Medium-sized cyclophanes. Part 59.[1] Preparation and acetylation of some 9-substituted [3.3]metaparacyclophanes

J. Chem. Research (S), 2002, 62–63
J. Chem. Research (M), 2002, 0256–0270

Takehiko Yamato[a]*, Kozo Noda[a] and Kan Tanaka[b]

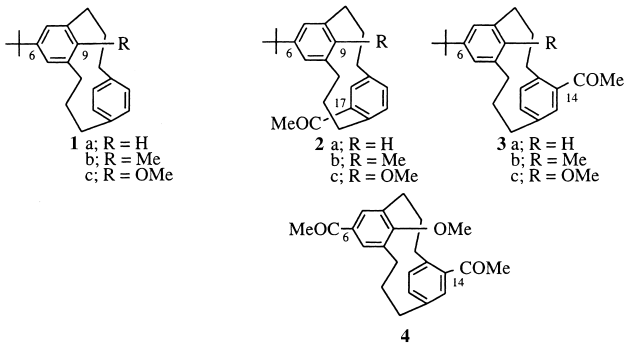
[a]*Department of Applied Chemistry, Faculty of Science and Engineering, Saga University, Honjo-machi 1, Saga 840-8502 Japan*
[b]*Department of Industrial Chemistry, Faculty of Science and Engineering, Tohwa University, 1-1-1 Chikushigaoka, Minami-ku, Fukuoka-shi, Fukuoka 815-8510, Japan*

The acetylation of 6-*tert*-butyl-9-methyl- (**1b**) and 6-*tert*-butyl-9-methoxy[3.3]metaparacyclophane **1c** with 1.1 equiv. of acetyl chloride in CH_2Cl_2 solution in the presence of $AlCl_3$ $MeNO_2$ afforded 6-*tert*-butyl-17-acetyl-9-methyl- (**2b**) and 6-*tert*-butyl-14-acetyl-9-methoxy[3.3]metaparacyclophane (**3c**) in 22% and 88% yields, respectively; different orientation for the electrophilic substitution was observed depending on the substituent at C(9) position.

Keywords: cyclophanes, acetylation

[3.3]MPCP (MPCP = metaparacyclophane) was first prepared by Shinmyozu and co-workers[2] using (*p*-tolylsulfonyl)methyl isocyanide (TosMIC) as the cyclisation reagent, followed by Wolff–Kishner reduction. The meta-bridged benzene ring of [3.3]MPCP **1** has been shown to undergo conformational flipping[2,3] with a significantly lower energy barrier than that in [2.2]MPCP (*ca* 80 kJ/mol).[4]

On the other hand, Cram reported[5] the acetylation of [2.2]MPCP with acetyl chloride in the presence of aluminum chloride to afford three kinds of monoacetylated derivatives along with the tetracyclic ketone. However, since the monoacetylated [2.2]MPCPs at the *para* benzene ring equilibrate by ring rotation at room temperature, the orientation of acetylation to the *para*-bridged benzene ring of [2.2]MPCP has not been established. We have investigated the acetylation of 8-substituted [2.2]MPCPs and different directive effects of 8-substituents on the para-bridged benzene ring on the position of electrophilic substitution were first observed with 8-substituted [2.2]MPCP derivatives.[6] Thus there is substantial interest in investigating the acetylation of larger ring sized 9-substituted [3.3]MPCPs, in which the through-space electronic interactions between two benzene rings could be reduced in comparison with those of [2.2]MPCPs. Also in order to study the orientation of acetylation of *para*-bridged benzene ring in detail, we have attempted to protect the 6-position of [3.3]MPCPs by the bulky *tert*-butyl substituent. We report here on the acetylation of 6-*tert*-butyl 9-substituted [3.3]MPCPs.



