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FUNCTIONALIZED NAPHTHALENES BY BENZOTRIAZOLE-MEDIATED ANNULATION

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ABSTRACT: The anions of 3-benzotriazolylphthalide (**1**) and of 2-(benzotriazolylmethyl)benzonitrile (**6**) condense regioselectively with a range of Michael acceptors to form 1,4-dihydroxynaphthalenes **4b-f** and 1-amino-2,3-di(methoxycarbonyl)naphthalene (**9**) in moderate to good yields.

Functionalized naphthalenes are common features of numerous biologically significant natural products and pharmaceuticals.[1] An important route to functionalized naphthalene systems is from benzenes containing an electrophilic and a potentially nucleophilic substituent in the *ortho* orientation *via* annulation with Michael acceptors.[2] Examples include (i) annulation of 3-cyano-,[1a,2a,d] 3-(phenylthio)-[2a] or 3-(sulfonyl)-phthalides;[1b,2b] (ii) a two step procedure *via* the annulation of phthalides with Michael acceptors followed by acid-catalyzed dehydration;[2c] and (iii) condensations of various *ortho*-substituted benzyl sulfones with Michael acceptors.[2e]

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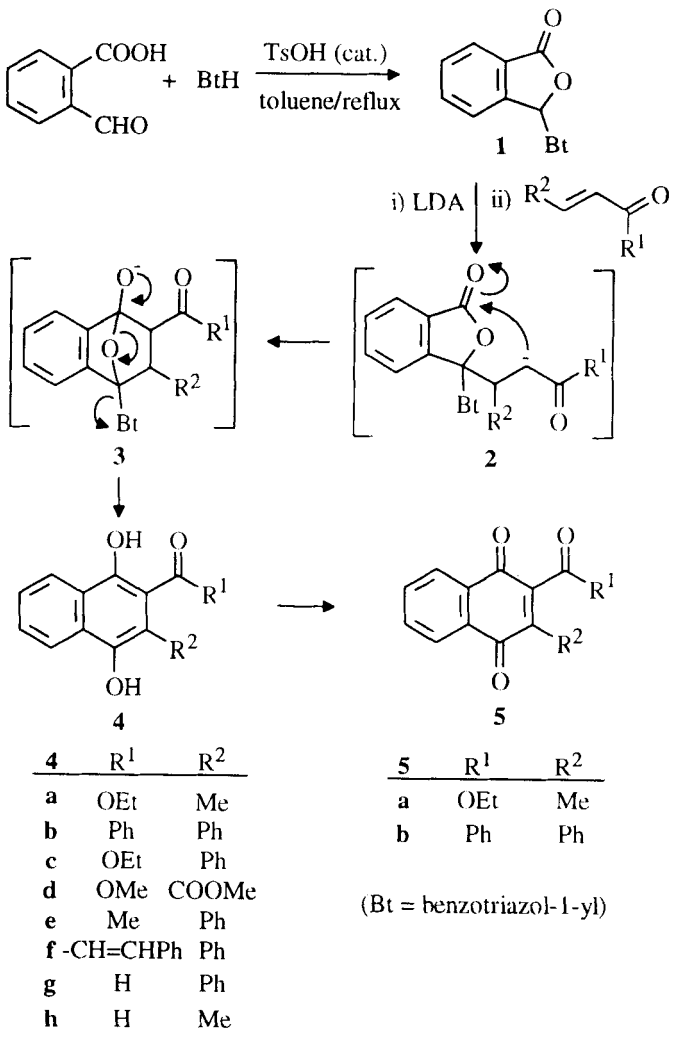
In the course of our investigation on the use of benzotriazole derivatives in organic synthesis,[3] we found that the benzotriazolyl group is both a good anion-stabilizing group and a good leaving group. Recently, we have demonstrated that 1-benzylbenzotriazoles can function as 1,3-dipole synthons in [3 + 3] annulations with α,β-unsaturated aldehydes and ketones to provide a wide range of polysubstituted naphthalenes.[4] We now report that 3-(benzotriazolyl)phthalide (**1**) and 2-(benzotriazolylmethyl)benzonitrile (**6**) can undergo [4 + 2] annulations, serving as 1,4-dipole synthons, with various Michael acceptors to furnish functionalized naphthalenes.

