An acid catalysed intramolecular C–C coupling reaction of 8-halomethyl-16-methoxy[2.2]metacyclophanes

Kan Tanaka[a*], Akira Miyazawa[a], Ai Hiate[b], Masashi Tashiro[b,d], Tatsunori Saisyo[c], Ryo Okabe[c], Kazufumi Kohno[c] and Takehiko Yamato[c]

[a]*National Institute of Advanced Industrial Science and Technology (AIST), AIST Central 5, Tsukuba, Ibaraki 305-8565, Japan*

[b]*Institute of Advanced Material Study, Kyushu University, Kasuga-kouen 6-1, Kasuga 816-8580, Japan*

[c]*Department of Applied Chemistry, Faculty of Science and Engineering, Saga University, Honjo-machi 1, Saga 840-8502, Japan*

[d]*Present address: Loker Hydrocarbon Research Institute, University of Southern California, 837 Bloom Walk LHI, Los Angeles Calfornia 90089-1661, USA*

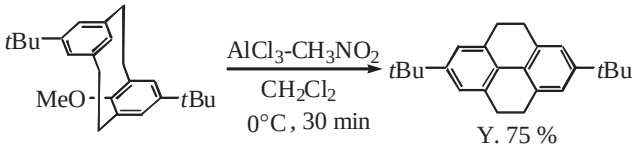
The hydrolysis of 8-bromomethyl[2.2]metacyclophane **1a** with a methoxy group at the 16-position was carried out in an 80% aqueous dioxane solution by refluxing in the presence of Nafion-H (a solid perfluorinated resin sulfonic acid) as a catalyst. The reaction yielded the corresponding 8-hydroxymethyl[2.2]metacyclophane **3** and the intramolecular C–C coupling product **2** with a spiro skeleton.

Keywords: metacyclophane, hydrolysis, reaction mechanism, C–C coupling reaction

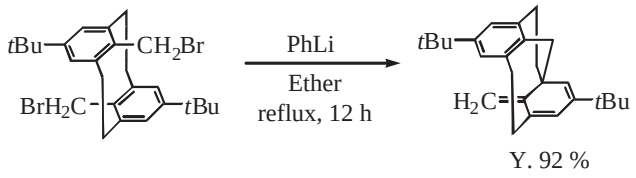
[2.2]Metacyclophane ([2.2]MCP) is prone to undergo transannular reactions due to the electronic interaction between the two benzene rings, the proximity of the 8,16-positions, and considerable strain energy.[1] Sato *et al.*[2-5] reported that the bromination of 8,16-unsubstituted [2.2]metacyclophane with bromine in the presence of Fe powder afforded the corresponding tetrahydropyrene by an addition-elimination mechanism. Similarly, we reported[6] that the reaction of 5,13-di-*tert*-butyl-8-methoxy[2.2]MCP with Lewis acid, $AlCl_3$-CH_3NO_2, in CH_2Cl_2 yielded the transannular cyclisation product, 2,7-di-*tert*-butyl-4,5,9,10-tetrahydropyrene, by releasing the strain in the molecule (Scheme 1). Subsequently, we reported[7] for the first time that the reaction of 8,16-bis(bromomethyl)[2.2]MCP with phenyl lithium afforded a novel intramolecular C–C coupling product with a spiro skeleton (Scheme 2).

Although the transannular cyclisation reaction of [2.2]MCPs has been reported to afford a tetrahydropyrene skeleton, there have been few investigations of [2.2]MCP's intramolecular C–C coupling reactions despite the numerous reports that detail the preparation, reactions and spectroscopic properties of these compounds.

We have discovered that the reaction of 8-bromomethyl-16-methoxy[2.2]MCP under hydrolysis conditions affords an intramolecular C–C coupling product with a spiro skeleton and the corresponding hydrolysis product, 8-hydroxymethyl-16-methoxy[2.2]MCP. Here, we report these novel results.



