

N-Methyl- and *N*-benzyl-4-amino[2.2]paracyclophanes as unique planar chiral auxiliaries

Andrew Pelter,* Huw Kidwell and Roger A. N. C. Crump

Department of Chemistry, University of Wales Swansea, Singleton Park, Swansea, UK SA2 8PP

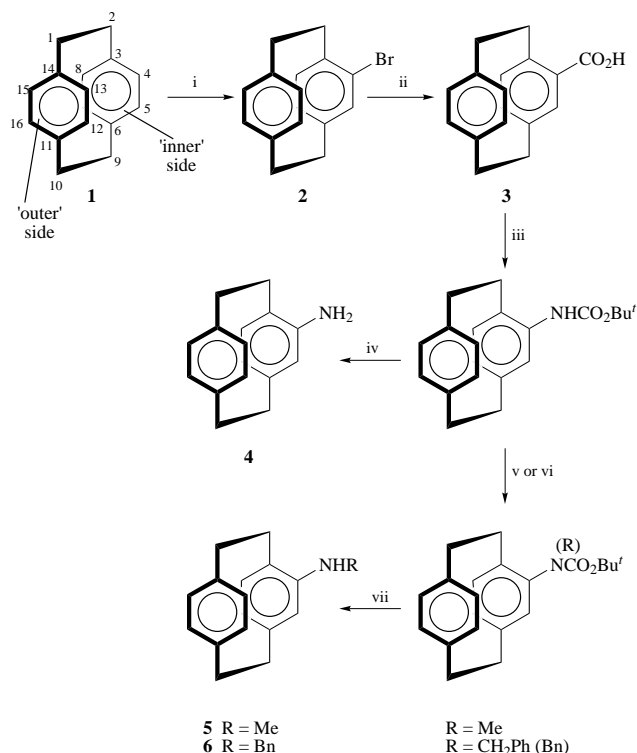
Efficient production of racemic and homochiral *N*-alkyl-[2.2]paracyclophanes from [2.2]paracyclophane *via* racemic and homochiral 4-carboxy[2.2]paracyclophane is described, including an excellent procedure for the synthesis of homochiral 4-amino[2.2]paracyclophane. Enolisation followed by electrophilic attack proceeds with diastereoselectivities varying from excellent to modest and the chiral auxiliaries are readily recovered in good yields; the configurational stability of the α -haloamides produced is examined.

[2.2]Paracyclophane (2.2PC), **1**, is a thick symmetrical molecule that contains two benzene rings held closely face to face by two 1,4-ethylene bridges.¹ Despite the benzene ring being shallow boats (strain energy 129.6 kJ mol⁻¹) almost all standard benzene reactions can be replicated. Rotation about the six non-benzenoid C–C bonds is restricted to a few degrees so that the molecule is effectively rigid.² Three important consequences follow: (i) all mono-substituted [2.2]PCs are chiral; (ii) there need be no consideration of conformation or conformational equilibria of the 2.2PC system;³ (iii) there is always a strong differentiation between the 'inner' and 'outer' space of the molecule.

[2.2]Paracyclophane **1** is commercially available and there exist many efficient methods for its synthesis.^{1,3–5} Its chemistry is well known and has been extensively reviewed.^{1,3,4} [2.2]Paracyclophanes are chirally stable up to 180–200 °C at which temperature racemisation proceeds through a dibenzyl radical.⁶ The inherent chirality and stability of 2.2PC derivatives make them ideal candidates as reagents, auxiliaries and catalysts for chiral synthesis as well as for incorporation into molecules which they may modify by their lipophilicity and chirality. Despite this, 2.2PC derivatives have been little used in any of the above categories.^{7–11} We were attracted by the idea that enolates derived from *N*-alkyl-*N*-acyl-4-amino[2.2]paracyclophanes would have a definite configuration and conformation (as indicated by calculations that will be given separately), due mainly to the interactions of the *N*-alkyl groups with the bridge protons, and that electrophilic attack on such enolates would then be from the 'outer' side of the 2.2PC system.