1 a; R = H, b; R = Me, c; R = OMe
2 a; R = H, b; R = Me, c; R = OMe
3 a; R = H, b; R = Me, c; R = OMe
4

Table 1 Acetylation of 6-*tert*-butyl-9-substituted [3.3]metaparacyclophanes **1** with acetyl chloride in the presence of aluminum chloride[a]

Run	Substrate	Catalyst	AcCl/**1** mol/mol	Product (%)[b]	Recovery of **1**
1	**1a**	A	1.1	–	100
2	**1a**	B	1.1	**2a** (95) [83]	5
3	**1b**	A	1.1	**2b** (22) [12]	78
4	**1b**	A	3.1	**2b** (94) [88]	6
5	**1c**	A	1.1[c]	**3c** (88) [73]	0
6	**1c**	A	3.1	**4** (100) [85]	0

[a]A: $AlCl_3$-$MeNO_2$; B: $AlCl_3$; [$AlCl_3$]/[AcCl] = 1.5/1 (mol/mol). [b]Yields are determined by GLC analysis. Isolated yields are shown in square bracket. [c]A trace amount of diacetylated product **4** was obtained.

Results and discussion

6-*tert*-Butyl 9-substituted [3.3]MPCPs **1** were prepared by coupling of 1,4-bis(bromomethyl)benzene with the TosMIC adduct of 2,6-bis(bromomethyl)-4-*tert*-butyl substituted benzenes under highly diluted conditions in dimethylformamide with an excess sodium hydride, followed by Wolff–Kishner reduction according to the reported procedure.[7]

Attempted acetylation of 6-*tert*-butyl[3.3]MPCP **1a** with 1.1 equiv. of acetyl chloride in methylene dichloride solution in the presence of $AlCl_3$–$MeNO_2$ failed. Only recovery of the starting compound in quantitative yield resulted. However, when aluminum chloride alone is employed as a catalyst under the same conditions, the 17-acetyl substitution product **2a** was obtained in 95% yield along with the recovery of the starting compound **1a**. Interestingly, acetylation of 6-*tert*-butyl 9-methyl[3.3]MPCP **1b** with 1.1 equiv. of acetyl chloride in methylene dichloride solution even in the presence of $AlCl_3$–$MeNO_2$ afforded the 17-acetyl substitution product **2b** in 22% yield along with the starting compound. No acetyl substitution at the 14-position was observed. A similar result was obtained in the case of 3.1 equiv. of acetyl chloride under the same reaction conditions also to afford 17-acetyl substitution product **2b** in 94% yield. In contrast, the 8-methoxy derivative **1c** afforded the 14-acetyl substitution product **3c** in 88% yield along with a trace amount of the 6,14-diacetyl derivative **4** (Table 1). It was also found that the same tendency was observed in the diacetyl substitution of **1c** with 3.1 equiv. of acetyl chloride to give the 6,14-diacetyl derivative **4** in quantitative yield arising from *ipso*-acetylation at the 6-position[9] as well as the acetylation at the 14-position of *para*-benzene ring. It is clear that the latter reaction was much faster than the former *ipso*-acetylation no formation of 6-acetyl-9-methoxy[3.3]MPCP was observed under the reaction conditions used. It was also found that the *ipso*-acetylation was completed within 30 min.

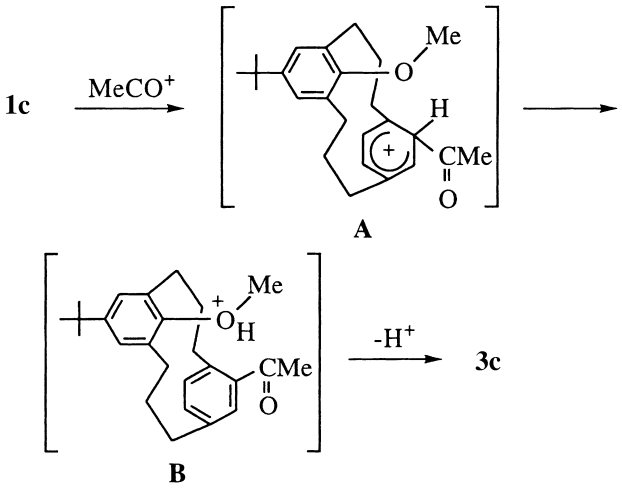
* To receive any correspondence. E-mail: yamatot@cc.saga-u.ac.jp

