An Annulation Reaction to Naphthalene-1,4-diols Using Dimethyl Phthalide-3-phosphonates

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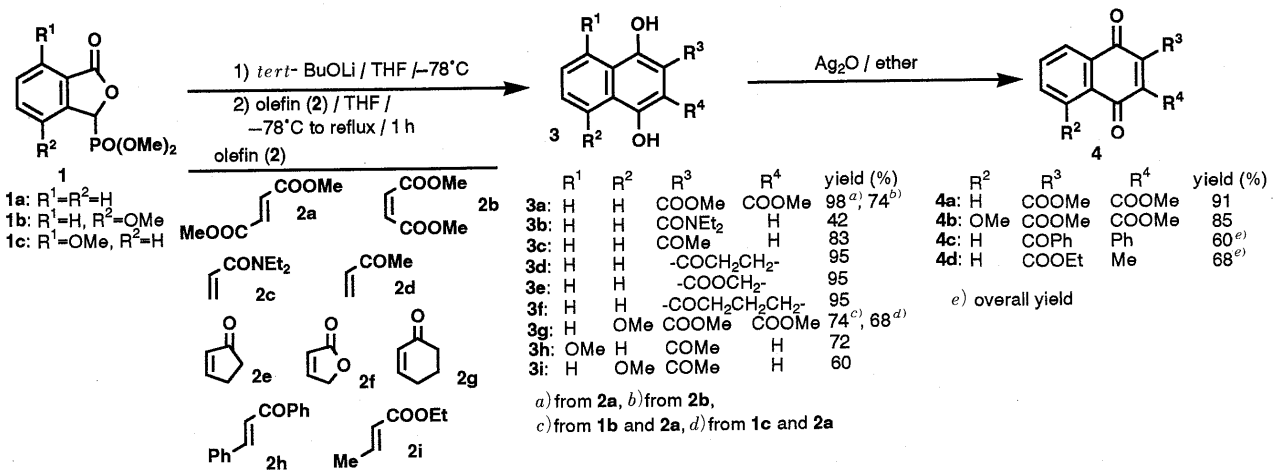
A regioselective annulation to naphthalene ring systems from dimethyl phthalide-3-phosphonates and electron-deficient olefins is described.

Keywords annulation; dimethyl phthalide-3-phosphonate; electron-deficient olefin; *tert*-BuOLi; naphthalene-1,4-diol; 1,4-naphthoquinone

In the course of our continuing research on the applications of phthalide-3-phosphonates in organic synthesis,[1] we investigated an annulation reaction of dimethyl phthalide-3-phosphonates with electron-deficient olefins. Annulation reactions using 3-functionalized phthalides such as 3-cyano-,[2] 3-phenylthio-[3] and 3-phenylsulfonylphthalides[3] had been developed for the construction of naphthalene ring systems in natural products synthesis. Phthalide-3-phosphonates have mainly been used for the syntheses of 3-alkylidene- and 3-benzylidenephthalides by Wittig–Horner reaction.[1c,4] However, the utilization of these compounds in annulation reactions has not been reported. A common feature of the phthalide annulation is that the metallated intermediates of 3-substituted phthalides undergo Michael addition to electron-deficient olefins followed by base-induced cyclization, accompanied by elimination of 3-substituents to give naphthol derivatives. We envisaged that dimethyl phthalide-3-phosphonates could be used in annulation reactions because the phosphonyl group would stabilize the phthalide anions and then leave as a stable phosphite anion after the cyclization had been accomplished. In this paper, a regioselective annulation to naphthalene ring systems using dimethyl phthalide-3-phosphonates is described.