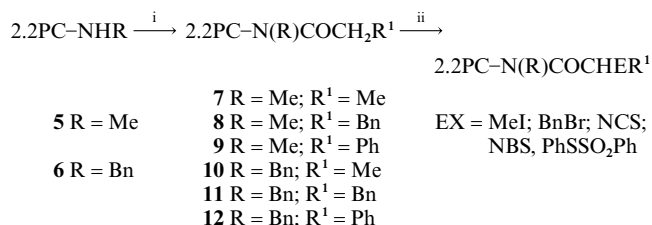
Scheme 1 outlines the synthesis of the required amines **5** and **6** using 4-carboxy-2.2PC **3** as a readily available, easily resolvable¹² intermediate of known configuration.¹³ Amine **4** is readily obtained from **1** in an overall yield of 79%, whilst **5** and **6** are available in overall yields of 65% each. From the resolved acid **3**, the yields are 91, 75 and 75% respectively and therefore the amines can be regarded as readily available auxiliaries. We have also been able to make **4** directly from **2** in 72% yield using NaNH₂ and NH₃ and very recently the resolution of **4** has been achieved.¹⁴ The carbamate route to substituted amines was the only method leading to **5**, though **6** could be obtained from **4** by direct benzylation. Our route gives homochiral **4** directly from homochiral **3**.

Amines **5** and **6** could be converted to amides by various reactions, the cleanest of which was the reaction of acid chlor-



Scheme 1 Reagents and conditions: i, Br₂-Fe (90%); ii, Mg, CO₂, H₃O⁺ (96%); iii, (a) SOCl₂, (b) NaN₃, (c) heat, Bu'OH-toluene (95%); iv, TFA (96%); v, NaH-MeI (82%); vi, NaH-PhCH₂Br (82%); vii, TFA (95%).

ides with the magnesium derivatives of **5** and **6**. This gave yields of 75–80% and made amides **7–12** available for study as shown in Scheme 2.



Scheme 2 Reagents and conditions: i, (a) MeMgBr, (b) R¹CH₂COCl; ii, (a) LiN(SiMe₃)₂, -78 °C, THF, (b) EX, -78 to 22 °C

The electrophiles chosen gave one extra centre only, and this allowed the use of racemic amines **5** and **6** followed by assessment of ratios of diastereoisomers. However homochiral **5** was also taken through the processes of Scheme 2 and was reacted not only with the electrophiles shown but also with aldehydes and epoxides in studies to be separately reported. The results of Scheme 2 are given in the Tables.

Table 1 Alkylation of 2.2PC-N(R)COCH₂R¹ according to Scheme 2

Experiment	Compound	Number	RX	Isomer ratio ^a	Yield (%) ^b
1	2.2PC-N(Me)COCH ₂ Me	7	BnBr	95:5 ^c	95
2	2.2PC-N(Me)COCH ₂ CH ₂ Ph	8	MeI	8:92	95
3	2.2PC-N(Me)COCH ₂ Ph	9	MeI	4:96	99
4	2.2PC-N(Me)COCH ₂ Ph	9	BnBr	91:9	81
5	2.2PC-N(Bn)COCH ₂ Me	10	BnBr	92:8	95
6	2.2PC-N(Bn)COCH ₂ CH ₂ Ph	11	MeI	5:95	81
7	2.2PC-N(Bn)COCH ₂ Ph	12	MeI	4:96	97
8	2.2PC-N(Bn)COCH ₂ Ph	12	BnBr	95:5	90

^a No differences in ratio of crude product and product after passing through silica. ^b Isolated yields of purified, isolated products in all cases. ^c All ratios established by ¹H NMR spectroscopy and HPLC.

Table 2 Chlorination of amides 7–12 with NCS according to Scheme 2

Experiment	Compound	Isomer ratio	Yield (%) ^a
9	7	83:17	68
10	8	99:1	78
11	9	85:15 ^b	91
12	10	92:8	96
13	11	79:21 ^c	73
14	12	83:17	93

^a Isolated yields. ^b Becomes 76:24 after 24 h standing. ^c Becomes 69:31 after silica column.

