Pergamon

Tetrahedron Letters 42 (2001) 1919–1921

TETRAHEDRON LETTERS

The formylation of *syn*-[2.*n*]metacyclophanes and application to multi-bridged cyclophane synthesis

Yukihiro Okada, Masatoshi Kaneko and Jun Nishimura*

Department of Chemistry, Gunma University, Tenjin-cho, Kiryu 376-8515, Japan

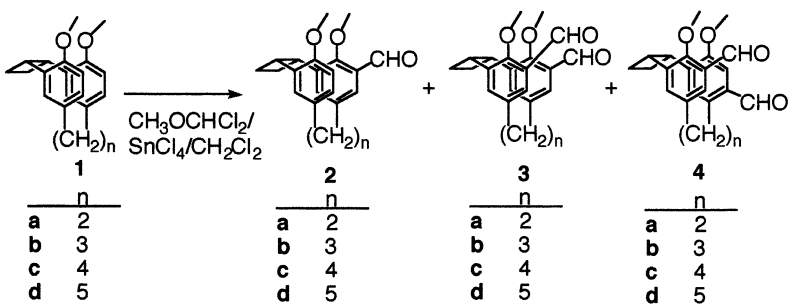
Received 9 November 2000; revised 14 December 2000; accepted 28 December 2000

Abstract—Dimethoxy[2.*n*]metacyclophanes ($n=2$–5) were formylated to produce pseudo-*ipso* and/or pseudo-*ortho* dialdehydes. The formyl group was transformed to a cinnamyl group to furnish multi-bridged cyclophanes.

The functionalization of metacyclophanes has mainly utilized the *anti*-conformer due to the synthetic difficulty of the conformationally stable *syn*-conformer.[1,2] Compared with paracyclophanes, *syn*-metacyclophanes have attracted much interest in their structures and reactivities. However, little is known of their behavior for some functionalizations.[3–5] Dimethoxy[2.*n*]metacyclophanes with a fused cyclobutane ring have demonstrated great potential for systematic examination of the reactivity, because they exclusively adopt a *syn* conformation.[4] Although their reactivity was reported in chloromethylation, the chloromethyl group incurs some limitations when it transformed other functional groups directly.[3] Therefore, we investigated their reactivity in formylation, because formyl groups are easily converted to many functional groups. In this paper, we report the formylation of *syn*-[2.*n*]metacyclophanes and their application to form multi-bridged cyclophanes.

Dimethoxy[2.*n*]metacyclophanes **1** ($n=2$–5) were used in this formylation, as shown in Scheme 1. This reaction was performed with **1** (40 mmol/l), dichloromethyl methyl ether (2–30 equiv.), and $SnCl_4$ (2–30 equiv.) in dry CH_2Cl_2 for 4–48 h at rt. After extraction, the mixture was purified by column chromatography (benzene/ethyl acetate = 19/1). The results are summarized in Table 1. Note the following: (1) **1a** only gave dialdehyde **3a** in 7.6–18% yields under several different reaction conditions (entries 1–4). On the other hand, **1b–d** gave both dialdehydes **3** and **4** in 25–50 and 6.8–16% yields, respectively (entries 5–12). (2) **1d** also gave monoaldehyde **2d** in 4.6–19% yields (entries 11 and 12). (3) Total yields gradually increased when the oligomethylene chain changed from $n=2$ to 5, probably due to the stability of the starting materials.

The structural determination was performed using ^1H NMR spectroscopy.[4,9] The molecular symmetry of **2–4**



Scheme 1.

Keywords: cyclophane; formylation; photocycloaddition.

* Corresponding author.

0040-4039/01/$ - see front matter
PII: S0040-4039(01)00021-1

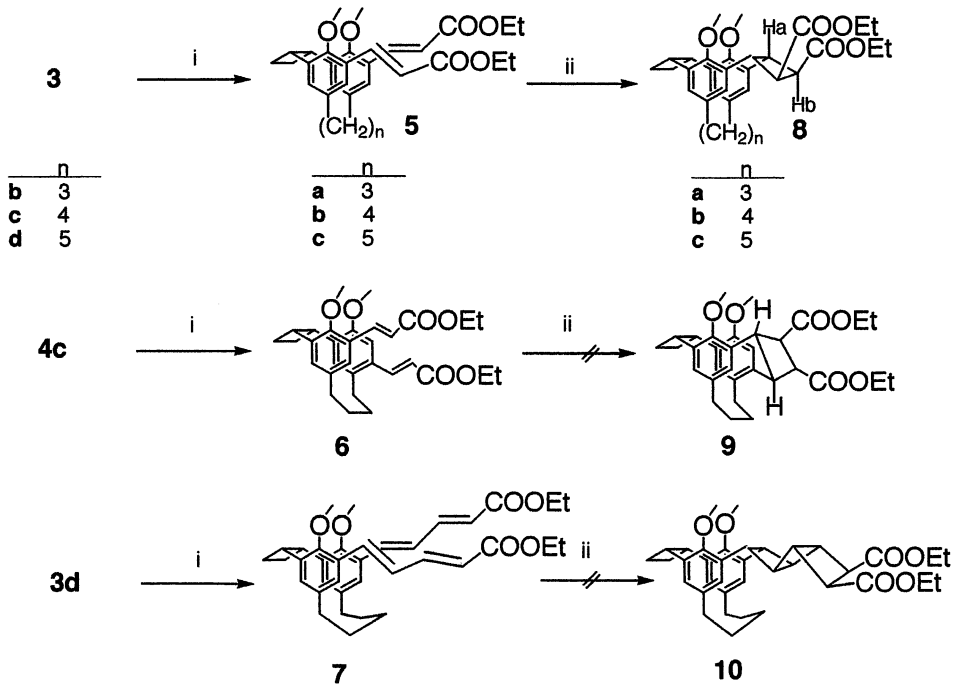
Table 1. The reaction conditions and product distribution of formylation in CH_2Cl_2

