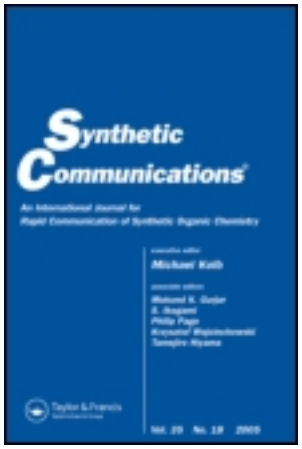


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Facile, One-Pot, Three-Component Synthesis of Benzo[a]naphthacene-8,13-diones

Vakiti Srinivas [a] & Vedula Rajeswar Rao [a]

[a] Department of Chemistry, National Institute of Technology, Warangal, India

Accepted author version posted online: 20 Jul 2011.Published online: 06 Oct 2011.

To cite this article: Vakiti Srinivas & Vedula Rajeswar Rao (2012) Facile, One-Pot, Three-Component Synthesis of Benzo[a]naphthacene-8,13-diones, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 42:3, 388-393, DOI: 10.1080/00397911.2010.524961

To link to this article: http://dx.doi.org/10.1080/00397911.2010.524961

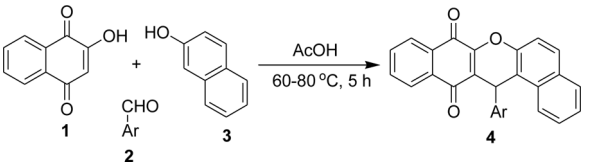
Synthetic Communications®, 42: 388–393, 2012

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2010.524961

FACILE, ONE-POT, THREE-COMPONENT SYNTHESIS OF BENZO[*a*]NAPHTHACENE-8,13-DIONES

Vakiti Srinivas and Vedula Rajeswar Rao
Department of Chemistry, National Institute of Technology, Warangal, India

GRAPHICAL ABSTRACT



Abstract *One-pot synthesis of 14-aryl-14*H*-7-oxa-benzo[*a*]naphthacene-8,13-diones was developed by the reaction of 2-hydroxynaphthalene-1,4-dione, aromatic aldehydes, and 2-naphthol in the presence of acetic acid. The structures of these compounds were identified by elemental analyses, infrared, ^1H NMR, and mass.*

Keywords Benzo[*a*]naphthacene-8,13-diones; lawsone; 2-naphthol

INTRODUCTION

The chemistry of quinones is of considerable interest, because this class of compounds includes many natural products and numerous important synthetic products.[1,2] Quinone derivatives may be toxic to cells by a number of mechanisms[3,4] including redox arylation, intercalation, induction of DNA strand breaks, generation of free radicals, and alkylation via quinone methide formation.[5] As a consequence, the molecular frameworks of a great number of pharmaceuticals and biologically important compounds contain a quinone moiety. Their importance in pharmocological activity is also attributed to the inhibition of special proteins, such as bacterial topoisomerase II-DNA gyrase (antibacterial),[6] mammalian topoisomerases I and II (antitumor),[7] and HIV-1 integrase and proteinase (antiviral).[8] Representative examples of this class of compounds are well-known anticancer drugs of the anthracycline series-doxorubicine and mitoxanthrone. The action of these compounds is believed to occur via topoisomerase II inhibition.[7]

Compounds containing the quinone group represent an important class of biologically active molecules that are widespread in nature.[9] However, to the best of

Received August 4, 2010.

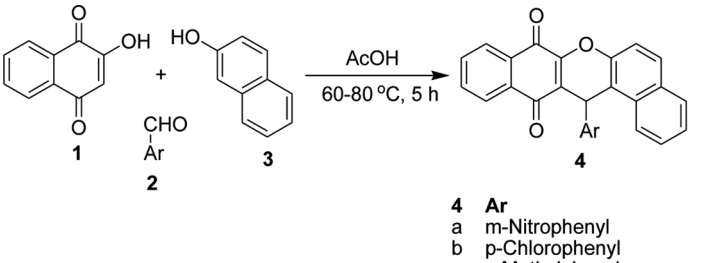
Address correspondence to V. Rajeswar Rao, Department of Chemistry, National Institute of Technology, Warangal 506 004, A.P., India. E-mail: vrajesw@yahoo.com

our knowledge, there are no reports on the synthesis of 14*H*-7-oxa-benzo [*a*]naphthacene-8,13-dione ring systems. The development of multicomponent reactions (MCRs) designed to produce elaborate biologically active compounds has become an important area of research in organic, combinatorial, and medicinal chemistry.[10–13] The MCR strategy offers significant advantages over conventional linear synthesis because of its flexible, convergent, and atom-efficient nature.[14,15] In continuation of our earlier work on the synthesis of heterocyclic quinones,[16,17] we report a one-pot synthesis of 14-aryl-14*H*-7-oxa-benzo [*a*]naphthacene-8,13-dione.

