Synthesis of Functionalized Naphthalenes from Substituted 1-Methoxybenzocyclobutenes

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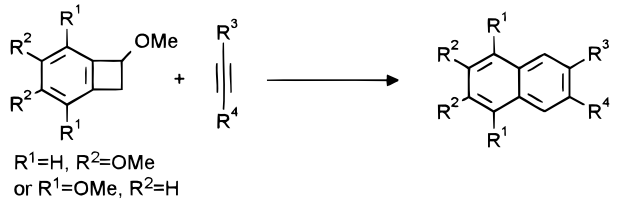
Received November 7, 1995

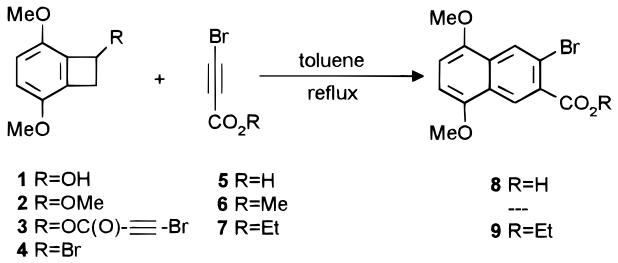
Multisubstituted naphthalene rings can be difficult to prepare by conventional electrophilic aromatic substitution reaction(s), since regiochemical control can be problematical.[1−3] Thus, new or improvements on known methods for the preparation of multisubstituted naphthalene rings are useful since substituted naphthalene rings are often found in natural products.[4] In particular, one of our synthetic routes[5] toward the pentacyclic polyketides halenaquinone[6] and xestoquinone[7] prompted this study. We report herein a simple improvement in the synthesis of naphthalene rings having an *ortho* or *para* arrangement of methoxy groups in one ring using a substituted 1-methoxybenzocyclobutene as an *o*-quinodimethane precursor with acetylenic dienophiles (Scheme 1).

It is well known that *o*-quinodimethanes have been used as intermediates toward the synthesis of functionalized naphthalene rings.[8] However, if the starting material is a benzocyclobuten*ol* (**1**), the *o*-quinodimethane intermediate may undergo a competing [1,5]-hydrogen rearrangement rather than the desired cycloaddition reaction. While attempting to synthesize some multifunctionalized naphthalene rings, we found that compound **1**[9] in the presence of 3-bromopropynoic acid (**5**, Scheme 2) formed both 2,5-dimethoxy-6-methylbenzaldehyde (**19**, Scheme 3), presumably resulting from a [1,5]-hydrogen shift, and the unexpected ester **3**; compound **8** was not detected in the reaction mixture. In an attempt to alleviate the formation of ester **3**, compound **1** was refluxed in toluene with methyl 3-bromopropynoate (**6**);[10] however, after 24 h a complex mixture of products was obtained in which the major product was identified as bromide **4**. These two results indicated that the alcohol group in **1** could be an interfering factor in the cycloaddition reaction.

Scheme 1



Scheme 2



To test this hypothesis, 1,3,6-trimethoxybenzocyclobutene (**2**) was prepared from **1** in quantitative yield according the procedure of Wallace *et al.*[11] and used as the Diels−Alder precursor.[12] Thermolysis of **2** in refluxing anhydrous toluene under an atmosphere of N_2 with ethyl 3-bromopropynoate (**7**) provided a disappointing 5% yield of naphthalene **9** plus aldehyde **19**. The yield of compound **9** was improved to 65% when compounds **2** and **7** were refluxed in anhydrous toluene in the presence of 4 Å molecular sieves, the remainder being aldehyde **19**. The formation of aldehyde **19** could be suppressed by the addition of solid K_2CO_3 or $MgCO_3$ to the reaction mixture; however, the yield of **9** was not improved. Interestingly, 1,4,5-trimethoxybenzocyclobutene (**10**)[13] reacted smoothly with dienophile **7** to provide naphthalene **13** in 82% yield (entry 3, Table 1).

Since compound **2** could be used to successfully prepare naphthalene **9**, we investigated using methoxybenzocyclobutenes **2** and **10** with a variety of acetylenic dienophiles. Refluxing compound **2** or compound **10** with a variety of acetylenic dienophiles in toluene (8 h, N_2) provided naphthalenes **11**−**15** in good to excellent yield (Table 1). The reaction is quite general and tolerates a variety of functional groups on the acetylenic dienophile. As expected, the more electron poor dienophiles gave rise to higher yields.