Dimethyl phthalide-3-phosphonate (**1a**) was treated with *tert*-BuOLi[3b] in tetrahydrofuran (THF) at −78 °C for 30 min under an argon atmosphere to generate the yellow anion. A THF solution of dimethyl fumarate (**2a**) was added to the anion at −78 °C and then the mixture was refluxed for 1 h. Quenching with saturated NH_4Cl solution and acidic work-up gave 1,4-dihydroxy-2,3-dimethoxycarbonylnaphthalene (**3a**)[5] in 97% yield (Chart 1). Although lithium diisopropylamide (LDA) and NaH could also be used instead of *tert*-BuOLi in this reaction, **3a** was obtained in lower yields (LDA: 72%, NaH: 65%). Therefore, we chose *tert*-BuOLi as a base for the following annulation reactions. As shown in Chart 1, when dimethyl maleate (**2b**), *N*,*N*-diethylacrylamide (**2c**), and 3-buten-2-one (**2d**) were used as olefins, the corresponding annulation products (**3a**, **3b** and **3c**[6]) were obtained in moderate to good yields. When cyclic olefins such as 2-cyclopenten-1-one (**2e**), 2(5*H*)-furanone (**2f**), and 2-cyclohexen-1-one (**2g**) were used, the fused-naphthalene derivatives (**3d**, **3e**[2d] and **3f**[3b]) were obtained in high yields. The annulation reaction of methoxy-substituted phthalides (**1b** and **1c**) with **2a** gave the same product (**3g**) in similar yields, while on treating **1b** or **1c** with **2d**, the annulation reaction proceeded in a regioselective manner and the regioisomers (**3h**[2d] and **3i**) were obtained in 72% and 60% yields, respectively. Some of the naphthalene-1,4-diols (**3a** and **3g**) were easily oxidized by Ag_2O in ether to give 1,4-naphthoquinones (**4a**[7] and **4b**) in moderate yields (Chart 1). In the annulation reaction of benzylideneacetophenone (**2h**) and ethyl crotonate (**2i**) with **1a**, the corresponding naphthols were directly converted into their naphthoquinones (**4c** and **4d**[8]) due to the difficulty in purification of



	R^1	R^2	R^3	R^4	yield (%)
3a:	H	H	COOMe	COOMe	98[a], 74[b]
3b:	H	H	$CONEt_2$	H	42
3c:	H	H	COMe	H	83
3d:	H	H	$-COCH_2CH_2-$		95
3e:	H	H	$-COOCH_2-$		95
3f:	H	H	$-COCH_2CH_2CH_2-$		95
3g:	H	OMe	COOMe	COOMe	74[c], 68[d]
3h:	OMe	H	COMe	H	72
3i:	H	OMe	COMe	H	60

a) from **2a**, b) from **2b**,
c) from **1b** and **2a**, d) from **1c** and **2a**

	R^2	R^3	R^4	yield (%)
4a:	H	COOMe	COOMe	91
4b:	OMe	COOMe	COOMe	85
4c:	H	COPh	Ph	60[e]
4d:	H	COOEt	Me	68[e]

e) overall yield

Chart 1

TABLE I. Physical Properties and Spectral Data of Naphthalene-1,4-diols (**3**) and 1,4-Naphthoquinones (**4**)

