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SYNTHESIS OF 1,2-DISUBSTITUTED BENZENES AND BIPHENYLS FROM PHTHALIC ACIDS THROUGH ELECTROREDUCTION FOLLOWED BY ELECTROCYCLIC REACTION WITH ALKYNES

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Abstract: Various substituted 1,2-dihydrophthalic acids were synthesized by electroreduction of phthalic acids in excellent yields. The electrocyclic reaction of 1,2-dihydrophthalic acids or the methyl ester with alkynes gave 1,2-disubstituted benzenes and biphenyls in good yields together with fumaric acid or methyl fumarate.

Much interest has been focused on the application of 1,2-dihydrophthalic acids as chemical intermediates possessing both dienes and dibasic acid moieties in a same molecule. For example, the reactions with maleic acid lead to the production of cyclic polycarboxylic acids, which are useful as plasticizers, reforming materials, and raw materials for polyimides.[1] In this work, we wish to report novel electroreductive synthesis of various substituted 1,2-dihydrophthalic acids and their transformation to 1,2-disubstituted benzenes and biphenyls by their electrocyclic reaction with alkynes.

It is known that 1,2-dihydrophthalic acid can be prepared by reduction of phthalic acid with sodium/amalgam[2] and electrochemical hydrogenation of o-phthalic acid with dilute sulfuric acid as catholyte above 70°C.[1,3] The former method causes serious problem of environmental pollution and the yield of the product is not so high even for the reduction of phthalic acid. The latter method resulted in formation of a complex mixture of many products in the electroreduction of various substituted o-phthalic acids under the similar conditions to those for the non-substituted one. Therefore, we attempted significant modification of the latter method for electroreduction of various substituted phthalic acids (catholyte: 1,4-dioxane/5%H_2SO_4=1/1, reaction temp.: 30°C) so that the corresponding 1,2-dihydrophthalic acids could be selectively obtained.[4] The yields and conditions of the present electroreduction of various substituted phthalic acids are tabulated in Table 1. Regardless of the character of the substituents on the phenyl ring of phthalic acids, the corresponding 1,2-dihydrophthalic acids **2a**–**2g** were selectively formed in good yields.

1,2-Dihydrophthalic acids **2** and esters **3** have diene systems which may be suitable for Diels–Alder reaction. In fact, the methyl esters **3** reacted with dienophiles like maleic anhydride, dimethyl maleate or, methyl acrylate, to yield bicyclo[2,2,2]octene systems (scheme 1, eq.1) in moderate to good yields as reported.[1,5] However, in the case of acetylenic dienophile, for example, dimethyl 1,2-dihydrophthalate **3a** underwent Diels–Alder reaction with them to afford substituted benzene derivatives **5** together with dimethyl fumarate **9** without isolation of a Diels–Alder adduct **4** (scheme 1, eq.2).[6]

Typical procedure is described below. Dimethyl 1,2-dihydrophthalate **3a** (1 g, 5.1 mmol), alkynes (5.1 mmol) were heated together at 190–220°C under nitrogen for 2–8 h until the disappearance of **3a** was con-

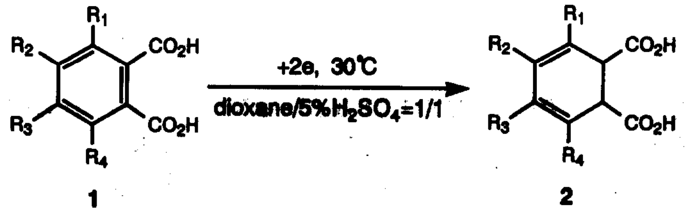


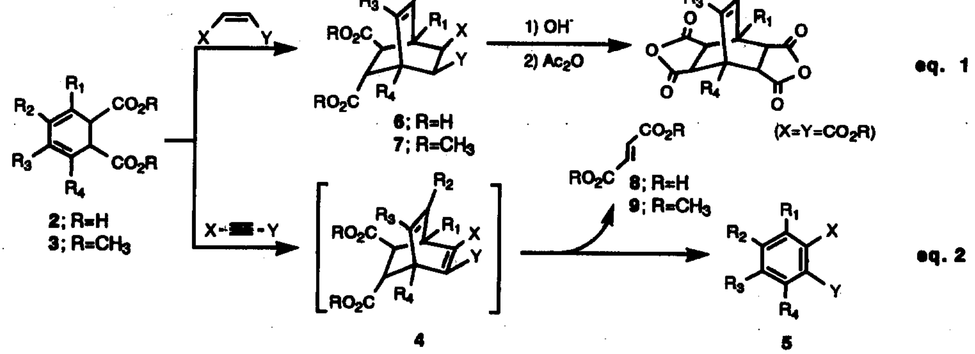
Table 1. Electroreduction of Phthalic acids 1 to 1,2-Dihydrophtalic acids 2

1	⟶ 2 [a]	Isolated Yield (%)
a	$R_1=R_2=R_3=R_4=H$	86
b	$R_1=R_3=R_4=H$, $R_2=CH_3$	89
c	$R_1=R_3=R_4=H$, $R_2=$*tert*-Bu	88
d	$R_1=R_4=H$, $R_2=R_3=CH_3$	90
e	$R_1=R_2=R_3=R_4=F$	83
f	$R_1=R_2=R_3=R_4=Cl$	86
g	$R_1=R_3=R_4=H$, $R_2=CF_3$ [b]	86

a) Ref. 4. b) **1g** was presented by Nihon Nohyaku Co., Ltd.