RESULTS AND DISCUSSION

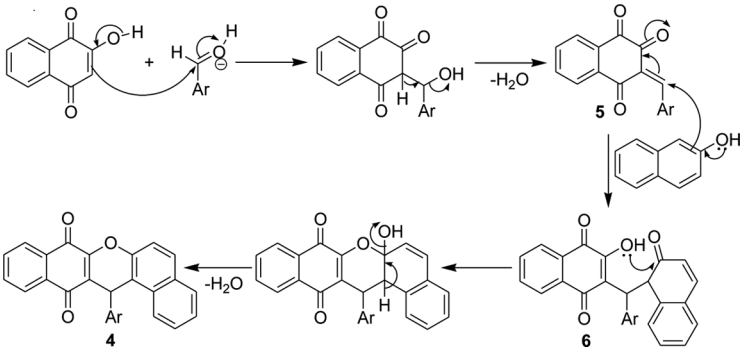
The one-pot, three-component reaction of lawsone **1** with various aromatic aldehydes **2** in the presence of 2-naphthol **3** proceeded rapidly in glacial acetic acid at 60–80 °C to afford 14-aryl-14*H*-7-oxa-benzo[*a*]naphthacene-8,13-dione **4** in good yields (Scheme 1).

A plausible mechanism for the formation of products **4** is proposed in Scheme 2. Acid-catalyzed condensation between **1** and **2** will give an intermediate **5**. The intermediate **5** on reaction with **3** gave another intermediate **6**. The intermediate formed in situ **6** undergoes cyclization to give the final product **4**. The newly prepared compounds revealed the presence of 1,4-quinone moiety by the reduction and aerial oxidation test with Zn/AcOH. The structures of products **4** were established on the basis of their elemental analyses, infrared (IR), ^{1}H and ^{13}C NMR, and mass spectral data. The ^{1}H NMR spectrum of **4a** exhibited one singlet for CH of pyranrine at δ 6.04 ppm and a multiplet observed at δ 7.52–8.28 ppm was assigned to aromatic protons. The proton decoupled ^{13}C NMR spectrum of **4a** displayed 27 distinct resonance signals, in agreement with the proposed structure. The quinone carbonyls appeared downfield at 182.0 and 182.9 respectively. The mass spectrum of **4a** showed a molecular ion peak at m/z 434 [M + H] (Table 1).



4	Ar
a	m-Nitrophenyl
b	p-Chlorophenyl
c	p-Methylphenyl
d	p-Methoxyphenyl
e	o-Hydroxy-m-methoxyphenyl
f	m,m,p-Trimethoxyphenyl
g	N,N-Dimethylaminophenyl
h	Phenyl
i	2-Naphthyl

Scheme 1. One-pot, three-component reaction of 2-hydroxy-1,4-naphthoquinone, aromatic aldehyde, and 2-naphthol.



Scheme 2. Mechanism of the reaction.

Table 1. One-pot, three-component reaction of 2-hydroxy-1,4-naphthoquinone, aromatic aldehyde, and 2-naphthol

Entry	Ar	Yield (%)[a]
4a	m-Nitrophenyl	94
4b	p-Chlorophenyl	92
4c	p-Methylphenyl	95
4d	p-Methoxyphenyl	93
4e	o-Hydroxy-m-methoxyphenyl	91
4f	m,m,p-Trimethoxyphenyl	96
4g	N,N-Dimethylaminophenyl	90
4h	Phenyl	93
4i	2-Naphthyl	96

[a]Isolated yields.

CONCLUSION

In conclusion, we have carried out a three-component synthetic method for preparation of some benzo[*a*]naphthacene-8,13-diones. This method has several advantages such as readily available starting materials, easy workup, and good yields of the products.

EXPERIMENTAL

Melting points were determined in open capillaries with a Cintex melting-point apparatus (Mumbai, India). Melting points are uncorrected, and CHNS analysis was done on a Carlo Erba EA 1108 automatic elemental analyzer. The purity of the compounds was checked by thin-layer chromatographic (TLC) plates (E. Merek, Mumbai, India), and IR spectra (KBr) were recorded on a Bruker WM-4(X) spectrometer (577 model). ^{1}H NMR spectra were recorded on a Bruker WM 400-MHz spectrometer in δ ppm using tetramethylsilane (TMS) as internal standard. Mass spectra (EI-MS) were determined on a Perkin-Elmer (SCIEX API-2000, ESI) instrument at 12.5 eV.