The structures of the products obtained in the present work were determined from their elemental analyses and spectral data. The ^{1}H NMR spectrum of **2b** in $CDCl_3$ shows a doublet (J= 1.0 Hz) at δ 6.33 for one aromatic C-18 proton which is in a strongly shielding region of the opposite meta-bridged benzene ring and δ 6.94, 6.98 for the external aromatic C-14 and C-15 protons, respectively. On the other hand, the signals of the two aromatic protons for C-17 and C-18 of **3c** were both observed at up field at δ 6.11 and in turn the signal for the external aromatic C-15 proton was deshielded at δ 7.30 by the neighbouring carbonyl group. These data strongly support the assignment of structures 6-*tert*-butyl-9-methyl-17-acetyl[3.3]MPCP **2b** and 6-*tert*-butyl-9-methoxy-14-acetyl[3.3]MPCP **3c**.

The different directive effects of the 9-substituent on the position of electrophilic substitution in the *para*-bridged benzene ring were first observed with these compounds. According to a molecular model, the 9-methyl group apparently sterically blocks electrophilic attack at C(14),C(15)-positions on the opposite *para*-bridged benzene ring. Therefore, internal attack of the electrophile on the para-bridged benzene ring of **1b** exclusively proceeds to give 17-acetyl derivative **2b**. On the other hand, with a methoxy group at this position, acetylation occurs predominantly in the pseudo-geminal position in spite of the above steric hindrance. This pseudo-geminal directing effect of the methoxy group may be attributed to the basicity and geometric availability of the oxygen of the methoxy group. The oxygen is probably the strongest base in the medium. In the rate- and product-controlling step, the oxygen accepts a proton from the pseudo-geminal σ-complex (**A**) to form intermediate (**B**) thus producing a pseudo-geminal substituted product **3c** as shown in Scheme 2. This result is consistent with Cram's reports[5,8] that acetyl and nitro groups in the C(4)-position of the [2.2]paracyclophane nucleus directed acetyl substitution to occur nearly exclusively in the C(14)-position to give the pseudo-geminal disubstituted hydrocarbon. In our case, the 9-methoxy group is located on the opposite *para*-bridged benzene ring which might apparently assist to accept a proton from the pseudo-geminal σ-complex (**A**) to form intermediate (**B**), thus electrophilic attack at C(13)-position might preferentially occur.

The *ipso*-acetylation at the 6-position of 6-*tert*-butyl-9-methoxy[3.3]MPCP **1c** is attributed to the highly activated character of the aryl ring and the increased stabilisation of a σ-complex intermediate arising from the dienone-type σ-complex intermediate possible in the case of a methoxy substituent.[9] However, the present *ipso*-acetylation has not been observed under mild reaction conditions such as acetyl chloride in the presence of $TiCl_4$ catalyst because of deactivation of the second aromatic ring by the introduced acetyl group on the para-benzene ring due to the through-space electronic interactions between two benzene rings.[10]

In conclusion, the different directive effects of 9-substituents on the para-bridged benzene ring on the position of electrophilic substitution were first observed with 9-substituted [3.3]MPCP derivatives. The presently developed procedure was further applied to the direct removal of a *tert*-butyl group by electrophilic substitution of 6-*tert*-butyl-9-methoxy-[3.3]MPCP **1c**. Further studies on the electrophilic substitution of 6-*tert*-butyl-9-substituted [3.3]MPCPs **1** are now in progress.



Scheme 2

Received 4 July 2001; accepted 31 December 2001
Paper 01/972

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