Table 3 Bromination of 2.2PC amides 7–12 with NBS according to Scheme 2

Experiment	Compound	Isomer ratio	Yield (%) ^a
15	7	72:28	89
16	8	59:42 ^b	83
17	9	63:37 ^c	93
18	10	79:21	80
19	11	89:11 ^d	80
20	12	59:41 ^e	84

^a Isolated yields. ^b Became 77:23 after column. ^c Became 55:45 after 24 h. ^d Became 79:21 after column. ^e Became <0.1:>99.9 (see text) after column.

It is clear that alkylation is highly stereoselective and that **5** and **6** are effective chiral auxiliaries. Benzylation takes place from the same side as methylation as shown by experiments 1 and 2 and all products are chirally and chemically stable.

Chlorination is dealt with in Table 2. In the chlorinations the stereoselectivity varies from excellent to moderate. Those products in which R¹ = Me are chirally stable but in particular in experiments 11 and 14, in which R¹ is phenyl, an equilibration occurs on standing. A change also occurred in experiment 13 but only on chromatographing on acidic silica. We have previously observed that certain chiral α -bromo sulfonamides undergo a similar equilibration¹⁵ as do α -bromo esters derived from pantolactone.¹⁶ It is clear that halogenation experiments to test the effectiveness of a chiral auxiliary must be treated with caution and that the history of each sample must be completely known. In our case NMR spectra were taken at intervals for each product.

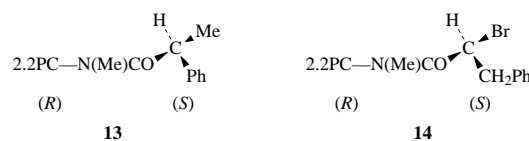
The results of brominations with NBS are given in Table 3. In general the initial diastereoisomeric excess fell for bromination as compared with alkylation and also, though to a lesser extent, as compared with chlorination. Thus the stereoselectivity does not depend solely on the enolate mixture but also on the electrophile. In the case of bromination *all* the α -bromo amides containing a phenyl group underwent equilibration at the α -CHBr position. An extreme case is the product of experiment 18 in which the de fell to zero over 24 h on standing in CDCl₃. On exposure to acidic silica, the initially minor isomer became essentially the only isomer present. We have used similar transformations to give high yields of homochiral α -aminoamides, α -alkoxyamides and α -alkylthioamides.¹⁵

Table 4 Phenylthiolation of 2.2PC-N(R)COCH₂R¹ according to Scheme 2

Experiment	Compound	Isomer ratio	Yield (%) ^a
21	7	93:7	83
22	9	86:14	91
23	10	98.4:1.6	99
24	12	97:3	96

^a Isolated yields.

The major isomer of the homochiral purified product of experiment 3 starting with the (*R*)-paracyclophane was assigned as **13**, (*R,S*) by X-ray analysis. In the same way the major product of experiment 16, starting with the racemic cyclophane was assigned as **14** (*R,S*) (or *S,R*).^{17,18}



The results of phenylthiolation of **7**, **9**, **10** and **12** are given in Table 4.

Thus phenylthiolation is comparable to alkylation in the degree of diastereoselectivity obtained and the products, like the alkylation products, are configurationally stable. It may be that in general products reflect, in major part, the enolate ratios and that equilibration of the α -halo products occurs *during* halogenation reactions. Alternatively it could be that alkylation and phenylthiolation are slow reactions and one enolate reacts faster than the other. The product mix would then reflect this preference rather than the ratio of enolates.

Our attempts to gain further insight into the reactions by trapping the enolates and studying the geometries and configurations of the products have, as yet, not met with success.

The non-halogenated amides have been hydrolysed back to chiral amines **5** and **6** in quantitative yield (HCl, H₂O, glycol) and therefore amines **5** and **6** are unique, readily available and synthetically useful chiral auxiliaries.

Acknowledgements

We thank the EPSRC for financial support for this project.