General Procedure for the Synthesis of 14-Aryl-14*H*-7-oxa-benzo[*a*]naphthacene-8,13-dione (4)

A mixture of lawsone (1 mmol), aromatic aldehyde (1 mmol), and 2-naphthol (1 mmol) was stirred at 60–80 °C for 5 h. The progress of the reaction was monitored by TLC (20% methanol in chloroform). After completion of the reaction, the solid separated was filtered and washed with water. The crude product was purified by recrystallization from ethanol to give **4**.

Data

14-(3-Nitrophenyl)-14*H*-7-oxa-benzo[*a*]naphthacene-8,13-dione (4a). Yellow powder, mp > 300 °C; IR (KBr) (ν_{max}/cm^{-1}): 3070 (C-H), 1698 (C=O), 1650 (C=O), 1527 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) (δ ppm): 6.04 (1H, s, CH of pyran ring), 7.52–8.28 (14H, m, ArH). Anal. calcd. for $C_{27}H_{15}NO_5$: C, 74.82; H, 3.49; N, 3.23%. Found: C, 72.77; H, 3.45; N, 3.19%.

14-(4-Chlorophenyl)-14*H*-7-oxa-benzo[*a*]naphthacene-8,13-dione (4b). Yellow solid, mp > 300 °C; IR (KBr) (ν_{max}/cm^{-1}): 2911 (C-H), 1703 (C=O), 1665 (C=O), 1576 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) (δ ppm): 5.83 (1H, s, CH of pyran ring), 7.26–8.27 (14H, m, ArH). Anal. calcd. for $C_{27}H_{15}ClO_3$: C, 76.69; H, 3.58%. Found: C, 76.61; H, 3.52%.

14-(4-Methylphenyl)-14*H*-7-oxa-benzo[*a*]naphthacene-8,13-dione (4c). Orange powder, mp > 300 °C; IR (KBr) (ν_{max}/cm^{-1}): 2914 (C-H), 1703 (C=O), 1665 (C=O), 1575 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) (δ ppm): 2.13 (3H, s, CH_3), 5.76 (1H, s, CH of pyran ring), 6.99–8.27 (14H, m, ArH). Anal. calcd. for $C_{28}H_{18}O_3$: C, 83.57; H, 4.51%. Found: C, 83.52; H, 4.48%.

14-(4-Methoxylphenyl)-14*H*-7-oxa-benzo[*a*]naphthacene-8,13-dione (4d). Yellow powder, mp > 300 °C; IR (KBr) (ν_{max}/cm^{-1}): 2931 (C-H), 1702 (C=O), 1666 (C=O), 1580 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) (δ ppm): 3.69 (3H, s, OCH_3), 5.97 (1H, s, CH of pyran ring), 6.75 (2H, d, $J = 8.8$ Hz, ArH), 7.13 (2H, d, $J = 8.8$ Hz, ArH), 7.75–7.98 (10H, m, ArH). Anal. calcd. for $C_{28}H_{18}O_4$: C, 80.37; H, 4.34%. Found: C, 80.31; H, 4.39%.

14-(2-Hydroxy-3-methoxylphenyl)-14*H*-7-oxa-benzo[*a*]naphthacene-8,13-dione (4e). Yellow powder, mp > 300 °C; IR (KBr) (ν_{max}/cm^{-1}): 2938 (C-H), 1683 (C=O), 1656 (C=O), 1575 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) (δ ppm): 3.88 (3H, s, OCH_3), 5.75 (1H, s, CH of pyran ring), 6.68–6.70 (1H, m, ArH), 6.96–7.07 (2H, m, ArH), 7.78–8.07 (10H, m, ArH). Anal. calcd. for $C_{28}H_{18}O_5$: C, 77.41; H, 4.18%. Found: C, 77.36; H, 4.39%.

14-(3,3,4-Trimethoxylphenyl)-14*H*-7-oxa-benzo[*a*]naphthacene-8,13-dione (4f). Yellow powder, mp > 300 °C; IR (KBr) (ν_{max}/cm^{-1}): 2937 (C-H), 1708 (C=O), 1673 (C=O), 1592 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) (δ ppm): 3.63 (9H, s, OCH_3), 5.98 (1H, s, CH of pyran ring), 6.52 (2H, s, ArH), 7.77–7.99 (10H, m, ArH). Anal. calcd. for $C_{30}H_{22}O_6$: C, 75.30; H, 4.63%. Found: C, 75.25; H, 4.69%.

14-(4-N,N-Dimethylaminophenyl)-14*H*-7-oxa-benzo[*a*]naphthacene-8,13-dione (4g). Brown powder, mp > 300 °C; IR (KBr) (ν_{max}/cm^{-1}): 3069 (C-H), 1693 (C=O), 1656 (C=O), 1587 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) (δ ppm): 2.50 (6H, s, N-CH_3), 3.95 (1H, s, CH of pyran ring), 6.78–8.10 (14H, m, ArH). Anal. calcd. for $C_{29}H_{21}NO_3$: C, 80.72; H, 4.91; N, 3.25%. Found: C, 80.65; H, 3.19; N, 3.20%.