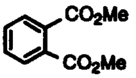
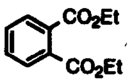
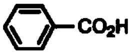
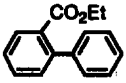
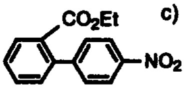
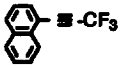
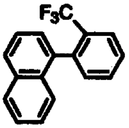
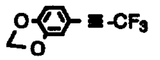
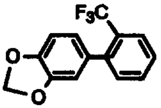
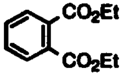
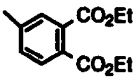
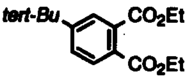
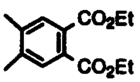
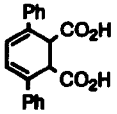
firmed by G.L.C., when the crystal of dimethyl fumarate sublimed at the upper part of a flask. The reaction mixture was cooled, dissolved in acetone, and chromatographed over silica gel. Elution with hexane/ethyl acetate (90/10) gave the corresponding 1,2-disubstituted benzenes. The results of reactions of **3a** with a variety of alkynes as a dienophile are exemplified in Table 2 (entry, 1-7). It is considered that Diels-Alder adducts were formed at the first step of reaction between **3a** and alkynes, and then it underwent retro Diels-Alder reaction to give 1,2-disubstituted benzenes **5** and dimethyl fumarate because of labile aromatization. In a similar way, electrocyclic reactions of other 1,2-dihydrophthalic acids **2** were also investigated. Some of **2** and diethyl acetylenedicarboxylate were refluxed in decalin under nitrogen for 3 -6 h. After washing with NaHCO$_3$ aq. to

Scheme 1



remove fumaric acid followed by column chromatography, diethyl phthalates can be obtained in moderate to good yield (Table 2, entry 8–12). 3,6–Diphenyldihydrophthalic acid[12] could not be converted to the corresponding benzene derivatives even at 250°C for 50 h in a sealed tube (Table 2, entry 12), because it would be difficult to form the Diels–Alder adduct 4 owing to the steric factor of the two phenyl groups.

Table 2. Transformation of Dihydrophthalic acids 2 and esters 3 to 1,2-Disubstituted benzenes 5

Entry	Dihydrophthalic acids 2 and esters 3	Alkynes	Product 5	Temp (°C)	Time(h)	Yield (%)
1	**3a**	$MeO_2C\text{-}\equiv\text{-}CO_2Me$	 a)	190	2	89
2	**3a**	$EtO_2C\text{-}\equiv\text{-}CO_2Et$	 a)	190	2	94
3	**3a**	$H\text{-}\equiv\text{-}CO_2H$	 a)	190	5	85
4	**3a**		 b)	220	4.5	77
5	**3a**	 f)	 c)	220	4	73
6	**3a**	 g)	 d)	220	8	42
7	**3a**	 g)	 e)	220	8	90
8	**2a**	$EtO_2C\text{-}\equiv\text{-}CO_2Et$	 j)	190 h)	3	87
9	**2b**	$EtO_2C\text{-}\equiv\text{-}CO_2Et$	 j)	190 h)	6	68
10	**2c**	$EtO_2C\text{-}\equiv\text{-}CO_2Et$	 j)	190 h)	4	87
11	**2d**	$EtO_2C\text{-}\equiv\text{-}CO_2Et$	 j)	190 h)	4	50
12	 k)	$EtO_2C\text{-}\equiv\text{-}CO_2Et$	—	250 i)	50	0

a) Ref. 7a. b) Ref. 7b. c) Ref. 7c. d) Ref. 7d. e) Ref. 7e. f) Ref. 8. g) Ref. 11. h) decalin, reflux. i) 250°C, in a sealed tube. j) Products were identified by comparison with authentic samples. k) Ref. 12.

In summary, various 1,2-dihydrophthalic acids **2** were newly synthesized by elctroreduction of easily available phthalic acids in excellent yields and their reaction with alkynes realized the efficient synthetic route to 1,2-disubstituted benzenes and biphenyls. The present reaction may be cited as another example of successive electrocyclic addition and cleavage of inner-ring dienes besides the reactions of limited activated cyclohexadienes[13] and 2-pyrones with alkynes.[14] Further investigation of chemical behaviors and applications of 1,2-dihydrophthalic acids **2** are now in progress.

