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Tetrahedron Letters 45 (2004) 6583–6585
Tetrahedron Letters

A preparative microwave method for the isomerisation of 4,16-dibromo[2.2]paracyclophane into 4,12-dibromo[2.2]paracyclophane

D. Christopher Braddock,* Simon M. Ahmad and Gordon T. Douglas

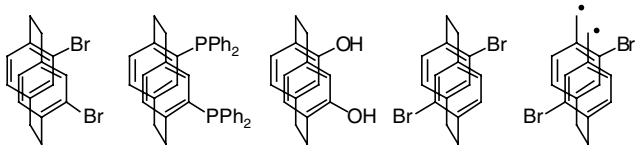
Department of Chemistry, Imperial College London, South Kensington, London SW7 2AZ, UK

Received 25 June 2004; accepted 9 July 2004
Available online 24 July 2004

Abstract—4,16-Dibromo[2.2]paracyclophane (**4**) is isomerised to 4,12-dibromo[2.2]paracyclophane (**1**) by the application of microwaves in DMF solution.

4,12-Dibromo[2.2]paracyclophane (**1**) is the key intermediate en route to PHANEPHOS **2**,[1] PHANOL **3**[2] and other functional C_2-symmetric planar-chiral 4,12-disubstituted[2.2]paracyclophanes.[3] Dibromide **1** was originally prepared by Cram via dibromination of [2.2]paracyclophane and separation from its other isomers by recrystallisation and repeated chromatography (16%).[4a] In this bromination reaction the 4,16-dibromide **4** is the major product, and by virtue of its relative low solubility can be isolated directly from the crude reaction mixture by crystallisation from chloroform (26%). Cram also showed that the pseudo-*para* dibromide **4** could be thermally isomerised ($K = 1$) into pseudo-*ortho* dibromide **1** by heating to 200 °C in triglyme (bp 216 °C) (100 mg **4**, 0.3 mL triglyme).[4b] The effect of heating at this temperature is to generate benzylic diradical **5**, which can undergo free rotation about the remaining ethylene bridge. Subsequent intramolecular radical recombination can lead back to **4** or alternatively to **1** thereby establishing an equilibrium between them. Cram used this method to elucidate the pseudo-*ortho*/pseudo-*para* and pseudo-*gem*/pseudo-*meta* relationships for a series of disubstituted [2.2]paracyclophanes. Later, Pye et al.[1a] showed that the sequence of bromination of [2.2]paracyclophane to give the 4,16-dibromide **4** followed by thermal isomerisation was a useful preparative method for 4,12-dibromide **1**. For example, 4,16-dibromide **4** (33.4 g) was heated at 230 °C in triglyme (130 mL) for 3 h and then allowed to cool to room temperature over 4 h. On cooling, the less soluble pseudo-*para* isomer **4** precipitates from the mixture. This material could be resubmitted for another isomerisation run (60 mL triglyme). The desired pseudo-*ortho* isomer **1** (23.0 g, 69%) was isolated from the combined mother liquors via removal of the triglyme by vacuum distillation.

We recently published an improved bromination method of [2.2]paracyclophane using dichloromethane rather than carbon tetrachloride as the solvent to give dibromide **4** (38%).[2a] We also presented a modified isolation procedure by repeated washing of an ethereal solution of **1** with water (6–10 washes) to remove the triglyme instead of its removal by vacuum distillation.[2a] However, the isolation of **1** by either procedure is time consuming and tedious. We now report a microwave method that obviates these disadvantages for the isomerisation of dibromide **4** into **1**.



1 **2** **3** **4** **5**

Keywords: Microwaves; Preparative; 4,16-Dibromo[2.2]paracyclophane; 4,12-Dibromo[2.2]paracyclophane.
* Corresponding author. E-mail: c.braddock@imperial.ac.uk

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doi:10.1016/j.tetlet.2004.07.043

Table 1. Microwave isomerisation of **4** into **1**[a]

Entry	T[b]	Hold time	Solvent	%Mass of insolubles[c]	%Mass of solubles[d]	Overall %mass recovery[e]	%**1**[f]
1[g]	220 (155)	10	MTBE	87	10 (0)	97	0
2[g]	210 (174)	10	1,2-DCE	73	21 (26)	94	5
3	202 (200)	10	DMF	20	36 (56)	56	20
4	180 (181)	10	DMF	24	48 (76)	72	36
5	180 (181)	8	DMF	40	50 (80)	90	40
6	**180 (181)**	**6**	**DMF**	**43**	**46 (83)**	**89**	**38**
7	180 (181)	4	DMF	43	41 (83)	84	29
8	180 (181)	2	DMF	52	31 (93)	83	29
9	170 (171)	6	DMF	59	33 (93)	92	31
10	160 (161)	6	DMF	83	17 (94)	100	16

[a] All reactions performed on 500 mg of **4** in 1 mL DMF in a sealed 10 mL vessel in a CEM Microwave Discover Instrument. The maximum pressure was set for 17.2 bar, and the power to 300 W.
[b] The programmed temperature. The figure in parentheses is the temperature that was attained.
[c] The percentage mass of the material isolated by filtration. ^{1}H NMR spectroscopy revealed this to be pure pseudo-*para* dibromide **4**.
[d] The percentage mass of the material isolated after work-up of the filtrate. The figure in parentheses indicates the percentage of pseudo-*ortho* dibromide **1** given by integration of the resonance at 7.17 ppm in the ^{1}H NMR spectrum for **1** versus the resonance at 7.13 ppm for **4**.
[e] The percentage total recovered mass based on the material submitted.
[f] The overall percentage conversion to **1**.
[g] Reactions performed on 200 mg of **4** in 1.5 mL of solvent.