Results and Discussion

3-(Benzotriazol-1-yl)phthalide (**1**) was prepared in 66% yield by condensing *o*-formylbenzoic acid with benzotriazole in the presence of a catalytic amount of *p*-toluenesulfonic acid in toluene (Scheme 1) and characterized by its NMR spectra and CHN analysis. Compound **1** was converted to its anion using LDA in THF in the presence of HMPA at -78 °C, then allowed to react with α,β-unsaturated esters, ketones and aldehydes. The initially formed conjugate addition products **2** underwent spontaneous intramolecular condensation to intermediates **3**, from which the departure of the benzotriazolyl anion yielded 1,4-dihydroxynaphthalenes **4b-h**. 1,4-Dihydroxynaphthalenes **4b-f** were isolated in 36-88% yields and characterized by ^{1}H and ^{13}C NMR and CHN analyses. However, attempts to isolate naphthalenes **4g,h** (derived from α,β-unsaturated aldehydes and compound **1**) failed although on the basis of the GCMS results and ^{1}H NMR

Scheme 1



4	R^1	R^2
a	OEt	Me
b	Ph	Ph
c	OEt	Ph
d	OMe	COOMe
e	Me	Ph
f	-CH=CHPh	Ph
g	H	Ph
h	H	Me

5	R^1	R^2
a	OEt	Me
b	Ph	Ph

(Bt = benzotriazol-1-yl)

spectra of the crude mixtures **4g** and **4h** each appeared to have been produced in *ca.* 50% yield.

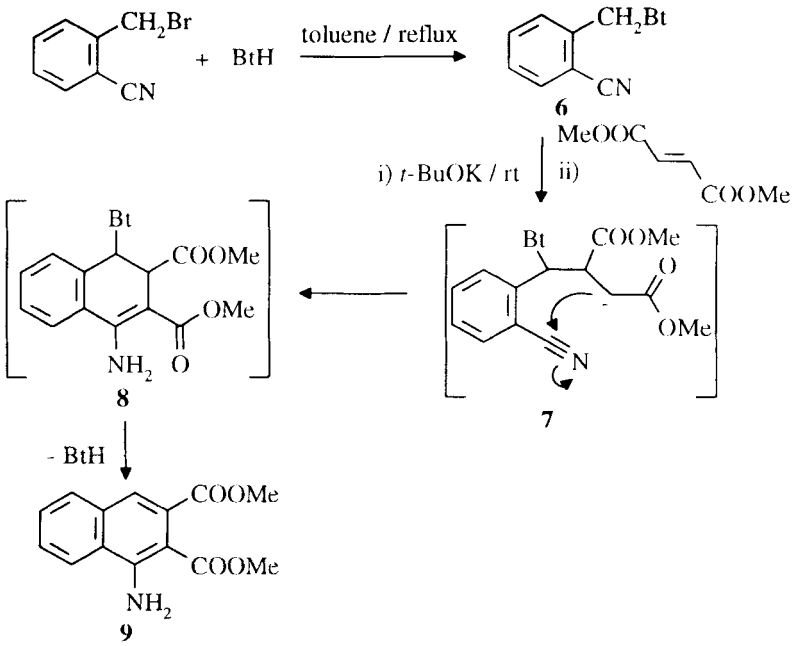
The 1,4-dihydroxynaphthalene products **4** readily underwent air oxidation to give naphthoquinones of type **5** during the purification process. In the case of

4b, 1,4-dihydroxynaphthalene **4b** and the corresponding naphthoquinone **5b** were each isolated, in 68% and 16% yields, respectively. Interestingly, in the reaction of ethyl crotonate with the anion of 3-(benzotriazolyl)phthalide (**3**), the expected 1,4-dihydroxynaphthalene product **4a** was completely oxidized to naphthoquinone **5a** after the crude mixture was kept standing for 30 days before separation by column chromatography. Thus, **5a** was isolated in 41% yield. The structures of naphthoquinones **5a** and **5b** were confirmed by their ^{1}H and ^{13}C NMR spectra and their CHN analyses.