Compd. No.	mp (°C) (Recryst. solv.)	Formula (MS, *m/z*; M^+)	Analysis (%) Calcd	(Found)	UV nm (log ε)	IR (KBr) ν CO (cm^{-1})	^{1}H-NMR[a] δ ($CDCl_3$, *J*=Hz)
3a	110—111[b] (Pentane)	$C_{14}H_{12}O_6$ (276)	C: 60.87 H: 4.38	(60.72) (4.40)	217.5 (4.45), 262 (4.33), 312 (s) (3.47), 360 (3.88)	1670	3.91 (6H, s), 7.68 (2H, dd, *J*=6.4, 3.1), 8.34 (2H, dd, *J*=6.4, 3.1), 10.34 (2H, s)
3b	147—148 (Ether)	$C_{15}H_{17}NO_3$ (259)	C: 69.48 H: 6.61 N: 5.40	(69.37) (6.56) (5.40)	218 (4.26), 243 (4.25), 267.5 (s) (3.76), 344 (3.64)	1630	1.13 (6H, t, *J*=7.0), 3.42 (4H, q, *J*=7.0), 6.58 (1H, s), 7.27—7.58 (2H, m), 7.98—8.32 (2H, m), 9.00—10.00 (2H, br s)
3c	210[c] (Ether–benzene)	$C_{12}H_{10}O_3$ (202)	C: 71.28 H: 4.99	(71.02) (5.01)	218 (4.12), 248 (s) (3.91), 267 (s) (4.00), 273 (4.01), 325 (s) (3.04), 395 (3.47)	1640	2.61 (3H, s), 7.05 (1H, s), 7.41—7.70 (2H, m), 8.07—8.41 (2H, m), 8.89 (1H, br s), 13.45 (1H, s)
3d	219—220 (MeOH–CH_2Cl_2)	$C_{13}H_{10}O_3$ (214)	C: 72.89 H: 4.71	(72.59) (4.90)	217 (4.36), 249 (4.39), 266 (4.40), 300 (s) (3.47), 397 (3.63)	1630	2.65—2.81 (2H, m), 3.07—3.22 (2H, m), 7.35—7.68 (2H, m), 8.08—8.24 (2H, m), 9.02 (1H, br s), 9.75 (1H, br s)[g]
3e	243 (MeOH)	$C_{12}H_8O_4$ (216)	C: 66.67 H: 3.73	(66.37) (4.00)	214 (4.42), 232 (4.38), 255 (4.35), 315 (3.50), 360 (3.68), 376 (s) (3.63)	1700	5.38 (2H, s), 7.40—7.70 (2H, m), 8.11—8.34 (2H, m), 9.43 (2H, br s)[g]
3f	167—172[d] (CH_2Cl_2)	$C_{14}H_{12}O_3$ (226)	C: 73.67 H: 5.30	(73.58) (5.35)	220 (4.45), 255 (s) (4.26), 273 (4.36), 330 (s) (4.18), 402 (3.67)	1640	2.02—2.26 (2H, m), 2.60—2.82 (2H, m), 3.00—3.18 (4H, m), 7.45—7.67 (2H, m), 8.15—8.37 (2H, m)
3g	188—189 (CH_2Cl_2–hexane)	$C_{15}H_{14}O_7$ (306)	C: 58.82 H: 4.61	(58.53) (4.57)	216 (4.49), 236 (4.47), 250 (s) (4.41), 308 (s) (3.70), 322 (3.72), 376 (4.30), 393 (s) (4.25)	1740, 1660	3.95 (6H, s), 4.06 (3H, s), 7.04 (1H, dd, *J*=7.9, 0.9), 7.48 (1H, dd, *J*=8.4, 7.9), 8.05 (1H, dd, *J*=8.4, 1.1), 9.24 (1H, s), 11.69 (1H, s)
3h	144 (Ether)	$C_{13}H_{12}O_4$ (232)	C: 63.93 H: 5.50	(63.81) (5.55)[f]	218 (4.27), 257 (4.37), 295 (s) (3.57), 310 (s) (3.49), 325 (s) (3.46), 400 (3.80)	1630	2.66 (3H, s), 2.40—3.00 (2H, br s), 4.05 (3H, s), 6.85 (1H, d, *J*=7.2), 7.41 (1H, s), 7.57 (1H, t, *J*=7.2), 7.80 (1H, d, *J*=7.2)
3i	132—134 (Ether)	$C_{13}H_{12}O_4$ (232)	C: 67.23 H: 5.21	(66.95) (5.24)	217 (4.44), 255 (4.40), 314 (s) (3.57), 328 (s) (3.60), 405 (3.84)	1630	2.64 (3H, s), 4.06 (3H, s), 6.99 (1H, dd, *J*=7.9, 0.9), 6.99 (1H, s), 7.40 (1H, t, *J*=7.7), 8.07 (1H, dd, *J*=8.3, 1.1), 8.78 (1H, s), 13.23 (1H, s)
4a	94—95[e] (CH_2Cl_2–ether)	$C_{14}H_{10}O_6$ (274)	C: 61.32 H: 3.68	(61.22) (3.72)	203 (4.34), 220 (s) (4.09), 248 (4.22), 265 (s) (4.03), 342 (3.52)	1720, 1680	3.94 (6H, s), 7.72—7.90 (2H, m), 8.02—8.22 (2H, m)
4b	125—126 (CH_2Cl_2–ether)	$C_{15}H_{12}O_7$ (304)	C: 59.21 H: 3.98	(59.16) (3.99)	213 (4.42), 250 (4.13), 350 (s) (3.36), 415 (3.54)	1740, 1660	3.92 (6H, s), 4.01 (3H, s), 7.26—7.44 (2H, m), 7.75 (1H, dd, *J*=4.8, 0.9)
4c	171—172 (Ether–pentane)	$C_{23}H_{14}O_3$ (338)	C: 81.64 H: 4.17	(81.76) (4.30)	203 (4.29), 248 (4.23), 252 (s) (4.22), 295 (s) (3.55)	1670, 1650	7.25 (5H, s), 7.32—7.50 (3H, m), 7.71—7.87 (4H, m), 8.01—8.21 (2H, m)
4d	98—99 (Ether–pentane)	$C_{14}H_{12}O_4$ (244)	C: 68.84 H: 4.95	(68.55) (4.98)	200 (4.22), 249 (4.22), 250 (4.23), 268 (s) (4.05), 335 (3.31)	1730, 1660	1.41 (3H, t, *J*=7.0), 2.19 (3H, s), 4.44 (2H, q, *J*=7.0), 7.69—7.84 (2H, m), 8.01—8.16 (2H, m)

a) Listed as chemical shifts (number of protons, multiplicity, coupling constant in Hz). *b*) Lit.,[5] mp 114—115 °C. *c*) Lit.,[6] mp 210—211 °C. *d*) Lit.,[3b] mp 167—168 °C. *e*) Lit.,[7] mp 100—101 °C. *f*) Calcd for $C_{13}H_{12}O_4 \cdot 2/3H_2O$. *g*) DMSO-$d_6$ as a solvent.

the naphthalene-1,4-diols. Various kinds of highly substituted 1,4-naphthoquinones are found in nature.[9] The above annulation to naphthalene-1,4-diols and their conversion to the corresponding quinones could be used for the regioselective synthesis of naphthoquinone natural products.