The reactions listed in Table 1 did not require the addition of 4 Å molecular sieves, potassium, or magnesium carbonate to effect a successful reaction. We feel that the difference in the reaction conditions needed for **2** to react with ethyl 3-bromopropynoate (**7**) when compared to the examples listed in Table 1 can be explained as follows. Due to steric hindrance between the adjacent methoxy groups, *o*-quinodimethane **16** forms and reacts slower than *o*-quinodimethane **20** (Scheme 3).[9] Inter-

† Awarded one of four Alfred Bader Awards (Canadian Society of Chemistry) for this work as a senior undergraduate student in 1995.

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(9) Azadi-Ardakani, M.; Wallace, T. W. *Tetrahedron* **1988**, *44*, 5939.

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(12) Although 1-methoxybenzocyclobutene has been reported to undergo the [4 + 2] cycloaddition reaction via the *o*-quinodimethane with olefins, we were surprised to find that substituted 1-methoxybenzocyclobutenes have not been used as Diels−Alder precursors, see: (a) Arnold, B. J.; Sammes, P. G.; Wallace, T. W. *J. Chem. Soc., Perkin Trans. 1* **1974**, 409. (b) Moss, R. J.; Rickborn, B. *J. Org. Chem.* **1984**, *49*, 3694. (c) Takahashi, Y.; Kochi, J. K. *Chem. Ber.* **1988**, *121*, 253. (d) Zhang, X.; Foote, C. S. *J. Org. Chem.* **1994**, *59*, 5235.

(13) 4,5-Dimethoxybenzocyclobuten-1-ol was prepared according to Charlton, J. L.; Koh, K.; Plourde, G. L. *Can. J. Chem.* **1990**, *68*, 2028 and methylated according to the procedure reported by Wallace *et al.*[11]

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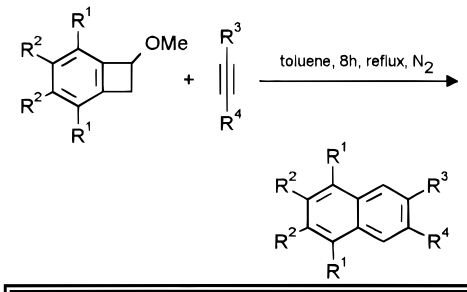
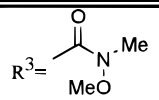
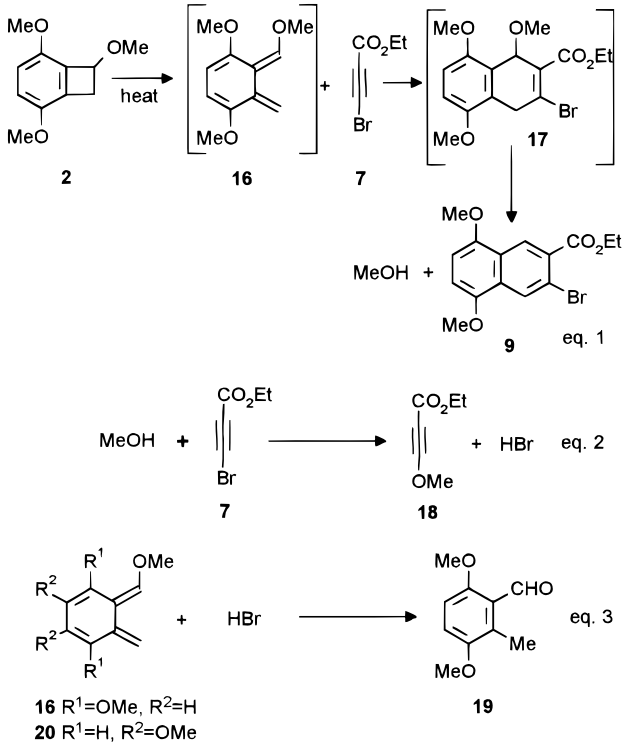
Table 1. Preparation of Naphthalenes from Substituted 1-Methoxybenzocyclobutenes



Starting Material	Dienophile	Product (%Yield)[a]
10 R^2=OMe R^1=H	R^3=  R^4=H	**11** (72)
10	$R^3=R^4=CO_2Me$	**12** (84)
10	$R^3=CO_2Et$; $R^4=Br$	**13** (82)
10	$R^3=CO_2Et$; $R^4=H$	**14** (93)
2 R^1=OMe R^2=H	$R^3=R^4=CO_2Me$	**15** (95)

a. Isolated yields.