The Michael addition-intramolecular cyclization strategy can be extended to the synthesis of other functionalized naphthalenes as exemplified by the synthesis of 1-amino-2,3-di(methoxycarbonyl)naphthalene (**9**) (Scheme 2). Accordingly, 2-(benzotriazolylmethyl)benzonitrile (**6**) was prepared in 60% yield *via* the nucleophilic substitution of benzotriazole with 2-(bromomethyl)-benzonitrile. Treatment of **6** with KOBu-*t* in THF at ambient temperature gave the corresponding anion, which reacted with dimethyl fumarate to give intermediate **7**. Intramolecular nucleophilic addition to the cyano group, followed by aromatization furnished 1-amino-2,3-di(methoxycarbonyl)naphthalene (**9**) in 41% yield. The structures of compounds **6** and **9** were confirmed by NMR spectra and elemental analyses.

In summary, a novel benzotriazole-mediated annulation route to hydroxy- and amino-naphthalenes has been provided where the benzotriazolyl group serves two purposes: initially, it provides stabilization for the carbanion generated on the benzyl carbon, and later, it becomes a leaving group allowing aromatization of the

Scheme 2



newly formed ring. Our route is thus conceptually similar to that mentioned above from 3-cyano-, 3-(phenylthio)- or 3-(sulfonyl)-phthalides but it avoids the manipulation of HCN and thiophenols for the preparation of the starting materials.

Experimental Section

Melting points were determined with a hot-stage apparatus and are uncorrected. NMR spectra were taken in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H (300 MHz) or solvent as the internal standard for ^{13}C (75 MHz). Tetrahydrofuran was distilled under nitrogen from sodium/benzophenone immediately prior to use. All reactions with air-sensitive compounds were carried

out under an argon atmosphere. Column chromatography was conducted with silica gel 230-400 mesh.

Preparation of 3-(Benzotriazo-1-yl)phthalide (**1**).

A solution of benzotriazole (8.6 g, 72 mmol), 2-formylbenzoic acid (9.8 g, 65 mmol) and *p*-toluenesulfonic acid (0.1 g) in toluene (150 mL) was refluxed for 24 h with Dean-Stark apparatus to remove the resulting water. After being cooled to room temperature, the solution was washed with aqueous sodium carbonate (10%, 2 × 100 mL) and water (100 mL). The toluene solution was dried ($MgSO_4$) and the solvent evaporated to give pure product (10.8 g, 66%); mp 159-160 °C; ^{1}H NMR δ 8.16-8.08 (m, 2H), 8.04 (s, 1H), 7.82-7.79 (m, 2H), 7.55-7.53 (m, 1H), 7.41-7.30 (m, 2H), 6.68-6.65 (m, 1H); ^{13}C NMR δ 167.3, 146.8, 142.4, 135.3, 131.8, 131.4, 128.5, 126.6, 126.2, 124.8, 124.0, 120.6, 109.6, 85.4. Anal. Calcd for $C_{14}H_9N_3O_2$: C, 66.93; H, 3.61; N, 16.72. Found: C, 66.96; H, 3.59; N, 16.71.

General Procedure for the Preparation of 1,4-Dihydroxynaphthalenes **4b-f** and 1,4-Naphthoquinones **5a,b**.