In conclusion, we have developed a new phthalide-annulation reaction using dimethyl phthalide-3-phosphonates. The yields of our reaction seem to be better than those of the previously reported procedures.[2,3] Therefore, dimethyl phthalide-3-phosphonates are good alternatives to other 3-substituted phthalides for use in annulation reactions.[2,3]

Experimental

Melting points were determined with a Yanagimoto micromelting point apparatus and are uncorrected. The IR spectra were measured with a JASCO 810 spectrophotometer. The UV spectra were recorded in 95% ethanol on a Hitachi 323 spectrophotometer. The NMR spectra were obtained on JEOL FX 90Q and JEOL GX-400 spectrometers using $CDCl_3$ as a solvent and tetramethylsilane as an internal reference. The MS were taken on a JEOL DX-303 mass spectrometer. Elemental analyses were performed at the Microanalytical Laboratory of the Center for Instrumental Analysis in Nagasaki University. Conventional column chromatography was carried out on a column of Kieselgel 60 (230—400 mesh).

General Procedure for Annulation Reaction The following procedure for the synthesis of 1,4-dihydroxy-2,3-dimethoxycarbonylnaphthalene (**3a**) is representative: other 1,4-dihydroxynaphthalene derivatives (**3b—i**) were obtained similarly.

1,4-Dihydroxy-2,3-dimethoxycarbonylnaphthalene (**3a**): A solution of **1a** (0.24 g, 1.0 mmol) in THF (30 ml) was added to a stirred solution of *tert*-BuOLi (2.0 mmol), prepared from *n*-BuLi (1.0 M solution in hexane, 2.0 ml, 2.0 mmol) and *tert*-BuOH (0.19 ml, 2.0 mmol) at −78 °C, under an argon atmosphere. The mixture was stirred at −78 °C for 0.5 h and then a solution of dimethyl fumarate (**2a**: 0.29 g, 2.0 mmol) in THF (10 ml) was injected into the yellow solution at −78 °C. After 0.5 h, the mixture was refluxed for 1 h and then THF was removed under reduced pressure to give a residue. Water and 10% HCl solution were added to neutralize the residue and the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried over Na_2SO_4 and evaporated to give a residue, which was purified by recrystallization from pentane to give **3a** (0.27 g, 98% yield), mp 110—111 °C (pentane) (see Table I). Compound **3a** was also prepared in 74% yield by employing dimethyl maleate (**2b**) instead of **2a** in the above reaction. 1,4-Dihydroxy-2-(*N*,*N*-diethylcarbamoyl)-naphthalene (**3b**), 2-acetyl-1,4-dihydroxynaphthalene (**3c**), 4,9-dihydroxynaphtho[2,3-*c*]cyclopenten-1-one (**3d**), 4,9-dihydroxynaphtho[2,3-*c*]-furan-1(3*H*)-one (**3e**), 4,9-dihydroxynaphtho[2,3-*c*]cyclohexen-1-one (**3f**), 1,4-dihydroxy-5-methoxy-2,3-dimethoxycarbonylnaphthalene (**3g**), 2-acetyl-1,4-dihydroxy-8-methoxynaphthalene (**3h**), and 2-acetyl-1,4-dihydroxy-5-methoxynaphthalene (**3i**) were obtained similarly (see Table I).

General Procedure for Oxidation of 1,4-Dihydroxynaphthalenes The following procedure for the synthesis of 2,3-dimethoxycarbonyl-1,4-naphthoquinone (**4a**) is representative: other 1,4-naphthoquinones (**4b—d**) were obtained similarly.

2,3-Dimethoxycarbonyl-1,4-naphthoquinone (**4a**): A solution of **3a** (0.21 g, 0.7 mmol) in ether (40 ml) was stirred with Ag_2O (0.49 g, 2.1 mmol) at room temperature for 6 h. The suspension was filtered and concentrated to give a residue, which was purified by recrystallization from CH_2Cl_2–ether to give **4a** (0.17 g, 91% yield), mp 94—95 °C (CH_2Cl_2–ether) (see Table I). 5-Methoxy-2,3-dimethoxycarbonyl-1,4-naphthoquinone (**4b**), 2-benzoyl-3-phenyl-1,4-naphthoquinone (**4c**), and 2-ethoxycarbonyl-3-methyl-1,4-naphthoquinone (**4d**) were obtained similarly (see Table I).

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