Entry	Compd	Conditions				Yield (%)			
		CH_3OCHCl_2 (equiv.)	$SnCl_4$ (equiv.)	Time (h)	Temp. (°C)	**2**	**3**	**4**	Total
1	**1a**	2.0	2.0	4	rt	0	18	0	18
2	**1a**	5.0	5.0	4	rt	0	14	0	14
3	**1a**	5.0	5.0	48	rt	0	7.6	0	7.6
4	**1a**	20	20	48	rt	0	8.4	0	8.4
5	**1b**	10	10	48	rt	0	30	12	42
6	**1b**	20	20	48	rt	0	29	12	41
7	**1c**	5.0	5.0	48	rt	0	27	8.5	36
8	**1c**	10	10	48	rt	0	45	11	56
9	**1c**	20	20	48	rt	0	50	6.8	57
10	**1c**	30	30	48	rt	0	35	10	45
11	**1d**	10	10	48	rt	4.6	34	12	51
12	**1d**	20	20	48	rt	19	25	16	60

was also used in this determination because of the C_1 symmetry for **2** and **4** and the C_s symmetry for **3**. The essential spectroscopic aspects were as follows: (1) monoaldehyde **2d** showed two doublets (δ 7.19 and 7.43, $J=1.9$ Hz) of Ar protons with *meta* coupling on the substituted Ar ring. (2) Dialdehyde **3** lost the *ortho* couplings of Ar protons in **2** and only showed two *meta* coupling peaks (δ 7.16–7.21 and 7.46–7.54, $J=1.9$–2.2 Hz). (3) Dialdehyde **4** showed two Ar ring peaks (δ 7.10–7.13 and 7.44–7.47, $J=2.0$–2.1 Hz) with *meta* coupling and the other two Ar ring singlets (δ 6.87–6.89 and 7.16–7.20).

The application of **3** and **4** toward the synthesis of three-bridged cyclophanes was examined in order to clarify the reactivity of the cinnamyl ester groups at different positions.[3,6] Dialdehydes **3** and **4c** (0.38 mmol) were directly converted to *trans*-olefins, **5**–**7**, with $(EtO)_2POCH_2COOEt$ or $(EtO)_2POCH_2CH{=}CHCOOEt$ (1.5 mmol) and NaH (2.5 mmol) in dry THF at rt for 12 h in 60–89% yields, as shown in Scheme 2.[5,6]

[2+2]Photocycloaddition of **5** under a 400 W high-pressure Hg lamp for 10–30 min easily afforded three-bridged cyclophane **8** as a single isomer in 57–100% yields. The structure of **8** was assigned by ^1H NMR spectroscopy.[5,7] The protons of the cyclobutane ring formed from the cinnamyl group (located at δ 3.67–3.79 and 4.59–4.67 $J=6.1$ Hz) demonstrated a *trans* configuration. Moreover, its Ha protons clearly exhib-



Scheme 2. (i) $(EtO)_2POCH_2COOEt$ or $(EtO)_2POCH_2CH{=}CHCOOEt$/NaH/THF; (ii) $h\nu$ (Pyrex)/benzene.

ited an NOE interaction with the methoxyl groups. Methine protons attached at the carbon with COOEt have another NOE interaction with aromatic protons. Accordingly, **8** was shown to be the isomer in Scheme 2. This result shows that pseudo-*ipso* isomers become potential precursors for synthesizing multi-bridged cyclophanes. On the other hand, photoirradiation of **6** did not afford any desired product, such as **9**, at all. Generally speaking, [2+2]photocycloaddition of cinnamyl groups is known to proceed when they are parallel and the distance between two olefin moieties is in the range 3.6–4.1 Å.[8] MM2 calculations showed that the distance between two olefin groups is 3.8–4.1 Å for **5** and 5.6 Å for **6**, and the former is nearly parallel but the latter is not. Accordingly, **5** can be converted to **8**, but **6** cannot be converted to **9**.