14-Phenyl-14*H*-7-oxa-benzo[*a*]naphthacene-8,13-dione (4h). Orange powder, mp > 300 °C; IR (KBr) (ν_{max}/cm^{-1}): 3021 (C-H), 1697 (C=O), 1654 (C=O), 1571 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) (δ ppm): 5.81 (1H, s, CH of pyran ring), 7.08–8.28 (15H, m, ArH). Anal. calcd. for $C_{27}H_{16}O_3$: C, 83.49; H, 4.15%. Found: C, 83.41; H, 4.12%.

14-(2-Naphthyl)-14*H*-7-oxa-benzo[*a*]naphthacene-8,13-dione (4i). Orange powder, mp > 300 °C; IR (KBr) (ν_{max}/cm^{-1}): 2918 (C-H), 1673 (C=O), 1636 (C=O), 1574 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) (δ ppm): 5.99 (1H, s, CH of pyran ring), 7.40–8.31 (17H, m, ArH). Anal. calcd. for $C_{31}H_{18}O_3$: C, 84.92; H, 4.14%. Found: C, 84.91; H, 4.10%.

ACKNOWLEDGMENT

We thank the University Grants Commission, New Delhi [F. no. 32-201/2006 (SR)] for financial support.

REFERENCES

1. Patai, S.; Rappoport, Z. *The Chemistry of Quinonoid Compounds*; Wiley Interscience: New York, 1988, vol. 2, pp. 552–570.
2. Ulrich, H.; Richter, R. In *Methoden der Organischen Chemie, Chinone Teil 1, p-Chinone der Benzol und Naphthalin Reihen*; C. Grundmann (Ed.); Georg-Thieme Verlag: Stuttgart, 1977.
3. Webb, J. L. In *Enzyme and Metabolic Inhibitors*; Academic Press: New York, 1996; vol. 3, pp. 421–594.
4. Marion, G. M.; Adrian, R.; Gerald, M. C. Mechanisms of toxicity of naphthoquinones to isolated hepatocytes. *Biochem. Pharmacol.* **1986**, *35*, 1177–1184.
5. Moore, H. W. Bioactivation as a model for drug design bioreductive alkylation. *Science.* **1977**, *197*, 527–532.
6. Barrett, J. F.; Gootz, T. D.; McGuirk, P. R.; Farrell, C. A.; Sokolowski, S. A. Use of in vitro topoisomerase II assays for studying quinolone antibacterial agents. *Antimicrob. Agents Chemother.* **1989**, *33*, 1697–1703.
7. Foglesong, P. D.; Reckord, C.; Swink, S. Doxorubicin inhibits human DNA topoisomerase I. *Cancer Chemther. Pharmacol.* **1992**, *30*, 123–125.
8. Fesen, M. R.; Kohn, K. W.; Leteurtre, F.; Pommier, Y. Inhibitors of human immunodeficiency virus integrase. *Natl. Acad. Sci. U.S.A.* **1993**, *90*, 2399–2403.
9. Dewick, P. M. In *Medicinal Natural Products*, 2nd ed.; Wiley: Chichester, UK, 2002.
10. Orru, R. V. A.; Greef, D. M. Recent advances in solution-phase multicomponent methodology for the synthesis of heterocyclic compounds. *Synthesis* **2003**, *10*, 1471–1499.
11. Balme, G.; Bossharth, E.; Monteiro, N. Pd-assisted multicomponent synthesis of heterocycles. *Eur. J. Org. Chem.* **2003**, 4101–4111.

12. Bräse, S.; Gil, C.; Knepper, K. The recent impact of solid-phase synthesis on medicinally relevant benzoannelated nitrogen heterocycles. *Bioorg. Med. Chem.* **2002**, *10*, 2415–2437.
13. Dömling, A.; Ugi, I. Multicomponent reactions with isocyanides. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168–3210.
14. Weber, L. Multi-component reactions and evolutionary chemistry. *Drug. Discov. Today* **2002**, *7*, 143–147.
15. Dömling, A. Recent advances in isocyanide-based multicomponent chemistry. *Curr. Opin. Chem. Biol.* **2002**, *6*, 306–313.
16. Srinivas, V.; Rajeswar Rao, V. Regioselective synthesis of thiadiazolo[3,2-*a*]benzimidazole-5,8-diones. *J. Chem. Res.* **2009**, 679–681.
17. Srinivas, V.; Rajeswar Rao, V. A highly regioselective synthesis of 8-hydroxy-3-sulfanyl-7-undecyl-5*H*-[1,2,4]triazolo[3,4-b][1,3,4]benzothiadiazole-6,9-dione and its derivatives. *J. Chem. Res.* **2010**, 80–82.