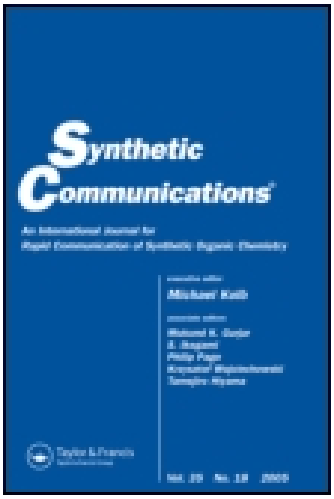

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 09 Dec 2009.

To cite this article: Ricardo A. Tapia, Juan Venegas & Lorena B. Cantuarias (2009) Copper Bromide-Catalyzed C-Alkylation of 2-Amino-1,4-Naphthoquinone: New Synthesis of 1-Azaanthraquinones, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 40:1, 151-156, DOI: 10.1080/00397910902963421

To link to this article: http://dx.doi.org/10.1080/00397910902963421

Synthetic Communications®, 40: 151–156, 2010

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910902963421

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COPPER BROMIDE–CATALYZED C-ALKYLATION OF 2-AMINO-1,4-NAPHTHOQUINONE: NEW SYNTHESIS OF 1-AZAANTHRAQUINONES

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Copper(I) bromide catalyzes the regioselective Michael addition reaction of 2-amino-1, 4-naphthoquinone (5) with methyl vinyl ketone and 2-propenal to provide easy access to C-alkylated quinone derivatives, useful precursors of 1-azaanthraquinones.

Keywords: 2-Amino-1,4-naphthoquinone; 1-azaantraquinones; catalysts; CuBr; Michael addition

INTRODUCTION

The azaanthraquinone framework occurs in natural alkaloids such as cleistopholine (**1**),[1] dielsiquinone (**2**),[2] and the fungal metabolite phomazarin (**3**).[3] The synthesis of **1** was successfully performed by Bracher[4] through a [4 + 2] cycloaddition between 2-bromonaphthoquinone and crotonaldehyde *N,N*-dimethylhydrazone. The Diels–Alder strategy was also used to obtain some substituted derivatives of **1**.[5,6]

The total synthesis of **3** has been recently described by Boger and coworkers using a selective nucleophilic addition of an aryllithium reagent to a pyridine anhydride followed by intramolecular Friedel–Craft acylation.[7]

Considering that Michael adducts of hydroxyquinones are useful intermediates for the synthesis of pyranonaphthoquinones,[8] we wanted to extend this methodology to the synthesis of aza-analogs **4** through the reaction of 2-amino-1, 4-naphthoquinone (**5**) with methyl vinyl ketone (**6**).

Despite the poor nucleophilicity of the amino group in quinone **5**, this quinone reacts with β-ketoesters or similar electrophiles to give *N*-alkylated products, which under cyclization afford azaanthraquinon-2-ones.[9,10] Taking into account that copper bromide catalyzes the conjugated additions of enaminones to quinones,[11,12] we decided to study the reaction of 2-amino-1,4-naphthoquinone (**5**) with ketone **6** in the presence of copper halides.

Received January 27, 2009.

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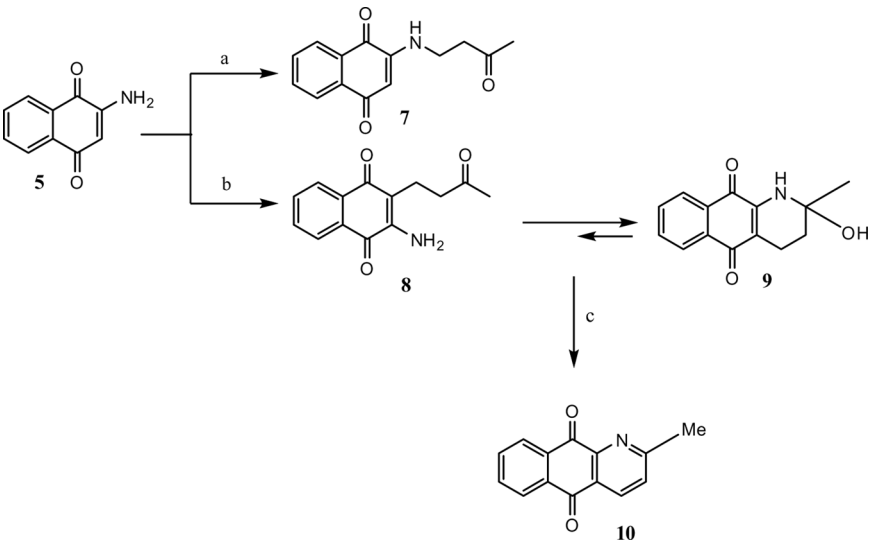
RESULTS AND DISCUSSION

