Tetrahedron Letters,Vol.23,No.50,pp 5335-5338,1982 0040-4039/82/505335-04$03.00/0
Printed in Great Britain

A FACILE SYNTHESIS OF [3^n]CYCLOPHANES, IN WHICH AROMATIC RINGS ARE CONNECTED WITH -CH_2-CO-CH_2- BRIDGES[1)]

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Summary: The title compounds, I, were synthesized by the dialkylation of TosMIC, II, with appropriate bis(halomethyl) compounds, III, under phase-transfer condition, followed by acid hydrolysis.

Cyclophanes constructed of aromatic rings connected with -CH_2-CO-CH_2- bridges are of particular interest, because of the capability of transforming carbonyl groups to many other functional groups. Furthermore, deuterated compounds prepared by reduction of C=O bonds may serve as suitable compounds for conformational analysis, because the deuteration of carbonyl groups sufficiently simplify the nmr spectra to make line shape analysis practical. Only several cyclophane-(one)$_n$[2)] have been reported because a few useful synthetic methods have been found as yet.

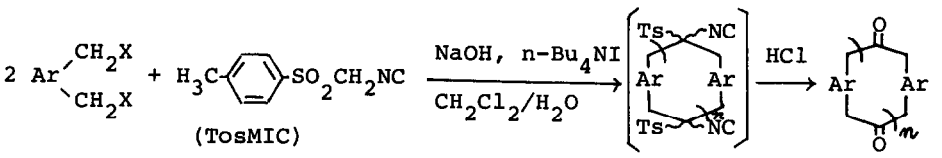
In this communication we report a simple and general method for the synthesis of [3^n]cyclophane-(one)$_n$ (n:2,3,4...), I or I', via coupling reaction between p-toluenesulfonylmethyl isocyanide (TosMIC[3)]), II, as carbonyl components and appropriate bis(halomethyl) compounds, III, followed by acid hydrolysis. The physical properties of the products are summarized in Table 1. The data of nmr spectra are shown in Fig. 1.

As an example of a one-step cyclization under phase-transfer condition (Scheme 1), [3^n]paracyclophane-(one)$_n$ (n:2,3,4...), I, were prepared by the dialkylation of TosMIC with 1 equiv of 1,4-bis(bromomethyl)benzene, followed by acid hydrolysis.

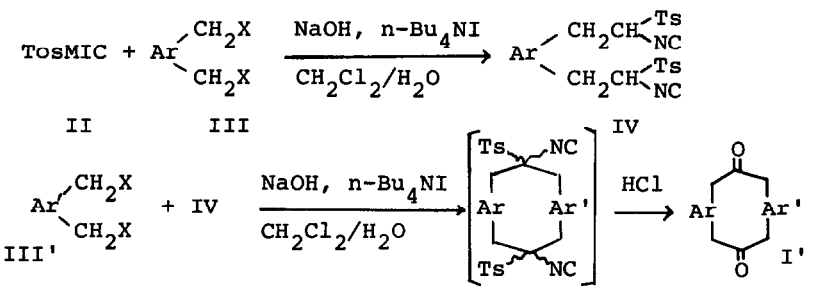
To a refluxed mixture of n-Bu_4NI (3.7 g, 10 mmol) in CH_2Cl_2 (1000 ml) and 30% aqueous NaOH solution (120 ml) was added a mixture of 1,4-bis(bromomethyl)benzene (15.8 g, 60 mmol) and TosMIC (11.7 g, 60 mmol) in CH_2Cl_2 (500 ml) over a period of 6 h. After the solution was refluxed for additional 2 h and allowed to cool, water (200 ml) was added. The organic layer was concentrated in vacuo. To the residue in CH_2Cl_2 (20 ml) was added conc HCl (20 ml) and stirred for 10 min at room temperature. After the usual work-up, the residue was chromatographed on silica-gel with CH_2Cl_2 to afford 1 (1.136 g), 2 (1.856 g), and 3 (988 mg)[4)].

As an example of a stepwise synthesis under phase-transfer condition (Scheme

2), [3.3]metacyclophane-2,11-dione, 4, was prepared by the coupling reaction of 1,3-bis(bromomethyl)benzene, and TosMIC derivative IV.



Scheme 1. Procedure A, one-step synthesis.



Scheme 2. Procedure B, stepwise synthesis.

1,3-Bis(2-isocyano-2-toluenesulfonylethyl)benzene, IV. TosMIC (5.28 g, 29.0 mmol), 1,3-bis(bromomethyl)benzene(1.95 g, 7.3 mmol) and n-Bu_4NI(0.74 g, 2 mmol) were dissolved in CH_2Cl_2(20 ml), and 30% aqueous NaOH solution (20 ml) was added. The mixture was stirred for 10 min at room temperature. After addition of water (100 ml), the reaction mixture was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated in vacuo. Recrystallization from CH_2Cl_2 gave colorless needles (1.77 g, 48.4%); mp 129°C(dec).