Two advantages of the application of microwaves in synthesis are that chemical reactions can be markedly accelerated and that solvents can be superheated past their normal boiling points.[5] In these respects, we were drawn to investigate the use of microwave irradiation for the isomerisation of **4** into **1** with the aim of reducing the overall reaction time and employing a solvent with a lower boiling point. Since heating (conductively or by microwave irradiation) of **4** will at best establish an approximate 1:1 equilibrium position with **1**, we were also mindful of the advantage of using a solvent (like triglyme above) in which the pseudo-*para* isomer is insoluble at room temperature and the pseudo-*ortho* isomer soluble (or vice versa), and the concomitant ease of separation by filtration. We have found that DMF is such a solvent for the isomerisation of **4** into **1** in less than 10 min under microwave irradiation (vide infra).

In an initial exploratory screen methyl-*tert*-butyl ether (MTBE, bp 55 °C, ε25 °C = 2.6), 1,2-dichloroethane (DCE, bp 83 °C, ε25 °C = 10.4) and dimethylformamide (DMF, bp 153 °C, ε25 °C = 37.7) were selected as potential solvents (Table 1, entries 1–3) to carry out the microwave isomerisation on the basis of their different boiling points, dielectric constants and their overall ability to absorb microwave radiation: ethers < 1,2-dichloroethane < DMF.[5d] We chose to set the desired temperature above 200 °C in order to promote the formation of the diradical **5** and to irradiate for 10 min. A protocol was adopted whereby after cooling, any insoluble material was isolated by filtration. The soluble material remaining in the filtrate was isolated by a routine work-up. It was the expectation that the former would prove to be pseudo-*para* dibromide **4**, and the latter to be enriched in the desired pseudo-*ortho* dibromide **1**. In the event, DMF proved to be a suitable solvent leading to the recovery of 20% of pure **4** after filtration. The remaining 36% of the mass obtained from the solvent proved to be 56% pseudo-*ortho* dibromide **1** (Table 1, entry 3). However, there were considerable quantities of impurities present in this mixture probably due to intermolecular recombination of benzylic radical centres and the overall mass recovery was poor (56%). It was considered that lowering the temperature and/or decreasing the irradiation time would lead to cleaner isomerisation and improved mass recovery.

Further experimentation in a second screen established that the microwave isomerisation could indeed proceed at lower temperatures and decreased reaction times (Table 1, entries 4–10). In general as the temperature and reaction times were decreased, the amount of impurities were reduced and the mass recovery improved, but the extent of isomerisation decreased. The optimum conditions in this second screen, maximising purity, mass recovery and extent of isomerisation was found to be 180 °C for 6 min (Table 1, entry 6) to give the dibromide **1** in 38% conversion.[†]

To demonstrate this method for the gram-scale preparation of bromide **1**, we elected to pursue a 'scale-out' approach rather than scale-up approach. Ten consecutive 500 mg (total 5.00 g) microwave irradiation runs at 180 °C for 6 min on **4** in DMF (1 mL) were performed,[‡]

[†] A representative microwave experiment was carried out as follows: in a 10 mL microwave vessel was placed pseudo-*para* dibromide **4** (500 mg, 1.4 mmol) and DMF (1 mL). The microwave machine was programmed to heat the mixture to 180 °C with a hold time set as 6 min. The maximum pressure for the system was set at 17.2 bar and the power was set for 300 W. During the run the temperature was noted and is recorded in Table 1. The internal pressure during the run was typically found to be 7–8 bar. The reaction mixture was allowed to cool, diluted with DMF (2 mL) and the insoluble solid was filtered. The filtrate was poured into water (75 mL) and extracted with Et_2O (3 × 100 mL). The combined organics were washed with water (100 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated to give pseudo-*ortho* bromide **1** as a pale yellow powder.
[‡] The fifth run inexplicably generated a much higher internal pressure (14.1 bar) than general (ca. 7–8 bar) and the run was terminated after 1 min. The material resulting from the run was still included in the overall work-up.

and all the reaction mixtures combined in a single work-up. Pure pseudo-*para* dibromide **4** (2.43 g (49%)) was recovered by filtration. After work-up, 2.39 g (48%) of the desired pseudo-*ortho* dibromide **1** was obtained (97% purity;[§] mp 198–200 °C [lit.[2a] 195–205 °C; lit.[4a] 200–207 °C]). Given that the equilibrium constant for thermal isomerisation between **4** and **1** has previously shown to be $K = 1$,[4b] the results from this experiment (97% mass recovery; 49% **4**; 48% **1**) give close to a perfect fit with the ideal (100% mass recovery; 50% **4**; 50% **1**). The separation of the two isomers by filtration due to the insolubility of the 4,16-dibromide **4** in DMF at room temperature renders the isolation of each in pure form facile.

In conclusion, we have shown that the use of microwave irradiation is a rapid and convenient method for the isomerisation of 4,16-dibromo[2.2]paracyclophane **4** into 4,12-dibromo[2.2]paracyclophane **1** in DMF. A 'scale-out' approach has shown that the method is applicable for the gram-scale preparation of 4,12-dibromo[2.2]paracyclophane.

References and notes

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[§] The ^{1}H NMR spectrum showed 3% of residual 4,16-dibromo[2.2]paracyclophane **4**.