A solution of LDA-HMPA complex was prepared by adding HMPA (2.9 g, 16 mmol) in THF (5 mL) to LDA (1 M in THF, 16 mmol, 10 mL) at -78 °C under argon. After the solution had been stirred at -78 °C for 30 min, a solution of **1** (2.0 g, 5 mmol) in THF (50 mL) was added to immediately afford a reddish-brown solution. After 1 h, a solution of an appropriate Michael acceptor (5 mmol) in THF (15 mL) was added. The mixture was stirred at -78 °C for an additional 2 h, then

allowed to warm to rt overnight. Water (20 mL) was added. The solution was neutralized with aqueous acetic acid (20%) to pH = 4 and extracted with methylene chloride (3 × 60 mL). The organic layer was washed with brine (50 mL), dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (hexanes:ethyl acetate = 5:1), followed by recrystallization from diethyl ether and hexane to give the pure product.

2-Phenacyl-3-phenyl-1,4-dihydroxynaphthalene (4b)[2a] **and 2-Phenacyl-3-phenyl-1,4-naphthoquinone (5b):** Both **4b** and **5b** were obtained from the reaction of **1** with chalcone. Compound **4b**: obtained as a colorless solid (0.80 g, 68%), mp 141-142 °C; ^{1}H NMR δ 10.99 (s, 1H), 8.49 (d, J = 8.3 Hz, 1H), 8.27 (d, J = 8.3 Hz, 1H), 7.70 (t, J = 8.2 Hz, 1H), 7.63 (t, J = 8.2 Hz, 1H), 7.28-7.25 (m, 2H), 7.20-7.10 (m, 5H), 7.07-7.01 (m, 3H), 5.59 (s, 1H); ^{13}C NMR δ 201.5, 153.5, 140.8, 140.3, 135.6, 131.3, 130.9, 129.3, 129.1, 128.7, 127.8, 127.6, 127.5, 126.8, 125.3, 124.1, 122.6, 118.0, 115.8. Anal. Calcd for $C_{23}H_{16}O_3$: C, 81.16; H, 4.74. Found: C, 81.12; H, 4.61. Compound **5b**: obtained as a colorless solid (0.27 g, 16%), mp 151-152 °C; ^{1}H NMR δ 8.25-8.22 (m, 1H), 8.17-8.14 (m, 1H), 7.85-7.82 (m, 2H), 7.79 (d, J = 8.0 Hz, 2H), 7.50 (t, J = 7.6 Hz, 1H), 7.36 (t, J = 7.6 Hz, 2H), 7.27 (s, 5H); ^{13}C NMR δ 192.9, 184.2, 183.8, 144.7, 143.9, 135.9, 134.4, 134.3, 134.0, 131.9, 131.7, 131.0, 129.8, 129.6, 129.0, 128.7, 128.0, 127.1, 126.4. Anal. Calcd for $C_{23}H_{14}O_3$: C, 81.64; H, 4.17. Found: C, 81.57; H, 4.24.

2-Ethoxycarbonyl-3-phenyl-1,4-dihydroxynaphthalene (4c): obtained from the reaction of **1** with ethyl cinnamate as a colorless solid (0.62 g, 40%), mp

157-158 °C; ^{1}H NMR δ 12.14 (s, 1H), 8.50 (d, J = 8.0 Hz, 1H), 8.24 (d, J = 8.4 Hz, 1H), 7.70 (t, J = 8.2 Hz, 1H), 7.63 (t, J = 8.2 Hz, 1H), 7.55-7.46 (m, 3H), 7.35 (d, J = 8.0 Hz, 2H), 5.10 (s, 1H), 4.00 (q, J = 7.1 Hz, 2H), 0.75 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 171.5, 155.9, 141.1, 137.2, 130.0, 129.3, 129.0, 127.8, 127.7, 126.5, 125.2, 123.9, 122.3, 118.1, 60.8, 12.9. Anal. Calcd for $C_{19}H_{16}O_4$: C, 74.01; H, 5.23. Found: C, 73.86; H, 5.17.

