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Chloromethylation of *syn*-[2.*n*]metacyclophanes and application toward multi-bridged cyclophane synthesis

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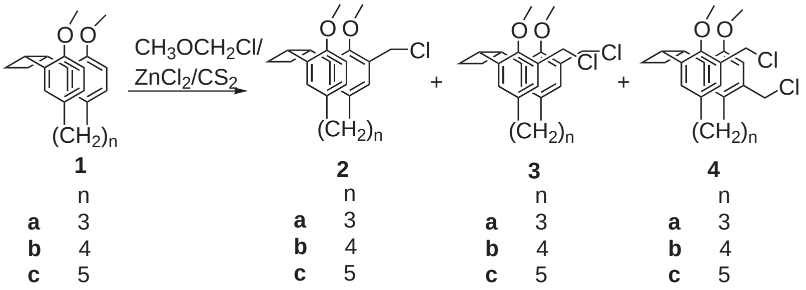
Abstract—Dimethoxy[2.*n*]metacyclophanes ($n = 3–5$) gave the pseudo-*ipso* or pseudo-*ortho* products of dichlorides by chloromethylation. Dichlorides were converted to furnish multi-bridged cyclophanes by changing the chloromethyl group to a vinyl group. © 2000 Elsevier Science Ltd. All rights reserved.

The functionalizations of benzene rings on cyclophanes have been studied to make a unique structure having chirality, binding ability, catalytic activity, etc.[1] [2.2]Meta- and paracyclophanes were used as starting materials for these purposes.[2–5] However, the reactivity of the *anti*-conformer of metacyclophanes is only known in some reactions.[3] Accordingly, the investigation of reactivity by using the *syn*-conformer of metacyclophane will be expected to give much information in cyclophane chemistry. Dimethoxy[2.*n*]metacyclophane fused cyclobutane rings fit the purpose to systematically examine the reactivity, because they are readily obtained in a series of different chain lengths and take exclusively the *syn*-conformation and arrange in a face-to-face fashion between two benzene rings.[4,5] Therefore, we investigated their reactivity in chloromethylation. In this paper, we report the synthesis of functionalized *syn*-[2.*n*]metacyclophanes and their application toward multi-bridged cyclophanes.

Dimethoxy[2.*n*]metacyclophanes **1** ($n = 3–5$) were used in this chloromethylation reaction as shown in Scheme 1. This reaction was performed with **1** (30 mmol/l), chloromethyl methyl ether (2–16 equiv.), and $ZnCl_2$ (0.5–1.0 equiv.) in CS_2 for 2–72 h at 0°C–rt. After acidic extraction, a mixture was purified by column chromatography (benzene/ethyl acetate = 9/1). The results are summarized in Table 1. Firstly, the conditions for this reaction were examined using [2.5]metacyclophane **1c** as a standard compound. Generally speaking, the product distribution in this reaction was greatly affected by the reaction time. That is, **1c** gave both dichlorides **3c** and **4c** after 2 h (entry 15) and **3c** as the sole product after 48–72 h (entries 12–14). These results strongly suggest that the pseudo-*ortho* product **4** is produced kinetically.

[2.4]Metacyclophane **1b** also gave **3b** and **4b**. Interestingly, the product ratio of **4b** to **3b** is much higher than



Scheme 1.

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Table 1. The reaction conditions and product distribution of chloromethylation

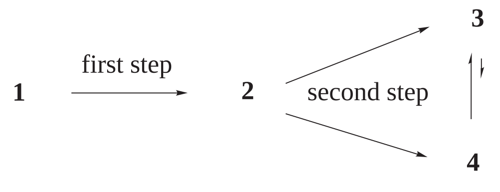
Entry	Compound	Conditions				Yield (%)			
		CH_3OCH_2Cl (equiv.)	$ZnCl_2$ (equiv.)	Time (h)	Temp. (°C)	**2**	**3**	**4**	Total
1	**1a**	2.0	0.5	2	0	20	0	0	20
2	**1a**	4.0	1.0	2	rt	0	9.2	6.1	15
3	**1a**	8.0	0.5	2	0	26	4.8	1.6	32
4	**1a**	8.0	1.0	2	0	12	9.9	3.8	26
5	**1a**	8.0	1.0	2	rt	0	12	6.9	19
6	**1b**	4.0	1.0	18	rt	0	21	6.6	28
7	**1b**	4.0	1.0	72	rt	0	21	3.8	25
8	**1b**	16.0	0.5	2	rt	0	34	23	57
9	**1b**	16.0	1.0	2	rt	0	34	28	62
10	**1b**	16.0	0.5	4	0	0	24	37	61
11	**1b**	16.0	1.0	3	0	0	34	23	57
12	**1c**	2.0	1.0	72	rt	0	42	0	42
13	**1c**	4.0	1.0	48	rt	0	82	0	82
14	**1c**	4.0	1.0	72	rt	0	53	0	53
15	**1c**	8.0	1.0	2	rt	0	45	27	72