Scheme 3



mediate **16**, therefore, has more time to be protonated by an acid source thereby forming aldehyde **19**. The proton source could be HBr formed by the addition of MeOH to acetylene **7** followed by the elimination of HBr to form ethyl 3-methoxypropynoate (**18**). Methanol is formed when the Diels–Alder adduct **17** aromatizes to form ester **9** (Scheme 3, eq 1). The increase in the yield of **9** in the presence of 4 Å molecular sieves is presumably due to the absorption of most of the MeOH resulting in a decrease in HBr production; however, due to the high temperature (110 °C) some of the MeOH is released and some HBr is formed (Scheme 3, eq 2) which results in the formation of some aldehyde **19** (Scheme 3, eq 3). The addition of solid carbonate removes the HBr completely resulting in no aldehyde formation. The lower reactivity of **16** (when compared to **20**) results in a poorer yield of **9** (when compared to **13**) due to decomposition of **16** via other pathways. The reaction of **16** with dimethyl acetylenedicarboxylate is higher yielding, presumably, due to the increased reactivity of the latter.

We have shown that substituted 1-methoxybenzocyclobutenes can be used successfully as precursors for the preparation of some functionalized naphthalenes.

Experimental Section

Methods and Materials. 3,6-Dimethoxybenzocyclobuten-1-ol (**1**),[9] 4,5-dimethoxybenzocyclobuten-1-ol,[13] 1,3,6-trimethoxybenzocyclobutene (**2**),[11] and methyl 3-bromopropynoate (**6**)[10] were prepared according to literature procedures. All melting points are uncorrected. Elemental analyses were obtained by Dorthy Fox at The University of Calgary.

3-Bromopropynoic Acid (5). Freshly distilled propiolic acid (0.63 g, 9.0 mmol) was dissolved in dry THF (10 mL) and added dropwise to a solution of LHMDS (5.32 g, 22.5 mmol) in THF (40 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 20 min and then warmed to 0 °C for a further hour. The solution was then cooled to −78 °C and Br_2 (0.47 mL, 9.2 mmol) added dropwise over a period of 10 min. The resulting solution was extracted with EtOAc (5 × 25 mL). The combined organic extracts were washed with saturated $Na_2S_2O_3$ (25 mL), dried (Na_2SO_4), and concentrated *in vacuo* to afford a dark brown oil which later crystallized. Recrystallization from ethyl acetate–petroleum ether gave the title compound as light brown needles (63%): mp 76–78 °C (lit.[14] 76–78 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 10.6–9.8 (bs, 1H, CO_2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 55.20, 72.27, 155.31; mass spectrum, 150/148 (88, $M^{\bullet+}$), 133/131 (95, $M^{\bullet+}$ − OH), 106/104 (100, $M^{\bullet+}$ − CO_2).

Ethyl 3-Bromopropynoate (7). Ethyl propiolate (1.8 g, 18.3 mmol) was dissolved in dry acetone (20 mL) and treated with *N*-bromosuccinimide (3.6 g, 20.2 mmol) and a catalytic amount of $AgNO_3$. After 2 h at ambient temperature, the mixture was quenched with water (20 mL) and filtered. The filtrate was extracted with hexanes, and the combined organic extracts were washed with 10% HCl (2 × 20 mL), dried (Na_2SO_4), and concentrated *in vacuo* to afford a clear oil which later crystallized (85%): mp 21–22 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.31 (t, 3H, OCH_2CH_3), 4.22 (q, 2H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 52.5, 62.5, 73.0, 152.5; HRMS calcd for C_3OBr: 132.9120/130.9135 (M^+ − OCH_2CH_3), found: 132.9127/130.9132.

1,4,5-Trimethoxybenzocyclobutene (10). Compound **10** was prepared in 94% yield from 4,5-dimethoxybenzocyclobuten-1-ol[13] according to the procedure reported for preparation of compound **2**:[11] bp 86–93 °C, 0.1 mmHg; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.03 (dd, 1H, J_{trans} = 2 Hz, J_{gem} = 13.5 Hz, H_2), 3.35 (dd, 1H, J_{cis} = 4 Hz, J_{gem} = 13.5 Hz, H_2), 3.47 (s, 3H, OMe), 3.86 (s, 3H, OMe), 3.87 (s, 3H, OMe), 4.91 (dd, 1H, J_{trans} = 2 Hz, J_{cis} = 4 Hz, H_1), 6.73 (s, 1H), 6.83 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 37.4, 55.7, 56.0, 56.2, 76.3, 106.9, 107.3, 134.2, 136.9, 149.7, 151.5; HRMS calcd for $C_{11}H_{12}O_3$: 194.0947, found: 194.0943.