References

- 1 F. Vögtle, *Cyclophane Chemistry*, J. Wiley and Sons, New York, 1993.
- 2 H. Hope, J. Bernstein and K. N. Trueblood, *Acta Crystallogr., Sect. B*, 1972, **28**, 1733.
- 3 D. J. Cram, R. B. Hornby, E. A. Truesdale, H. J. Reich, M. M. Delton and J. M. Cram, *Tetrahedron*, 1974, **30**, 1757.
- 4 (a) F. Vögtle and P. Neumann, *Synthesis*, 1973, 85; (b) F. Vögtle, *Top. Curr. Chem.*, 1974, **48**, 67; (c) V. Bockelheide, *Top. Curr. Chem.*, 1983, **113**, 89; (d) J. Kleinschroth and H. Hopf, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 469; (e) *Cyclophanes*, ed. P. M. Keehn and S. M. Rosenfeld, Academic Press, New York, vols. 1 and 2, 1983.

- 5 M. Brink, *Synthesis*, 1975, 807; M. L. Kaplan and E. A. Truesdale, *Tetrahedron Lett.*, 1976, 3665; S. H. El Tamany and H. Hopf, *Tetrahedron Lett.*, 1980, **21**, 4901; H. Hopf, I. Boehm and J. Kleinschroth, *Org. Synth.*, 1981, **60**, 41; G. Bornenge, A. Malacride, S. Compolini and M. A. Beretta, *Eur. Pat. Appl.*, 1987, 252 402; *Ind. Eng. Chem. Res.*, 1989, **28**, 1125; R. Ungarelli, M. A. Beretta and L. Sogli, *Eur. Pat. Appl.*, 1988, 307 934.
- 6 H. J. Reich and D. J. Cram, *J. Am. Chem. Soc.*, 1969, **91**, 3517.
- 7 R. Yanada, M. Higashikawa, Y. Miwa, T. Taga and F. Yoneda, *Tetrahedron Lett.*, 1992, **3**, 1387.
- 8 H. J. Reich and K. E. Yelm, *J. Org. Chem.*, 1991, **56**, 5672.
- 9 D. Y. Antonov, Y. N. Belekon, N. S. Ikonnikov, S. A. Orova, A. P. Pisarevsky, N. I. Raevski, V. I. Rozenberg, E. V. Sergeeva, Y. T. Struchkov, V. I. Tararov and E. V. Vorontsov, *J. Chem. Soc., Perkin Trans. I*, 1995, 1873.
- 10 E. V. Sergeeva, V. I. Rozenberg, E. V. Vorontsov, T. I. Danilova, Z. A. Starikova, A. I. Yanovsky and Y. N. Belekon, *Tetrahedron: Asymmetry*, 1996, **7**, 3445.
- 11 A. Pelter, R. A. N. C. Crump and H. Kidwell, *Tetrahedron Lett.*, 1996, **37**, 1273.
- 12 D. J. Cram, W. J. Wechter and R. W. Kierstead, *J. Am. Chem. Soc.*, 1958, **80**, 3126; J. L. Marshall and L. Hall, *Tetrahedron*, 1981, **37**, 1271.
- 13 H. Falk, P. Reich-Rohrwig and K. Schlögl, *Tetrahedron*, 1970, **26**, 511; N. Nakazaki, K. Yamamoto and M. Maeda, *Chem. Lett.*, 1980, 1553; W. Tochtermann, G. Olsson, C. Vogt, K. Peters and H. G. von Schnering, *Chem. Ber.*, 1987, **120**, 1523; A. Pelter, H. Kidwell and D. Hibbs, unpublished X-ray analysis of *R*-(-)-13-bromo-4-methoxycarbonyl[2.2]paracyclophane.
- 14 A. Cipiciani, F. Fringuelli, V. Mancini, O. Piermatti, F. Pizzo and R. Ruzzicorni, *J. Org. Chem.*, 1997, **62**, 3744.
- 15 R. S. Ward, A. Pelter, D. Goubet and M. C. Pritchard, *Tetrahedron: Asymmetry*, 1995, **6**, 469.
- 16 K. Koh and T. Durst, *Tetrahedron Lett.*, 1993, **34**, 4473.
- 17 We thank Dr D. Hibbs, EPSRC X-ray crystallography centre, Cardiff, for this analysis.
- 18 R. S. Cahn, C. Ingold and V. Prelog, *Angew. Chem., Int. Ed. Engl.*, 1966, **5**, 385.

Paper 7/05449A
Received 28th July 1997
Accepted 29th July 1997