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4. Typical procedure is described below. A 1/1 mixture of 1,4-dioxane/5% H_2SO_4 aq. and 20 ml of 5% H_2SO_4 aq. were used as catholyte and anolyte, respectively, which were placed in a divided cell equipped with lead plates (3.0 X 3.5 X 0.1 cm) and a ceramic diaphragm. To the anolyte was added 5 or 10 mmol of phthalic acids **1**. The catholyte was stirred with a magnetic bar and elctrochemically reduced with a constant current of 0.20 A (current density: 19 mA/cm^2) at 25°C. After 8 F/mol of electricity was passed, catholyte was evaporated below 30°C until 1,2-dihydrophthalic acids formed **2** began to crystallize, which was left at −20°C overnight. The product crystallized out were separated in usual way and washed with water and dried (yield 73−90%). They are single isomers, though their configurations were not determined. It is known that almost of **2a** is trans-configuration.[3d] **2a**: mp 202−206°C(dec.); ^{1}H-NMR(d$_6$-acetone, 270 MHz) δ 3.74(m, 2H), 5.90(m, 2H), 6.03(m, 2H). **2b**: mp 167−170(dec.); ^{1}H-NMR(d$_6$-acetone, 270 MHz) δ 1.75(s, 3H), 3.59(ABq, 2H, J=9.2 Hz), 5.74(br s, 1H), 5.83(ABq, 2H, J=9.2 Hz). **2c**: mp 192−193°C(dec.); ^{1}H-NMR(d$_6$-acetone, 270 MHz) δ 1.09(s, 9H), 3.53(ddABq, 1H, J=16 Hz, 1.5 Hz, 1.5 Hz), 3.58(dABq, J=16 Hz, 3 Hz), 5.65(m, 1H), 5.95(dABq, 1H, J=9.9 Hz, 3 Hz), 6.27(ddABq, 1H, J=9.9 Hz, 1.5 Hz, 1.5 Hz). **2d**: mp 136−139°C(dec.); ^{1}H-NMR(d$_6$-acetone, 270 MHz) δ 1.79(s, 6H), 3.51(m, 2H), 5.82(br s, 2H). **2e**: mp 191−193°C(dec.); ^{1}H-NMR(d$_6$-acetone, 270 MHz) δ 4.18(m, 2H). **2f**: mp 254−256°C(dec.); ^{1}H-NMR(d$_6$-acetone, 270 MHz) δ 4.22(s, 2H). **2g**: mp 141−144°C(dec.); ^{1}H-NMR(d$_6$-acetone, 270 MHz) δ 3.88(ddABq, 2H, J=13 Hz, 2.3 Hz, 2.3 Hz), 4.02(ddABq, 2H, J=13 Hz, 3.1 Hz, 3.1 Hz), 6.17(m, 2H), 6.54(br s, 1H).
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6. In the case of the reaction of **3a** with diethyl acetylenedicarboxylate, **4a** could not be isolated even at room temperature whereas the transformation reaction proceeded.
7. (a) Products were identified by comparison with authentic samples. (b) bp 130−135°C/1 mmHg, ^{1}H-NMR(CDCl$_3$, 270 MHz) δ 1.00(t, 3H), 4.09(q, 2H), 7.27−7.85(m, 9H), M$^+$=226. (c) mp 65−66°C, ^{1}H-NMR(CDCl$_3$, 270 MHz) δ 1.08(t, 3H), 4.13(q, 2H), 7.20−8.05(m, 4H), 7.46(d, 2H, J=9.0 Hz), 8.26(d, 2H, J=9.0 Hz), M$^+$=271. (d) mp 78−81°C, ^{1}H-NMR(CDCl$_3$, 270 MHz) δ 7.30−7.65(m, 8H), 7.80−7.90(m, 3H), M$^+$=272 (e) bp 94−96°C/1 mmHg, ^{1}H-NMR(CDCl$_3$, 270 MHz) δ 5.98(s, 2H), 6.74−6.84(m, 3H), 7.28−7.73(m, 4H), M$^+$=266.
8. This acetylene was synthesized by esterification of 4-nitrophenylpropiolic acid, which was given by electrooxidation of 4-nitrophenylpropargyl alcohol in 15% H_2SO_4 aq..[9] 4-Nitrophenylpropargyl alcohol was synthesized by palladium-catalyzed cross-coupling of 4-nitrobenzene with commercial propargyl alcohol.[10]
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12. H. Lohaus, *Liebigs Ann, Chem.*, **1935**, 516, 295.
13. There are two examples for the similar reaction of only activated cyclohexadienes, like trimethylsilyloxycyclohexadienes[a)] and methoxycyclohexadienes.[b)] a) G. M. Rubottom, D. S. Krueger, *Tetrahedron Lett.*, **1977**, 611−614. b) P. A. Harland, P. Hodge, *Synthesis*, **1982**, 223−225.
14. F. Fringuelli, A. Taticchi, *"Dienes in the Diels-Alder Reaction"*, John Wiley & Sons, Inc. New York, 1990, p 320.

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