A mixture of n-Bu_4NI(144 mg, 4 mmol), CH_2Cl_2(300 ml), and 30% aqueous NaOH solution (20 ml) was stirred at reflux. To this mixture was added dropwise a solution of 1,3-bis(bromomethyl)benzene(958 mg, 1.94 mmol) and IV(380 mg, 1.44 mmol) in CH_2Cl_2(250 ml) over a period of 5.5 h. After the solution was refluxed for additional 2 h and allowed to cool, water (200 ml) was added. The organic layer was evaporated. To the residue in CH_2Cl_2(20 ml), conc HCl was added and stirred for 10 min at room temperature. After usual work-up, the residue was chromatographed on silica gel with CH_2Cl_2 to afford [3.3]metacyclophane-2,11-dione, 4, (209 mg).

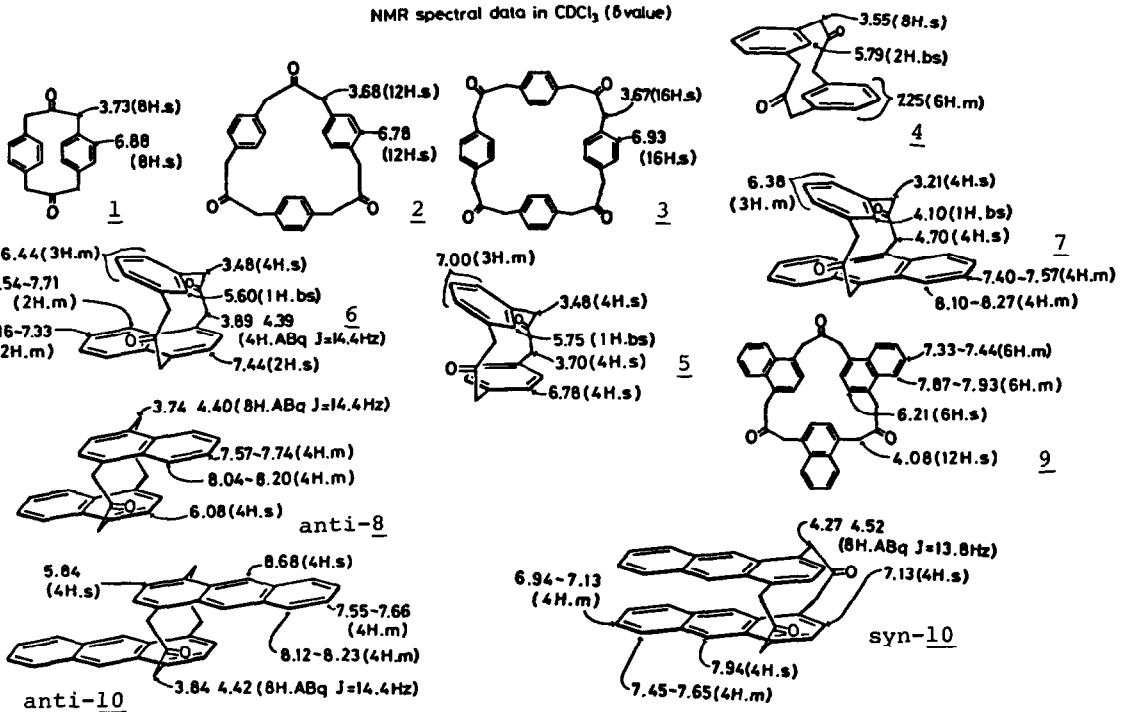
One of the advantages of this procedure over conventional synthetic methods[5] of [3.3]cyclophanes resides in mildness of the reaction conditions[6] and its brevity and simplicity. In addition, the results obtained reveal this procedure to be an efficient [3^2]cyclophane synthetic method, and an acceptable approach even for the synthesis of [3^3]cyclophanes and [3^4]cyclophanes as host molecule of inclusion compounds[7,8]. This synthetic method has been successfully applied to other cyclophane systems, such as [n]paracyclophanes[9], [3.3](1,3,5)cyclophane and several substituted [3^n]cyclophanes[10].