Scheme 1



Scheme 2

Results and discussion

The hydrolysis of 8-bromomethyl-16-methoxy[2.2]MCP **1a** was carried out in an 80% aqueous dioxane solution while refluxing in the presence of various catalysts. Table 1 summarises the results.

The reaction of **1a** in the presence of strong acid such as Nafion-H,[8] $La(OTf)_3$,[9] or CF_3SO_3H gave the intramolecular C–C coupling product **2** along with the corresponding hydrolysis product **3** and ether **4**, which was formed from the dehydration[10] of two molecules of **3**. Interestingly, 20–30% of **4** was obtained in a heterogeneous system using Nafion-H or $La(OTf)_3$ as a catalyst, but only a trace amount of **4** was obtained in the homogeneous system using CF_3SO_3H. It was reported[8,9,11] that Nafion-H and $La(OTf)_3$ tend to adsorb alcohols or amines rather than alkyl halides during catalytic action. Therefore, alcohol **3** was easily adsorbed onto the catalyst and dehydration to afford **4** would have been promoted. Also, the yield of **3** differs depending on the catalyst used, 10% in Nafion-H, 20% in $La(OTf)_3$, and 50% in CF_3SO_3H. These facts indicate that water molecules may not easily attack the benzyl carbon atom of **1a** when Nafion-H is the catalyst since the counter ion in Nafion-H is larger than those in the other catalysts, $La(OTf)_3$ and CF_3SO_3H.

For bases such potassium hydroxide or triethylamine (Et_3N), and weak acid, 0.1 M hydrochloric acid, as the catalyst, only **3** was obtained in a satisfactory yield. The reaction of 8-chloromethyl-16-methoxy[2.2]MCP **1b** prepared by treating **3** with 36%-hydrochloric acid in toluene was carried out in an 80% aqueous dioxane solution while refluxing in the presence of Nafion-H for 29 h, **3** and **4** were obtained in 40% and 32% yields, respectively, and only a trace amount of **2** was produced. When CF_3SO_3H was the catalyst, **3** was obtained in 68% yield and trace amounts of **2** and **4** were obtained. Since the intramolecular C–C coupling reaction is more important with **1a** rather than **1b** it is suggested that this reaction proceeds by nucleophilic attack on the benzyl carbon atom at the 8-position by π electrons of the opposite benzene ring. Generally, nucleophilic reaction occurs at a benzyl carbon atom in a benzyl halide having a halogen with a large polarisability.[12] This experimental fact strongly suggests that the intramolecular C–C coupling reaction is caused by attack on the benzyl carbon atom by π electrons of the opposite benzene ring. On the other hand, reactions of **1a** in dry dioxane or dichloromethane in the presence of Nafion-H did not afford a product despite prolonged reaction time and only starting compound **1a** was recovered in > 90% yield. This result shows that water is critical for forming **2**.