Ethyl 3-Bromo-5,8-dimethoxy-2-naphthoate (9). A mixture of benzocyclobutene **2** (60 mg, 0.31 mmol) and ethyl 3-bromopropynoate (109 mg, 0.62 mmol) in dry toluene (1.5 mL) was refluxed in the presence of 4 Å molecular sieves under a nitrogen atmosphere for 24 h. The mixture was filtered and

(14) Straus, F.; Kollek, L.; Heyn W. *Ber.* **1930**, *63*, 1868.

concentrated *in vacuo* to afford a dark orange oil. The crude material was purified by column chromatography with silica gel (9:1 hexanes/EtOAc) and purified by distillation (bp 140 °C/0.1 mmHg) (65%): IR (KBr) 1712 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.46 (t, 3H, J = 7.1 Hz, $CO_2CH_2CH_3$), 3.96, 3.97 (s, 3H each, 2 × OMe), 4.45 (q, 2H, J = 7.1 Hz, $CO_2CH_2CH_3$), 6.73 and 6.80 (ABq, 2H, J = 8.6 Hz, H_6 and H_7), 8.50 (s, 1H, H_4), 8.66 (s, 1H, H_1); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.3, 55.8, 55.7, 61.6, 104.3, 106.4, 117.6, 124.3, 126.3, 127.5, 128.1, 129.6, 148.3, 149.7, 166.6; mass spectrum, 338/340 (100, $M^{\bullet+}$), 323/325 (88, $M^{\bullet+} - CH_3$). Anal. Calcd for $C_{15}H_{15}BrO_4$: C, 53.12; H, 4.46. Found: C, 53.13, H, 4.51.

Dimethyl 5,8-Dimethoxy-2,3-dinaphthoate (15). A mixture of benzocyclobutene **2** (130 mg, 0.67 mmol) and dimethyl acetylenedicarboxylate (670 mg, 4.7 mmol) in dry toluene (1.0 mL) was refluxed under a nitrogen atmosphere for 24 h. The crude mixture was filtered, concentrated *in vacuo*, and recrystallized from CH_2Cl_2/hexanes to afford the title compound as yellow cubes (95%): mp 127−128 °C; IR (KBr) 1716 cm^{-1} (2 × C═O); ^1H NMR ($CDCl_3$, 200 MHz) δ 3.96 (s, 6H, 2 × OMe), 3.98 (s, 6H, 2 × OMe), 6.84 (s, 2H, H_6 and H_7), 8.62 (s, 2H, H_1 and H_4); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.6, 55.8, 106.1, 124.3, 126.2, 128.2, 149.7, 168.4; mass spectrum, 304 (90, $M^{\bullet+}$), 289 (100, $M^{\bullet+} - CH_3$), 273 (23, $M^{\bullet+} - OCH_3$). Anal. Calcd for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 62.86, H, 5.30.

***N*,5,8-Trimethoxy-*N*-methyl-2-naphthamide (11).** A mixture of benzocyclobutene **10** (118.5 mg, 0.61 mmol) and *N*-methoxy-*N*-methylpropynamide (173 mg, 1.53 mmol) in dry toluene (1.5 mL) was refluxed under a nitrogen atmosphere for 24 h. The crude mixture was filtered, concentrated *in vacuo*, and recrystallized from CH_2Cl_2/hexanes to afford the title compound as light brown plates (72%): mp 123−124 °C; IR (KBr) 1637 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 400 MHz) δ 3.40 (s, 3H, NCH_3), 3.57 (s, 3H, $NOCH_3$), 3.99, 4.00 (s, 3H each, 2 × OMe), 7.12 and 7.15 (s, 1H each, H_5 and H_8), 7.62, 7.68 (ABq, 2H, J = 8.0 Hz, H_2 and H_3), 8.08 (s, 1H, H_1); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.0, 55.9, 61.0, 106.0, 107.0, 123.6, 125.8, 127.2, 128.2, 129.6, 130.4, 149.9, 150.7, 170.1; mass spectrum, 275 (8, $M^{\bullet+}$), 215 (100, $M^{\bullet+}$ − N(OMe)Me), 187 (18, $M^{\bullet+}$ − C(O)N(OMe)Me). Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 64.67; H, 6.18; N, 4.98.