2,3-Dimethoxycarbonyl-1,4-dihydroxynaphthalene (4d): obtained from the reaction of **1** with dimethyl fumarate as a colorless solid (1.2 g, 88%), mp 115-116 °C; ^{1}H NMR δ 10.30 (s, 2H), 8.22 (dd, J = 6.2 and 3.3 Hz, 2H), 7.58 (dd, J = 6.2 and 3.3 Hz, 2H), 3.88 (s, 6H); ^{13}C NMR δ 170.3, 151.9, 129.1, 127.4, 123.6, 103.1, 52.2. Anal. Calcd for $C_{14}H_{12}O_6$: C, 60.87; H, 4.38. Found: C, 61.24; H, 4.50.

2-Acetyl-3-phenyl-1,4-dihydroxynaphthalene (4e): obtained from the reaction of **1** with 4-phenyl-3-buten-2-one as a colorless solid (0.50 g, 36%), mp 123-124 °C; ^{1}H NMR δ 13.86 (s, 1H), 8.51 (d, J = 8.1 Hz, 1H), 8.19 (d, J = 8.1 Hz, 1H), 7.70 (t, J = 7.0 Hz, 1H), 7.62-7.51 (m, 4H), 7.43 (d, J = 6.6 Hz, 2H), 5.18 (s, 1H), 1.80 (s, 3H); ^{13}C NMR δ 205.4, 157.2, 140.7, 136.6, 136.5, 130.8, 130.0, 129.0, 128.1, 126.7, 125.8, 124.6, 122.4, 117.5, 114.1, 31.5. Anal. Calcd for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07. Found: C, 77.56; H, 5.08.

2-[(2-Phenyl)ethenylcarbonyl]-3-phenyl-1,4-dihydroxynaphthalene (4f): obtained from the reaction of **1** with dibenzylideneacetone as a colorless solid (0.62 g, 34%), mp 107-108 °C; ^{1}H NMR δ 13.96 (s, 1H), 8.53 (d, J = 8.1 Hz,

1H), 8.24 (d, J = 8.1 Hz, 1H), 7.70 (t, J = 6.8 Hz, 1H), 7.63-7.49 (m, 6H), 7.44 (t, J = 6.8 Hz, 1H), 7.36-7.21 (m, 3H), 7.01 (d, J = 7.2 Hz, 2H), 6.38 (d, J = 15.5 Hz, 1H), 5.47 (s, 1H); ^{13}C NMR δ 194.6, 158.0, 143.3, 141.8, 140.6, 136.7, 134.8, 130.9, 130.1, 130.0, 128.9, 128.8, 128.6, 128.3, 126.7, 126.5, 125.7, 124.5, 122.5, 117.0, 114.5. Anal. Calcd for $C_{25}H_{18}O_3$: C, 81.95; H, 4.95. Found: C, 81.68; H, 5.07.

2-Ethoxycarbonyl-3-methyl-1,4-naphthoquinone (5a): obtained from the reaction of **1** with ethyl crotonate as a colorless solid (0.40 g, 41%) (the crude mixture was kept standing for 30 days before column separation), mp 101-102 °C; ^{1}H NMR δ 8.12-8.07 (m, 2H), 7.78-7.75 (m, 2H), 4.46 (q, J = 7.1 Hz, 2H), 2.20 (s, 3H), 1.42 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 184.7, 181.5, 164.5, 143.7, 139.6, 134.0, 131.7, 131.6, 131.4, 126.6, 126.4, 62.1, 14.2, 13.7. Anal. Calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found: C, 68.81; H, 5.13.

Preparation of 2-(Benzotriazol-1-ylmethyl)benzonitrile (**6**).