TABLE 1

Compd I[11]	°C mp	Prd	Cryst. solv	Cryst. form	Yield[15] %	νC=O cm^{-1}	M^+ (m/e)
[3.3]PCP-2,11-dione, 1[12]	266.5-267.7	A	B	w.n.	14.3	1689	264
[3.3.3]PCP-2,11,20-trione, 2[12]	220.0-221.4 (dec)	A	M	w.n.	23.4	1699 1710	396
[3.3.3.3]PCP-2,11,20,29-tetraone, 3[12]	272.6-276.5 (dec)	A	THF	w.n.	12.4	1707	528
[3.3]MCP-2,11-dione, 4[12],13)	194.0-195.0	A B	M	w.n.	48.5 55-60	1694	264
[3.3]MPCP-2,11-dione, 5[12]	170-171	B	M	w.pr.	52.0	1694	264
[3.3]MC(1,4)NP-2,11-dione, 6[12]	227.5-228	B	B	w.pr.	44.5	1695	314
[3.3]MP(9,10)ACP-2,15-dione, 7[12]	244-245	B	M-DM	y.pr.	39.3	1697	364
syn-[3.3](1,4)NP-2,13-dione, syn-8[12],14)		A			13.9		
anti-[3.3](1,4)NP-2,13-dione, anti-8[12]	>300	A	CCl_4-DM	w.pr.		1687	364
[3.3.3](1,4)NP-2,13,24-trione, 9[12]	273-277	A	M-DM	w.n.	6.9	1717	546
syn-[3.3](1,4)ACP-2,15-dione, syn-10	180-202 (dec)	A	M-DM	y.pr.	4.5	1695	464
anti-[3.3](1,4)ACP-2,15-dione, anti-10	136-156 (dec)	A	M-DM	y.pr.	2.0	1702	464

ACP=anthracenophane, B=benzene, DM=CH_2Cl_2, M=methanol, MCP=metacyclophane, MPCP=metaparacyclophane, n=needles, NP=naphthalenophane, PCP=paracyclophane, pr=prisms, prd=procedure, w=white, y=yellow.

NMR spectral data in $CDCl_3$ (δ value)



References and Notes

1) Presented at the 45th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1982.

2) a) Several cyclophane-α-diones were obtained from acyloins; [9]paracyclophane-4,5-dione, N. L. Allinger and L. A. Freiberg, J. Org. Chem., 27, 1490(1962); b) cis- and trans-[8]paracyclophane-3,6-dione-4-ene from [2.2](2,5)furanoparacyclophane, D. J. Cram and G. R. Knox, J. Am. Chem. Soc., 82, 2204(1961); c) [2.2]Paracyclophane-1,9- and-1,10-dione from 1,1,9,9- and 1,1,10,10-tetrabromides, D. J. Cram and R. C. Helgeson, J. Am. Chem. Soc., 86, 3515(1966); d) [3.3]Metacyclophane-1,10-dione from 3-cyanopropylbenzene and $Cr(CO)_6$. M. F. Semmelhack, Y. Thebtaranoth, and L. Keller, J. Am. Chem. Soc., 99, 959(1977); e) [3.3]Metacyclophane-diones from [2.2]metacyclophane-1,10-dione with diazomethane, D. Krois and H. Lehner, J. C. S., Perkin I, 477(1982).

3) O. Possel and A. M. van Leusen, Tetrahedron Lett., 4229(1977).

4) Besides these, [3^5]paracyclophane-pentaone (331 mg, 4.2%), [3^6]paracyclophane-hexaone (152 mg, 2.0%), and [3^n]paracyclophane-(one)$_n$ (n>6, 867 mg, 10.9%) were obtained.

5) a) T. Shinmyozu, T. Inazu, and T. Yoshino, Chem. Lett., 1976, 1405; b) T. Shinmyozu, K. Kumagae, T. Inazu, and T. Yoshino, Chem. Lett., 1977,43; c) D. T. Longone, S. H. Kusefoglu, and J. A. Gladsz, J. Org. Chem., 42, 2787 (1977); d) M. W. Haenel, A. Flatow, V. Taglieber, and H. Al Staab, Tetrahedron Lett., 1977, 1733; e) T. Otsubo, M. Kitasawa, and S. Misumi, Chem. Lett., 1977, 977; f) L. Rossa and F. Vögtle, J. Chem. Res.(S), 1977, 3010.

6) The coupling reactions can be carried out under usual conditions (e.g., NaH, DMSO).

7) a) J.-L. Pierre, P. Baret, P. Chautemps, and M. Armand, J. Am. Chem. Soc., 103, 2986(1981); b) [3.3.3]Paracyclophane-CF_3SO_3Ag complex was isolated as white powder ($CDCl_3$: δ 6.89s, aromatic H; δ 2.66 m, benzylic H).

8) Y. Urushigawa, T. Inazu, and T. Yoshino, Bull. Chem. Soc. Jpn., 44, 2546(1971).

9) [10]- and [9]paracyclophane and [8]paracyclophane-4-ene.

10) To be published.

11) New compounds have been fully characterized by spectra and elemental analyses.

12) Parent [3^n]cyclophanes were prepared by Wolff-Kishner reduction of carbonyl groups in good yields.

13) Considered to adopt an anti conformation.

14) Not isolated in pure state.

15) Yields are not optimized.

(Received in Japan 4 September 1982)