* Correspondent. E-mail: tanaka.kan@aist.go.jp

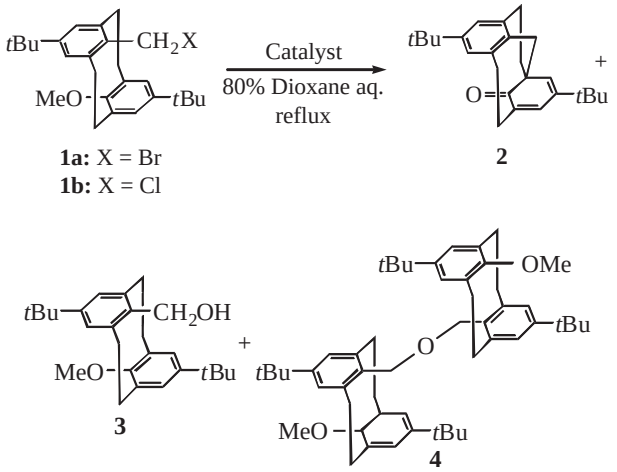


Table 1 Reaction of **1** under hydrolysis conditions

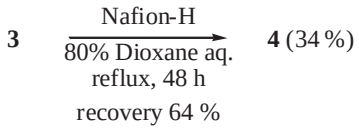
Run	Substrate	Catalyst	Time /h	Products/%[a]		
				2	**3**	**4**
1	**1a**	Nafion-H	22	29	10	20
2	**1a**	$La(Otf)_3$	24	25	20	30
3	**1a**	CF_3SO_3H	24	38	50	Trace
4	**1a**	KOH	24		93	
5	**1a**	Et_3N	14		82	
6[b]	**1a**	0.1M-HC1	48		96	
7	**1b**	Nafion-H	29	Trace	40	32
8	**1b**	CF_3SO_3H	24	Trace	68	Trace

[a]Isolated yields are shown. [b]Carried out at 30 °C.

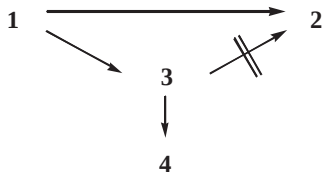
Reaction of **3** was carried out in an 80% aqueous dioxane solution in the presence of Nafion-H but **2** was not obtained. Starting compound **3** was recovered in a 64% yield and **4** was obtained in 34% yield (Scheme 3). When dry dichloromethane was the solvent, starting compound **3** was recovered in a 96% yield. These findings indicate that **2** was directly formed from **1a** and the reaction does not proceed *via* **3** (Scheme 4).

Since the hydroxy group in a hydroxymethyl group is a poor leaving group the S_N2 reaction that would afford **2** from **3** does not easily occur and a competitive reaction, the dehydration preferentially affords **4**.

Scheme 5 proposes a tentative mechanism for forming **2** from **1a**. In the reaction of **1a**, cation **A**, with a spiro skeleton, a positive charge in the opposite benzene ring and the benzyl carbon atom bonded to the *ipso* carbon of the ethano bridge, is formed by nucleophilic attack of the π electrons on the opposite benzene ring on the benzylic carbon atom. Nucleophilic attack of the non-bonding electron pairs of the oxygen atom in a water molecule occurs at the carbon with a positive charge in the benzene ring to give **B**, which is then converted in to **C** by a proton shift.[6] Elimination of methanol stabilises cation **C** to give **D**, which produces **2** by deprotonation.



Scheme 3



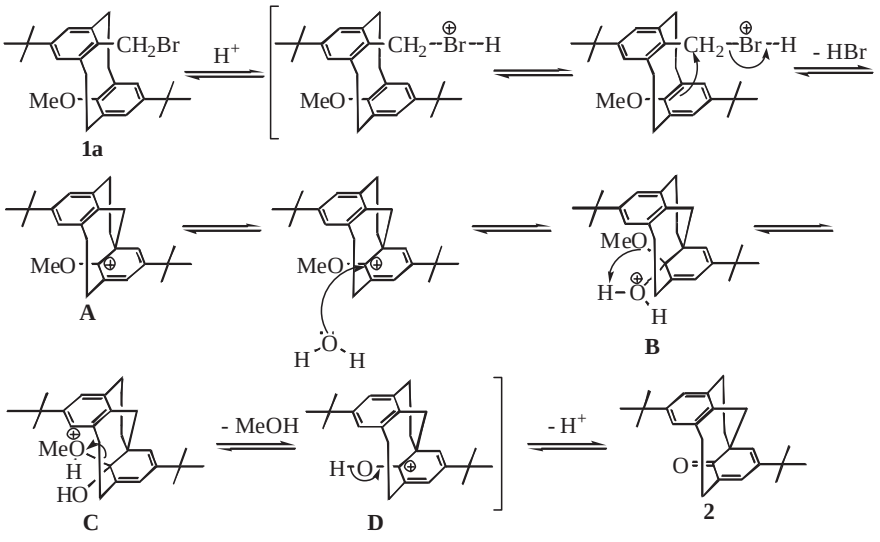
Scheme 4

Conclusion

We have found that the reaction of 8-bromomethyl-16-methoxy[2.2]MCP **1a** in an 80% aqueous dioxane solution in the presence of a strong acid affords the intramolecular C–C coupling product **2** with a spiro skeleton. The novel intramolecular C–C coupling reaction mentioned above must be ascribed to the special geometrical characteristics of [2.2]MCP systems. Further studies on the chemical properties of intramolecular C–C coupling product **2** are now in progress.

