworthy that when the reaction time is not long enough, traces of *syn*-**4a** and *syn*-**4b** diastereomers can be characterized. In this case, integration of the signals can still be correlated to the enantiomeric purity of the considered halohydrin.

10. ^{31}P NMR enantiomeric composition of racemic and enantiomerically enriched chlorohydrin **5**. Enantiomeric excess of **5** has also been determined by HPLC analysis on a Daicel Chiralcel OD-H column using hexane:*i*-PrOH (90:10) as eluent (flow rate: 0.5 mL/min, 254 nm), t_R: 13.46 min (minor); t_S: 14.53 min (major).

racemic

70% ee

11. Brunel, J. M.; Constantieux, T.; Buono, G. *J. Org. Chem.* **1999**, *64*, 8940.