Treatment of 2-amino-1,4-naphthoquinone (**5**) with methyl vinyl ketone (**6**) in a pyridine-*t*-butanol (10:1) mixture under reflux resulted in recovery of starting material. However, the acid-catalyzed reaction of compound **5** with ketone **6** in refluxing toluene for 5 h gave the *N*-alkylated compound **7** in 50% yield. The ^{1}H NMR spectrum of **7** shows one quinone proton signal at δ 5.76, together with signals for C*H*$_3$CO (δ 2.21), COC*H*$_2$ (δ 2.83), C*H*$_2$NH (δ 3.49), and NH (δ 6.18), confirming the structure of *N*-alkylated product **7**.

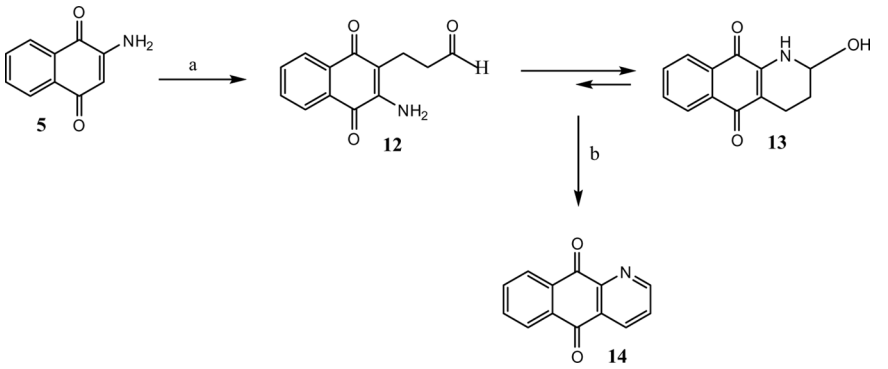
Then, the reaction of aminonaphthoquinone **5** with methyl vinyl ketone (**6**) in the presence of copper halides was examined. Copper(II) halides were less suitable catalysts than copper(I) halides, and copper(I) bromide gave cleaner and faster reactions. Thus, reaction of **5** with methyl vinyl ketone (**6**) in acetonitrile at room temperature for 5 days in the presence of 10 mol% of copper(I) bromide afforded *C*-alkylated product **8** (78%). The ^{1}H NMR spectrum suggests that **8** exists in the cyclic form **9** in solution, showing singlet peaks for methyl (δ 1.60 ppm), hydroxy (δ 3.03 ppm), and amino protons (δ 6.10 ppm), respectively. Treatment of compound **9** with silica gel and tetrachloro-1,4-benzoquinone (*p*-chloranil) gave azaanthraquinone **10** in 69% yield (Scheme 1).

We also examined the copper(I) bromide–catalyzed reaction of **5** with methyl vinyl ketone (**6**) in acetonitrile under reflux, giving a mixture of the *N*-alkylated product **7 a**nd aza-anthraquinone **10** in 14% and 35% yields, respectively.

The regioselective *C*-alkylation procedure was next studied with 2-propenal. Thus, reaction of 2-amino-1,4-naphthoquinone (**5**) with 2-propenal in acetonitrile at room temperature for 3 days in the presence of 10 mol% copper(I) bromide afforded *C*-alkylated product **11** in 63% yield. As in the case of compound **8**, the



Scheme 1. Reagents and conditions: a) toluene, HOAc, **6**, reflux, 5 h; b) CH_3CN, K_2CO_3, CuBr, **6**; and c) silica gel, *p*-chloranil, CH_2Cl_2, reflux, 1 h.



Scheme 2. a) CH_3CN, K_2CO_3, CuBr, 2-propenal; and b) silica gel, *p*-chloranil, CH_2Cl_2, reflux, 1 h.

C-alkylated product **12** also exists as its cyclic isomer **13**. Then, treatment of compound **12** with silica gel and *p*-chloranil led to azaanthraquinone **14** in 64% yield (Scheme 2).

In conclusion, copper(I) bromide–catalyzed *C*-alkylation of 2-amino-1,4-naphthoquinone provides another useful methodology to reach the azaanthraquinone system.

EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus and were not corrected. Infrared (IR) spectra were obtained on a Bruker model Vector 22 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-200 spectrometer, using tetramethylsilane (TMS) as internal reference. Column chromatography was performed on Merck silica gel 60 (70–230 mesh). Elemental analyses were performed on a Fisons EA 1108 CHNS-O analyzer.