Experimental

All melting points are uncorrected. IR spectra were measured on KBr pellets in a Nippon Denshi JIR-AQ2OM spectrometer. NMR spectra were recorded at 300 MHz on a Nippon Denshi JEOL FT-300 NMR spectrometer in deuteriochloroform with $SiMe_4$ as internal reference. Mass spectra were measured on a Nippon Denshi JMS-01SA-2 spectrometer at 75 eV using a direct inlet method. Column chromatography was carried out on silica gel (Wako gel, C-300).



Scheme 5

Preparation of 5, 13-di-tert-butyl-8-chloromethyl-16-methoxy[2.2] MCP **1b**: To a solution of 8-hydroxymethyl[2.2]MCP **3** (600 mg, 1.57 mmol) in toluene (5 ml) was added 36% hydrochloric acid (2 ml) and the solution was stirred for 3 h at room temperature. The reaction mixture was poured into a large amount of ice-water and extracted with $CHCl_3$. The organic layer was washed with water, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was recrystallised from *n*–hexane to afford 274 mg (41%) of compound **2b** as colourless prisms, m.p. 250–251 °C; ν_{max}(KBr)/ cm^{-1} 2904, 1450, 1360, 1276, 1184, 1102, 1022; δ_H($CDCl_3$) 1.31 (18H, s), 2.87 (3H, s), 2.64-3.01 (8H, m), 3.08 (2H, s), 7.10 (4H, s); MS *m/z* 398 (M^+). HRMS (CI): *m/z* Calc. for $C_{26}H_{35}OCl$ (M^+) 398.2376; Found 398.2370.

Hydrolysis of **1a** *to give C–C coupling compound* **2** *Typical procedure*: Nafion-H catalysed hydrolysis of **1a** in 80% aqueous dioxane solution.

A mixture of 5, 13-di-*tert*-butyl-8-bromomethyl-16-methoxy[2.2] MCP **1a** (100 mg, 0.22 mmol) and Nafion-H (10 mg) in 80% aqueous dioxane solution (5 ml) was refluxed for 22 h. The solid resinsulfonic acid was then filtered off, and the filtrate was poured into a large amount of 5%-NH_4Cl aq. and extracted with $CHCl_3$. The organic layer was washed with water, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was chromatographed over silica gel using a 20:1 mixture of *n*-hexane and ether as an eluent to give 23 mg (29%) of **2**, 9 mg (10%) of **3** and 17 mg (20%) of **4**.

2: Colourless prisms (*n*-hexane), m.p. 278–281 °C; ν_{max} (KBr)/ cm^{-1}: 2916, 1702, 1450, 1360, 1200, 868; δ_H ($CDCl_3$): 1.09 (9H, s), 1.28 (9H, s), 2.32–3.03 (8H, m), 2.61 (1H, d, *J* 12.2 Hz), 3.50 (1H, d, *J* 12.2 Hz), 5.90 (1H, s), 6.30 (1H, s), 6.94 (1H, s), 7.42 (1H, s); δ_C ($CDCl_3$): 24.59, 28.96, 29.30, 31.45, 34.06, 34.37, 35.66, 36.07, 37.53, 55.39, 122.96, 123.88, 125.47, 129.33, 133.13, 137.67, 139.88, 143.42, 146.29, 150.25, 210.66; *m/z*: 348 (M^+). HRMS (CI): *m/z* Calcd for $C_{25}H_{32}O$ (M^+): 348.2453. Found: 348.2455.