that of **4c** to **3c**. In this case, pseudo-*ortho* product **4b** was obtained even after 72 h (entry 7), although its yield decreased considerably. [2.3]Metacyclophane **1a** also gave **3a** and **4a**, although the total yield decreased. In particular, monochloride **2a**, which demonstrated that this reaction proceeded stepwise, was obtained only in this system (entries 1, 3, and 4). Accordingly, the reactivity of **1a** is less than that of **1b** and **1c**.

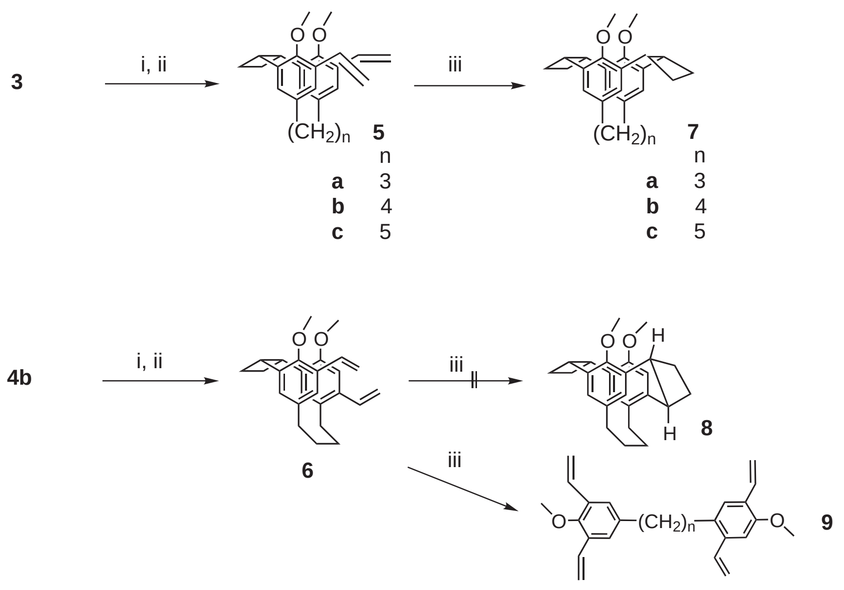
The mechanistic features are depicted in Scheme 2.[2] In the first step, **1** gave monochloride **2** in the usual manner. In the second step, **2** mainly gave pseudo-*ipso* isomer **3**. In fact, MOPAC (PM3) calculations of **2** show that the electron density at the pseudo-*ipso* position is much higher than that at the pseudo-*ortho* position. However, the steric hindrance of pseudo-*ipso* position for **2** is greater than that of the pseudo-*ortho* position due to the concealment of the CH_2Cl group on the other benzene ring. As a result of these reasons, the reactivity of both reaction sites is competitive. Accordingly, the pseudo-*ortho* isomer **4** was moderately produced in the initial stage of the second step. By proceeding this reaction, the ratio of pseudo-*ipso* isomer **3** for pseudo-*ortho* isomer **4** gradually increased through the equilibrium. In fact, MM2 calculations show that the steric energy of **3** is less by ca. 2 kcal/mol than that of **4**. As mentioned above, each regioisomer **3** or **4**, which have bifunctional groups that can easily transform to another functional groups, can be easily obtained by controlling the reaction conditions.

The structure of products was determined by ^1H NMR spectroscopy.[4,9] The molecular symmetry of **2**–**4** was also used to determine the structure because **2** and **4** both had C_1 symmetry and **3** had C_s symmetry. The essential spectroscopic aspects are as follows: (1) monochloride **2** shows two doublets (δ 6.68 and 7.10, $J = 2.0$ Hz) of Ar protons with *meta* coupling on the substituted Ar ring; (2) dichloride **3** only showed two *meta* coupling peaks (δ 6.68–6.82 and 7.13–7.25, $J = 2.0–2.1$ Hz) as a result of the disappearance of the *ortho* couplings of Ar protons on **2**; (3) dichloride **4** showed two peaks (δ 6.64–6.80 and 7.11–7.17, $J = 2.0$ Hz) for one Ar ring with *meta* coupling and two singlets (δ 6.34–6.55 and 6.98–7.30) for the other Ar ring.