N-(3-Oxobutyl)-2-amino-1,4-naphthoquinone (7)

A mixture of 2-amino-1,4-naphthoquinone **5**[13] (200 mg, 1.16 mmol), five drops acetic acid, and ketone **6** (0.5 mL, 6.2 mmol) in toluene (5.0 mL) was heated to reflux for 5 h. The reaction mixture was evaporated under vacuum, and the residue was purified by column chromatography using chloroform–ethyl acetate (1:1) as eluent to give compound **7** (140 mg, 50%), mp 175–177°C; IR (KBr): 3260, 1710, 1670 cm^{-1}; ^1H NMR δ: 2.21 (s, 3H, CH_3), 2.83 (t, 2H, $J = 6.1$ Hz, CH_2CO), 3.49 (c, 2H, $J = 6.1$ Hz, CH_2NH), 5.76 (s, 1H, 3-H), 6.18 (br. s, 1H, NH), 7.61 (ddd, 1H, $J = 7.5$, 7.5, and 1.5 Hz, 7-H), 7.73 (ddd, 1H, $J = 7.5$, 7.5, and 1.5 Hz, 6-H), 8.01 (dd, 1H, $J = 7.3$ and 1.4 Hz, 5-H), 8.07 (dd, 1H, $J = 7.4$ and 1.4 Hz, 8-H); ^{13}C NMR δ: 30.1 (CH_3), 41.2 (CH_2), 100.7 (CH), 126.1 (CH), 126.3 (CH), 130.5 (C), 132.0 (CH), 133.5 (C), 134.7 (CH), 147.6 (C), 181.6 (C), 182.9 (C), 206.1 (C). Anal. calcd. for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.08; H, 5.42; N, 5.71.

2-Amino-3-(3-oxobutyl)-1,4-naphthoquinone (8)

A mixture of 2-amino-1,4-naphthoquinone **5** (200 mg, 1.16 mmol), ketone **6** (190 μL, 2.32 mmol), potassium carbonate (700 mg, 5.04 mmol), and copper(I) bromide (16.6 mg, 0.116 mmol) in acetonitrile (20 mL) was stirred at room temperature for 5 days under nitrogen. The reaction mixture was filtered, the filtrate was evaporated under vacuum, and the residue was recrystallized from benzene to give compound **8** (190 mg, 78%), mp 95°C (d); IR (ν_{max}): 3420, 3320, 1660 cm^{-1}; ^1H NMR δ: 1.42–1.69 (m, 4H, 3-H and CH_3), 2.05–2.14 (m, 1H, 3-H), 2.52 (ddd, 1H, $J = 18.2$, 13.0 and 5.8 Hz, 4-H), 2.90 (ddd, 1H, $J = 18.2$, 13.0, and 2.6 Hz, 4-H), 3.03 (br. s, 1H, OH), 6.07 (s, 1H, NH), 7.55 (dt, 1H, $J = 7.5$ and 1.5 Hz, 7-H or 8-H), 7.66 (dt, 1H, $J = 7.5$ and 1.5 Hz, 8-H or 7-H), 7.85 (d, 1H, $J = 7.4$ Hz, 6-H or 9-H), 7.99 (d, 1H, $J = 7.4$ Hz, 9-H or 6-H); ^{13}C NMR δ: 16.4 (CH_2), 28.9 (CH_3), 32.6 (CH_2), 78.1 (C), 113.1 (C), 125.8 (CH), 126.1 (CH), 130.3 (C), 132.1 (CH), 132.9 (C), 134.5 (CH), 142.2 (C), 180.4 (C), 181.7 (C). Anal. calcd. for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 68.34; H, 4.97; N, 5.89.

2-Methybenzo[g]quinoline-5,10-dione (10)

A suspension of compound **8** (270 mg, 1.11 mmol), silica gel (1.0 g), and *p*-chloranil (273 mg, 1.11 mmol) in dichloromethane (DCM) (50 mL) was heated to reflux for 1 h. After filtration and evaporation, the residue was purified by column chromatography using DCM as eluent to afford **10** (170 mg, 69%); mp 181–183°C. IR (ν_{max}): 1680, 1660 cm^{-1}; ^1H NMR δ: 2.83 (s, 3H, CH_3), 7.59 (d, 1H, $J = 8.1$ Hz, Hz, 3-H), 7.82–7.86 (m, 2H, 7-H and 8-H), 8.33–9.27 (m, 2H, 6-H and 9-H), 8.53 (d, 1H, $J = 8.1$ Hz, 4H); ^{13}C NMR δ: 25.4 (CH_3), 127.1 (CH), 127.9 (CH), 128.0 (CH), 128.5 (C), 132.7 (C), 133.5 (C), 134.4 (CH), 134.6 (CH), 135.6 (CH), 148.4 (C), 165.4 (C), 181.8 (C), 182.6 (C). Anal. calcd. for $C_{14}H_9NO_2$: C, 75.33; H, 4.06; N, 6.27. Found: C, 75.50; H, 3.98; N, 6.33.