3: Colourless prisms (*n*-hexane), m.p. 238–240 °C (lit.,[13] 249–250 °C).

4: Colourless prisms (*n*-hexane), m.p. 245–246 °C; ν_{max} (KBr)/ cm^{-1}: 2924, 1456, 1358, 1276, 1200, 1020; δ_H ($CDCl_3$): 1.22 (18H, s), 1.32 (18H, s), 2.19 (4H, s), 2.33–2.74 (16H, m), 2.77 (6H, s), 6.78 (4H, s), 6.98 (4H, s); δ_C ($CDCl_3$): 31.54, 33.90, 34.00, 35.00, 36.67, 59.14, 62.23, 124.83, 130.19, 136.82, 138.00, 145.24, 148.80, 158.49; *m/z*: 742 (M^+). HRMS (CI): *m/z* Calcd for $C_{52}H_{70}O_3$ (M^+): 742.5325. Found: 742.5325.

Nafion-H catalysed reaction of **3** *in 80% aqueous dioxane solution*: According to the procedure for the reaction of **1a** in 80% aqueous dioxane solution in the presence of Nafion-H, **3** (100 mg, 0.26 mmol) was converted into **4** in 34% yield (33 mg, 0.044 mmol) by reaction in 80% aqueous dioxane solution (5 ml) in the presence of Nafion-H (10 mg). Starting compound **3** was recovered in 64% yield (63 mg, 0.16 mmol).

Received 12 January 2005; accepted 21 April 2005
Paper 05/3003

References

1 (a) R.W. Griffin, Jr. *Chem. Rev*., 1963, **63**, 45; (b) B.H. Smith, *Bridged Aromatic Compounds*, Academic Press, New York, 1964; (c) N.L. Allinger, M.A. DaRooge and R.B. Herman, *J. Am. Chem. Soc*., 1961, **83**, 1974.
2 T. Sato, M. Wakabayashi and Y. Okamura, *Bull. Chem. Soc. Jap*, 1967, **40**, 2363.
3 T. Sato and K. Nishiyama, *J. Chem. Soc., Chem. Commun*., 1972, 163.
4 T. Sato and K. Nishiyama, *J. Org. Chem*., 1972, **37**, 3254.
5 T. Sato and T. Takemura, *J. Chem. Soc., Perkin Trans 2*, 1976, 1195.
6 M. Tashiro, T. Yamato, K. Kobayashi and T. Arimura, *J. Org. Chem*., 1987, **52**, 3196.
7 M. Tashiro and T. Yamato, *Chem. Lett*., 1982, 61.
8 G.A. Olah, P.S. Iyer and G.K. Prakash, *Synthesis*, 1986, 513.
9 (a) S. Fukuzawa, T. Tsuchimoto and T. Hiyama, *J. Org. Chem*., 1997, **62**, 151; (b) T. Hanamoto, Y. Sugimoto, A. Sugino and J. Inanaga, *Synlett*, 1994, 377; (c) N. Mine, Y. Fujiwara and H. Taniguchi, *Chem. Lett*., 1986, 357.
10 (a) T. Yamato, N. Sakaue, T. Frusawa, M. Tashiro, G.K. Prakash and G.A. Olah, *J. Chem Res. (S)*, 1991, 241; *(M)* 1991, 2414; (b) T. Yamato, C. Hideshima, G.K. Prakash and G.A. Olah, *J. Org. Chem*., 1991, **56**, 2089.
11 G.A. Molandar, *Chem. Rev*., 1992, **92**, 29.
12 (a) V.P. Vitullo, J. Grabowski and S. Sridharan, *J. Am. Chem. Soc*., 1980, **102**, 6463; (b) A. Pross and S. Shaik, *J. Am. Chem. Soc*., 1981, **103**, 3702.
13 M. Tashiro, T. Arimura and T. Yamato, *Chem. Pharm. Bull*., 1983, **31**, 370.