Photoirradiation of **7** did not afford the desired product **10**. Olefin **7** mainly showed complex isomerization of its olefin moieties, as evidenced by NMR spectroscopy. This result suggests that the diene moieties introduced on metacyclophane consumed the singlet energy in the isomerization more than those introduced on [2.2]paracyclophane compared with the reported results.[6] The results are rationalized by the difference in diene arrangements between **7** and [2.2]paracyclophane. The former has a rather open arrangement of diene moieties, while the latter has a considerably tight one. Accordingly, the behavior of **7** resembles that of an isolated *trans*-cinnamyl system.

In conclusion, dimethoxy[2.*n*]metacyclophanes **1** gave pseudo-*ipso* and/or pseudo-*ortho* dialdehydes. Dialdehydes **3** are potential precursors for synthesizing multi-bridged cyclophanes by changing the formyl group to a cinnamyl one. Further investigation is under way and will be reported elsewhere.

Acknowledgements

This work was partly supported by grants from the Ministry of Education, Science, and Culture, Japan.

References

1. *Cyclophanes, I and II*; Keehn, P. M.; Rosenfeld, S. M., Eds.; Academic Press: New York, 1983.
2. (a) Yamato, T.; Matsumoto, J.; Tokuhisa, K.; Shigekuni, M.; Suehiro, K.; Tashiro, M. *J. Org. Chem.* **1992**, *57*, 395; (b) Yamato, T.; Ide, S.; Tokuhisa, K.; Tashiro, M. *J. Org. Chem.* **1992**, *57*, 271.
3. Okada, Y.; Kaneko, M.; Nishimura, J. *Tetrahedron Lett.*, in press.
4. (a) Okada, Y.; Mabuchi, S.; Kurahayashi, M.; Nishimura, J. *Chem. Lett.* **1991**, 1345; (b) Okada, Y.; Ishii, F.; Kasai, Y.; Nishimura, J. *Tetrahedron* **1994**, *42*, 12159.
5. (a) Okada, Y.; Sugiyama, K.; Kurahayashi, M.; Nishimura, J. *Tetrahedron Lett.* **1991**, *32*, 2367; (b) Okada, Y.; Ishii, F.; Akiyama, I.; Nishimura, J. *Chem. Lett.* **1992**, 1579.
6. (a) Hopf, H.; Greiving, H.; Jones, P. G.; Bubenitschek, P. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 685; (b) Cohen, M. D.; Schmidt, G. M. J. *J. Chem. Soc., Chem. Commun.* **1964**, 2000.
7. Okada, Y.; Sugiyama, K.; Wada, Y.; Nishimura, J. *Tetrahedron Lett.* **1990**, *31*, 107.
8. Schmidt, G. M. *J. Chem. Soc., Chem. Commun.* **1964**, 2014.
9. Compound: ^{1}H NMR δ (intensity, multiplicity, J in Hz). **2d**: 0.11 (1H, m), 0.92 (1H, m), 1.50–1.80 (4H, m), 2.40–2.80 (8H, m), 3.64 (3H, s), 3.66 (3H, s), 4.50 (1H, m), 4.52 (1H, m), 6.52 (1H, d, 8.0), 6.79 (1H, dd, 1.9 & 8.0), 7.11 (1H, d, 1.9), 7.19 (1H, d, 1.9), 7.43 (1H, d, 1.9), 10.07 (1H, s). **3a**: 2.50–3.10 (8H, m), 3.69 (6H, s), 4.07 (2H, m), 7.16 (2H, d, 2.0), 7.46 (2H, d, 2.0), 10.01 (2H, s). **3b**: 1.45 (1H, m), 2.33 (1H, m), 2.53 (2H, m), 2.69 (4H, m), 3.06 (2H, m), 3.70 (6H, s), 4.65 (2H, m), 7.17 (2H, d, 2.2), 7.48 (2H, d, 2.2), 10.03 (2H, s). **3c**: 1.45 (2H, m), 2.00 (2H, m), 2.44 (2H, m), 2.52 (2H, m), 2.65 (4H, m), 3.73 (6H, s), 4.60 (2H, m), 7.17 (2H, d, 2.1), 7.54 (2H, d, 2.1), 10.11 (2H, s). **3d**: 0.12 (1H, m), 0.94 (1H, m), 1.57 (2H, m), 1.77 (2H, m), 2.46 (4H, m), 2.58 (2H, m), 2.72 (2H, m), 3.69 (6H, s), 4.54 (2H, m), 7.21 (2H, d, 1.9), 7.46 (2H, d, 1.9), 10.10 (2H, s). **4b**: 1.50 (1H, m), 2.38 (2H, m), 2.56 (1H, m), 2.72 (4H, m), 3.10 (1H, m), 3.60 (3H, s), 3.66 (3H, s), 3.87 (1H, m), 4.61 (1H, m), 4.79 (1H, m), 6.87 (1H, s), 7.13 (1H, d, 2.0), 7.20 (1H, s), 7.44 (1H, d, 2.0), 10.01 (1H, s), 10.04 (1H, s). **4c**: 1.34 (1H, m), 1.60 (1H, m), 1.98 (1H, m), 2.09 (1H, m), 2.37 (3H, m), 2.57 (1H, m), 2.67 (3H, m), 3.47 (1H, m), 3.65 (3H, s), 3.71 (3H, s), 4.57 (1H, m), 4.71 (1H, m), 6.88 (1H, s), 7.10 (1H, d, 2.1), 7.16 (1H, s), 7.46 (1H, d, 2.1), 10.07 (1H, s), 10.13 (1H, s). **4d**: 0.11 (1H, m), 0.93 (1H, m), 1.50–1.90 (4H, m), 2.45–2.80 (6H, m), 3.13 (2H, m), 3.63 (3H, s), 3.68 (3H, s), 4.55 (1H, m), 4.70 (1H, m), 6.89 (1H, s), 7.11 (1H, d, 2.0), 7.18 (1H, s), 7.47 (1H, d, 2.0), 10.09 (1H, s), 10.15 (1H, s). **5a**: 1.30 (6H, t, 7.0), 1.48 (1H, m), 2.28 (1H, m), 2.47 (2H, m), 2.61 (2H, m), 2.68 (2H, m), 2.99 (2H, m), 3.54 (6H, s), 4.21 (4H, q, 7.0), 4.58 (2H, m), 6.21 (2H, d, 18), 6.88 (2H, dd, 1.8), 7.27 (2H, d, 1.8), 7.64 (2H, d, 18). **5b**: 1.30 (6H, t, 7.0), 1.43 (2H, m), 1.99 (2H, m), 2.34 (2H, m), 2.46 (2H, m), 2.62 (4H, m), 3.58 (6H, s), 4.20 (4H, q, 7.0), 4.36 (2H, m), 6.27 (2H, d, 16), 6.88 (2H, d, 1.8), 7.32 (2H, d, 1.8), 7.72 (2H, d, 16). **5c**: 0.24 (1H, m), 0.95 (1H, m), 1.29 (6H, t, 7.0), 1.59 (2H, m), 1.85 (2H, m), 2.47 (4H, m), 2.58 (2H, m), 2.77 (2H, m), 3.61 (6H, s), 4.21 (4H, q, 7.0), 4.35 (2H, m), 6.31 (2H, d, 16), 6.99 (2H, d, 1.8), 7.31 (2H, d, 1.8), 7.77 (2H, d, 16). **6**: 1.23 (6H, t, 7.0), 1.42 (1H, m), 1.86 (1H, m), 1.93 (1H, m), 2.18 (1H, m), 2.27 (3H, m), 2.41 (1H, m), 2.53 (3H, m), 2.82 (1H, m), 3.49 (3H, s), 3.52 (3H, s), 4.16 (4H, q, 7.0), 4.42 (1H, m), 4.53 (1H, m), 6.04 (1H, d, 16), 6.22 (1H, d, 16), 6.48 (1H, s), 6.73 (1H, d, 1.8), 7.00 (1H, s), 7.12 (1H, d, 1.8), 7.66 (1H, d, 16), 7.12 (1H, d, 16). **8a**: 1.28 (6H, t, 7.0), 2.03 (2H, m), 2.40 (2H, m), 2.50 (2H, m), 2.70 (4H, m), 3.42 (6H, s), 3.79 (2H, d, 6.1), 4.24 (4H, q, 7.0), 4.50 (2H, m), 4.67 (2H, d, 6.1), 6.44 (2H, d, 1.8), 6.60 (2H, d, 1.8). **8b**: 1.30 (6H, t, 7.0), 1.80 (4H, m), 2.26 (4H, m), 2.36 (2H, m), 2.44 (2H, m), 3.43 (6H, s), 3.74 (2H, d, 6.1), 4.24 (4H, q, 7.0), 4.46 (2H, m), 4.63 (2H, d, 6.1), 6.24 (2H, d, 1.5), 6.39 (2H, d, 1.5). **8c**: 1.24 (6H, t, 7.0), 1.44 (2H, m), 1.51 (4H, m), 2.27 (5H, m), 2.37 (3H, m), 3.38 (6H, s), 3.67 (2H, d, 6.1), 4.18 (4H, q, 7.0), 4.40 (2H, m), 4.59 (2H, d, 6.1), 6.21 (2H, d, 1.5), 6.35 (2H, d, 1.5).