A solution of benzotriazole (3.72 g, 31.2 mmol) and 2-(bromomethyl)-benzonitrile (5.1 g, 26 mmol) in toluene (75 mL) was refluxed for 3 days. After being cooled to room temperature, the solution was washed with aqueous sodium carbonate (10%, 2 × 70 mL) and water (70 mL). The organic layer was dried ($MgSO_4$) and the solvent evaporated to give the crude product, which was purified by column chromatography (EtOAc/hexane = 1:3) to afford the pure product (3.6 g, 60%); mp 135-136 °C; ^{1}H NMR δ 8.09 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 7.7 Hz, 1H), 7.58-7.37 (m, 5H), 7.24 (d, J = 7.7 Hz, 1H), 6.08 (s, 2H); ^{13}C NMR δ 146.0,

138.2, 133.5, 132.9, 132.7, 129.0, 128.8, 127.9, 124.2, 120.1, 117.0, 111.5, 109.3, 49.4. Anal. Calcd for $C_{14}H_{10}N_4$: C, 71.78; H, 4.30; N, 23.92. Found: C, 71.55; H, 4.36; N, 24.00.

Preparation of 1-Amino-2,3-(dimethoxycarbonyl)naphthalene **9**.

To a solution of **6** (0.94 g, 4 mmol) and dimethyl fumarate (1.2 g, 8 mmol) in THF (70 mL) under argon was added *t*-BuOK (0.94 g, 8 mmol) in THF (40 mL). The mixture was stirred for 2 days at rt. Water (10 mL) was added and the mixture was acidified with HCl (1 *N*) to pH = 6. The mixture was then extracted with methylene chloride (3 × 80 mL) and the combined organic extracts were washed with brine (70 mL) and water (70 mL). After being dried over $MgSO_4$, the solvent was removed to give the crude product, which was purified by column chromatography (EtOAc/hexane = 1:5) to afford the pure product as a colorless solid (0.51 g, 49%); mp 75-76 °C (lit.[2e] bp 180 °C/0.001 mm); ^{1}H NMR δ 7.87-7.84 (d, J = 7.7 Hz, 1H), 7.76 (d, J = 8.2 Hz, 1H), 7.59-7.49 (m, 2H), 7.37 (s, 1H), 6.37 (br s, 2H), 3.90 (s, 3H), 3.86 (s, 3H); ^{13}C NMR δ 169.9, 168.7, 147.3, 134.2, 131.1, 129.3, 128.9, 127.0, 124.1, 121.5, 118.3, 103.5, 52.4, 52.0. Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.85; H, 5.05; N, 5.40. Found: C, 65.10; H, 5.31; N, 5.41.

References

(1) (a) Li, T.-t.; Walsgrove, T. C. *Tetrahedron Lett.* **1981**, *22*, 3741. (b) Hauser, F. M.; Hewawasam, P.; Rho, Y. S. *J. Org. Chem.* **1989**, *54*, 5110. (c)

Hauser, F. M.; Hewawasam, P.; Baghdanov, V. M. *J. Org. Chem.* **1988**, *53*, 223. (d) Hauser, F. M.; Mal, D. *J. Am. Chem. Soc.* **1984**, *106*, 1098.

(2) (a) Kraus, G. A.; Cho, H.; Crowley, S.; Roth, B.; Sugimoto, H.; Prugh, S. *J. Org. Chem.* **1983**, *48*, 3439. (b) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1978**, *43*, 178. (c) Broom, N. J. P.; Sammes, P. G. *J. Chem. Soc., Chem. Comm.* **1978**, 162. (d) Kraus, G. A.; Sugimoto, H. *Tetrahedron Lett.* **1978**, 2263. (e) Wildeman, J.; Borgen, P. C.; Pluim, H.; Rouwette, P. H. F. M.; van Leusen, A. M. *Tetrahedron Lett.* **1978**, 2213.

(3) (a) Katritzky, A. R.; Rachwal, S.; Hitchings, G. J. *Tetrahedron* **1991**, *47*, 2683. (b) Katritzky, A. R.; Yang, Z.; Cundy, D. J. *Aldrichim. Acta* **1994**, *27*, 31. (c) Katritzky, A. R.; Lan, X. *Chem. Soc. Rev.* **1994**, 363. (d) Katritzky, A. R.; Lan, X.; Fan, W.-Q. *Synthesis* **1994**, 445.

(4) Katritzky, A. R.; Zhang, G.; Xie, L. *J. Org. Chem.* **1997**, *62*, 721.

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