The application of **3** and **4** toward the synthesis of multi-bridged cyclophanes is examined to clarify the reactivity of vinyl groups at different positions.[6,7] Dichlorides **3** and **4b** (6.2 mmol) were directly converted to the vinyl groups of **5** and **6** with PPh_3 (0.19 mol) in benzene for 12 h under reflux and then 35% HCHO (92 ml) and aq. NaOH (0.34 mol) in THF at rt for 12 h in 73–100% yields, as shown in Scheme 3. [2+2]Photocycloaddition of **5** under a 400 W high-pressure Hg lamp for 2 h afforded the three-bridged cyclophane **7** as only one isomer in 67–95% yield. The structure of **7** was assigned using ^1H NMR spectroscopy and comparing the results with the reference compounds.[7] This result shows that pseudo-*ipso* isomers become potential precursors for making multi-bridged cyclophanes. On the other hand, photoirradiation of **6** could not afford the desired product **8**. In fact, this reaction only produced the ring-opened product **9** in 9.5% yield. Generally speaking, [2+2]photocycloaddition is known to proceed when the distance between two olefin moieties fits in the range 3.6–4.1 Å.[8] MM2 calculations showed that the distance between two vinyl groups is 3.8–4.1 Å for **5** and 4.5 Å for **6**. Accordingly, **5** can be converted to **7**, but **6** cannot be converted to **8**.



Scheme 2.



Scheme 3. (i) PPh_3/benzene. (ii) HCHO/NaOH/THF. (iii) *hv* (Pyrex)/benzene

In conclusion, dimethoxy[2.*n*]metacyclophanes **1** ($n = 3-5$) gave the pseudo-*ipso* or pseudo-*ortho* products of dichlorides as regioisomers. Dichlorides **3** were a powerful precursor for making multi-bridged cyclophanes by changing the chloromethyl group to a vinyl group. Further investigations are currently in progress and will be reported elsewhere.

Acknowledgements

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9. Compd; anal. calcd (found); MS (M^+); ^1H NMR δ (intensity, multiplicity, *J* in Hz). **3c**; calcd for $C_{25}H_{30}Cl_2O_2 \cdot 2H_2O$: C, 63.96 (63.77); H, 7.30 (7.31); 432; 0.27 (1H, m), 0.97 (1H, m), 1.59 (2H, m), 1.83 (2H, m), 2.48 (4H, m), 2.57 (2H, m), 2.76 (2H, m), 3.69 (6H, s), 4.37 (2H, d, 11), 4.48 (2H, m), 4.55 (2H, d, 11), 6.82 (2H, d, 2.1), 7.25 (2H, d, 2.1). **4c**; calcd for $C_{25}H_{30}Cl_2O_2 \cdot 2H_2O$: C, 63.96 (63.87); H, 7.30 (7.36); 432; 0.30 (1H, m), 1.01 (1H, m), 1.65 (1H, m), 1.86 (2H, m), 2.19 (1H, m), 2.40 (1H, m), 2.46 (2H, m), 2.68 (3H, m), 2.79 (2H, m), 3.63 (3H, s), 3.64 (3H, s), 4.38 (1H, d, 11), 4.44 (1H, d, 11), 4.44 (1H, m), 4.53 (1H, d, 11), 4.56 (1H, d, 11), 4.64 (1H, m), 6.55 (1H, s), 6.80 (1H, d, 2.0), 7.17 (1H, s), 7.30 (1H, d, 2.0). **5c**; calcd for $C_{27}H_{32}O_2$: C, 83.53 (83.57); H, 8.27 (8.11); 388; 0.36 (1H, m), 0.95 (1H, m), 1.59 (2H, m), 1.84 (2H, m), 2.46 (4H, m), 2.54 (2H, m), 2.76 (2H, m), 3.57 (6H, s), 4.54 (2H, m), 5.14 (2H, dd, 1.2 and 11), 5.58 (2H, dd, 1.2 and 18), 6.82 (2H, dd, 11 and 18), 6.94 (2H, d, 2.0), 7.23 (2H, d, 2.0).