Dimethyl 6,7-Dimethoxy-2,3-dinaphthoate (12). A mixture of benzocyclobutene **10** (90 mg, 0.46 mmol) and dimethyl acetylenedicarboxylate (197 mg, 1.4 mmol) in dry toluene (1.5 mL) was refluxed under a nitrogen atmosphere for 24 h. The crude mixture was filtered, concentrated *in vacuo*, and recrystallized from CH_2Cl_2/hexanes to afford the title compound as clean white prisms (84%): mp 177−178 °C; IR (KBr) 1724 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 400 MHz) δ 3.94 (s, 6H, 2 × OMe), 4.02 (s, 6H, 2 × OMe), 7.17 (s, 2H, H_5 and H_8), 8.09 (s, 2H, H_1 and H_4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 52.5, 56.0, 106.7, 126.9, 128.3, 129.6, 151.5, 166.4; mass spectrum, 304 (74, $M^{\bullet+}$), 273 (100, $M^{\bullet+} - OCH_3$). Anal. Calcd for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 62.66, H, 5.41.

Ethyl 3-Bromo-6,7-dimethoxy-2-naphthoate (13). A mixture of benzocyclobutene **10** (137 mg, 0.7 mmol) and ethyl 3-bromopropynoate (250 mg, 1.4 mmol) in dry toluene (1.5 mL) was refluxed under a nitrogen atmosphere for 24 h. The crude mixture was filtered, concentrated *in vacuo*, and recrystallized from CH_2Cl_2/hexanes to afford the title compound as long, light brown needles (82%): mp 128−129 °C; IR (KBr) 1712 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.45 (t, 3H, J = 7.14 Hz, $CO_2CH_2CH_3$), 4.01, 4.02 (s, 3H each, 2 × OMe), 4.45 (q, 2H, J = 7.14 Hz, $CO_2CH_2CH_3$), 7.03, 7.14 (s, 1H, H_5 and H_8), 7.98 (s, 1H, H_4), 8.22 (s, 1H, H_1); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 55.9, 56.0, 61.4, 104.9, 106.6, 115.4, 127.0, 131.7, 127.2, 130.6, 131.2, 150.30, 151.8, 166.3; mass spectrum, 338/340 (100, $M^{\bullet+}$), 310/312 (14, $M^{\bullet+} - C_2H_4$), 293/295 (71, $M^{\bullet+} - Et$). Anal. Calcd for $C_{15}H_{15}BrO_4$: C, 53.12; H, 4.46. Found: C, 53.38; H, 4.67.

Ethyl 6,7-Dimethoxy-2-naphthoate (14). A mixture of benzocyclobutene **10** (26.4 mg, 0.14 mmol) and ethyl propiolate (67 mg, 0.68 mmol) in dry toluene (1.0 mL) was refluxed under a nitrogen atmosphere for 24 h. The crude mixture was filtered, concentrated *in vacuo*, and recrystallized from CH_2Cl_2/hexanes to afford the title compound as clean white prisms (93%): mp 103−104 °C; IR (KBr) 1712 cm^{-1} (C═O); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.45 (t, 3H, J = 7.12 Hz, $CO_2CH_2CH_3$), 4.02, 4.04 (s, 3H each, 2 × OMe), 4.43 (q, 2H, J = 7.12 Hz, $CO_2CH_2CH_3$), 7.15, 7.23 (s each, 1H, H_5 and H_8), 7.72 (d, 1H, J_{34} = 8.84 Hz, H_4), 7.95 (dd, 1H, J_{34} = 8.84 Hz, J_{13} = 1.70 Hz, H_3), 8.47 (d, 1H, J_{13} = 1.70, H_1); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.4, 55.9, 60.9, 106.1, 107.4, 124.0, 126.3, 129.2, 126.1, 128.3, 131.9, 150.0, 151.3, 167.0; mass spectrum, 260 (100, $M^{\bullet+}$), 245 (8, $M^{\bullet+} - CH_3$), 232 (26, $M^{\bullet+} - C_2H_4$), 215 (76, $M^{\bullet+} - OEt$); HRMS calcd for $C_{15}H_{16}O_4$: 260.1029, found: 260.1049.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada and the University of Calgary for financial support. We also thank Human Resources Development Canada for a SEED grant (to N.G.A.).

Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds **7**, **10**, and **14** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO951978V