2-Amino-3-(2-formylethyl)-1,4-naphthoquinone (12)

A mixture of 2-amino-1,4-naphthoquinone **5** (200 mg, 1.16 mmol), 2-propenal (155 μL, 2.32 mmol), potassium carbonate (560 mg, 5.04 mmol), and copper(I) bromide (16.6 mg, 0.116 mmol) in acetonitrile (15 mL) was stirred at room temperature for 3 days under nitrogen. The reaction mixture was filtered, the filtrate was evapo-

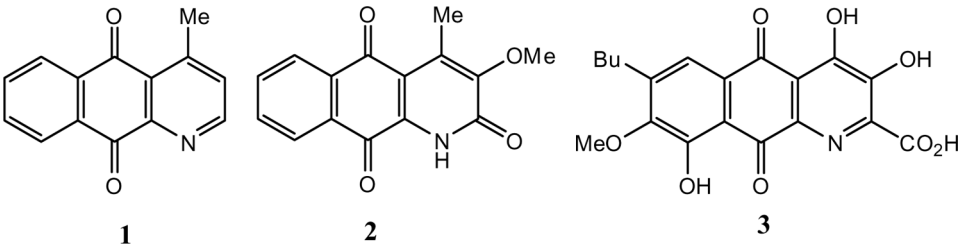


Figure 1. Cleistopholine, dielsiquinone, and phomazarin.

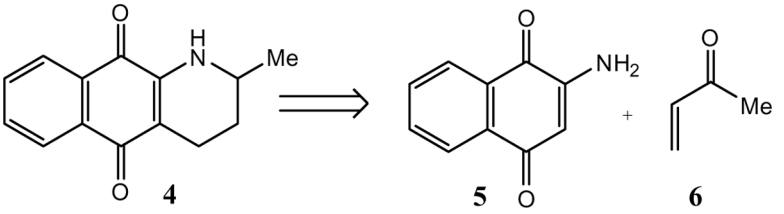


Figure 2. Retrosynthetic analysis.

rated under vacuum, and the residue was purified by column chromatography on neutral alumina using methylene chloride–ethyl acetate–methanol 85:15:5. Evaporation of the solvent gave compound **12** (167 mg, 63%), mp 115°C (d); IR (ν_{max}): 3340, 1660 cm^{-1}; ^1H NMR δ: 1.60–180 (m, 1H, 3-H), 2.05–2.20 (m, 1H, 3-H), 2.49 (ddd, 1H, $J = 18.0$, 13.4 and 5.7 Hz, 4-H), 2.69 (br. s, 1H, OH), 2.90 (ddd, 1H, $J = 18.0$, 5.5, and 2.2 Hz, 4-H), 5.23 (m, 1H, 2-H), 6.36 (br. s, 1H, NH), 7.59 (dt, 1H, $J = 7.5$ and 1.5 Hz, 7-H or 8-H), 7.69 (dt, 1H, $J = 7.5$ and 1.5 Hz, 8-H or 7-H), 7.94 (dd, 1H, $J = 7.5$ and 1.5 Hz, 6-H or 9-H), 8.06 (dd, 1H, $J = 7.5$ and 1.5 Hz, 9-H or 6-H); ^{13}C NMR δ: 15.5 (CH_2), 27.6 (CH_2), 73.2 (CH), 114.1 (C), 126.6 (CH), 128.6 (CH), 132.0 (C), 133.1 (CH), 134.6 (C), 135.5 (CH), 143.9 (C), 181.9 (C), 182.1 (C). Anal. calcd. for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.34; H, 4.97; N, 5.89.

Benzo[g]quinoline-5,10-dione (14)

A suspension of compound **12** (100 mg, 0.44 mmol), silica gel (0.5 g), and *p*-chloranil (108.2 mg, 0.44 mmol) in DCM (25 mL) was heated to reflux for 1 h. After filtration and evaporation, the residue was purified by column chromatography using DCM as eluent to afford **14** (59 mg, 65%); mp 274–275°C (lit.[14] mp 275–276°C).

ACKNOWLEDGMENTS

We are grateful to Fondo Nacional de Desarrollo Científico y Tecnológico (FONDECYT, Research Grant 1060592) and Comisión Nacional de Investigación Científica y Tecnológica (CONICYT, fellowship to L. C. and Research Grant AT24080019).

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