Simple Synthesis of Benzo[*g*]imidazo[1,2-*a*]quinolinedione Derivatives *via* a One-Pot, Four-Component Reaction

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Simple Synthesis of Benzo[*g*]imidazo[1,2-*a*]quinolinedione Derivatives *via* a One-Pot, Four-Component Reaction

Mohammad Bayat[*a], Fahimeh Hosseini[a], Behrouz Notash[b]

[a] *Chemistry Department, Imam Khomeini International University, Qazvin, Iran*
Tel: +98 (28)33780040; Fax: +98 (28)33780040; E-mail: bayat_mo@yahoo.com; m.bayat@sci.ikiu.ac.ir
[b] *Department of Chemistry, Shahid Beheshti University, G. C., Evin, Tehran 1983963113, Iran*

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ABSTRACT

The one-pot multicomponent synthesis of benzo[*g*]imidazo[1,2-*a*]quinolone-6,11-dione derivatives in good to high yields, from readily available starting materials including ethylenediamine, 1,1-bis(methylthio)-2-nitroethene, 2-hydroxy-1,4-naphthoquinone and aromatic aldehydes is described. This protocol has the advantages of simple work-up, mild reaction conditions and provides a powerful entry into fused polycyclic structures related to bioactive heterocycles.

Introduction

Heterocyclic compounds, especially nitrogen containing heterocycles, are important natural and synthetic materials.[1,3] Among them, benzo[*g*]quinoline-5,10-dione derivatives exhibit significant biological activities (Fig. 1).[4] Representative naturally occurring compounds containing benzo[*g*]quinoline-5,10-dione skeletons[4] are cleistopholine[5] (antimicrobial, anticancer), phomazarin[6] (cytotoxic), and the jadomycins[7] (antibacterial, anti-tumor, antiviral, cytotoxic, aurora-B kinase inhibitor).

Multicomponent reactions (MCRs) play an important role in organic and medicinal chemistry because of their ability to synthesize drug-like compounds[8-12] with large degrees of structural diversity in a single step. MCRs also offer the advantage of simplicity and synthetic efficiency over conventional chemical reactions as well as selectivity, convergency, and atom-economy.[13]

The numerous attractive features of cyclic ketene aminals have made them important intermediates for the construction of a wide variety of heterocyclic systems. During recent years, they have been used for the synthesis of various fused heterocycles and drug-like compounds.[1,4,8,14-18] An examination of the literature showed that ethanol was often used as a compatible solvent.[19]

Herein, we report the regioselective synthesis of a new class of 5-aryl-4-nitro-1,2,3,5-tetrahydro-benzo[*g*]imidazo[1,2-*a*]quinolone-6,11-dione derivatives *via* a catalyst free, one-pot, four-component condensation reaction.

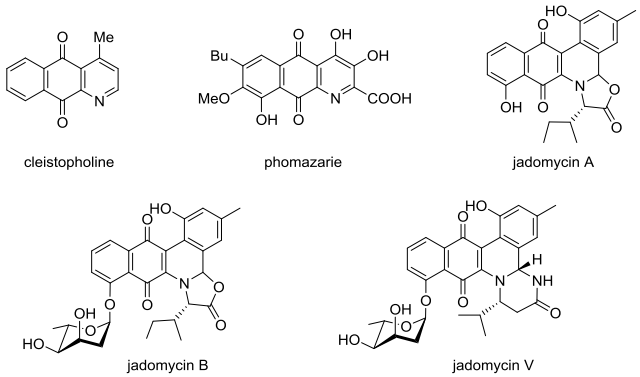
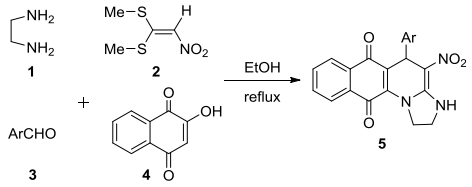


Figure 1. Selected examples of naturally occurring benzo[*g*]quinoline-5,10-dione skeletons.

Result and discussions

Benzo[*g*]imidazo[1,2-*a*]quinolinedione **5** were synthesised *via* a four-component reaction from ethylenediamine, 1,1-bis(methylthio)-2-nitroethene, 2-hydroxy-1,4-naphthoquinone and aromatic aldehydes in EtOH at reflux (Scheme 1).



Scheme 1. Preparation of 5-aryl-4-nitro-1,2,3,5-tetrahydro-benzo[*g*]imidazo[1,2-*a*]quinolone-6,11-dione **5**.

The structures of compounds **5a-l** (Table 1) were characterized on the basis of IR, ^{1}H NMR, ^{13}C NMR and mass spectra. The mass spectrum of **5a** displayed the molecular ion peak at *m/z* 373, which was in agreement with the proposed structure. The IR spectrum of this compound showed absorption bands due to NH stretching (3320 cm^{-1}) as well as bands at 1641, 1480 and 1438, 1357 cm^{-1} due to the C=O, C=C and NO_2 groups. The ^{1}H NMR spectrum of **5a** showed three multiplets for two CH_2 groups (δ 3.83-3.89, 4.42-4.52, 4.62-4.68 ppm), one singlet for the CH methine (δ 5.45 ppm), one singlet for the NH group (δ 9.67 ppm) and a multiplet in the aromatic region of the spectrum (δ 7.09-8.01 ppm) for the aromatic moieties. The ^{1}H-decoupled ^{13}C NMR spectrum of **5a** showed 19 distinct resonances.[20] Two signals at 180.1 and 181.3 ppm, which were assigned as two unsaturated 1,4-dicarbonyl groups, revealed the selective formation of **5a**. The product **5** is the more stable one owing to effective conjugation of the double bond with the 1,4-dicarbonyl groups. Unambiguous evidence for the selectivity and structure of **5** was obtained from single crystal X-ray crystallographic analysis.[21] An ORTEP diagram of **5b** is shown in Figure 2.

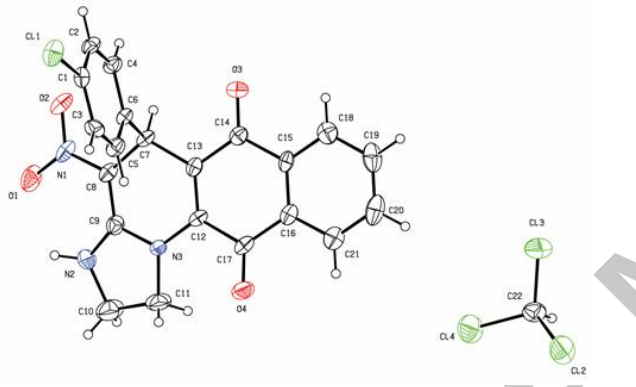
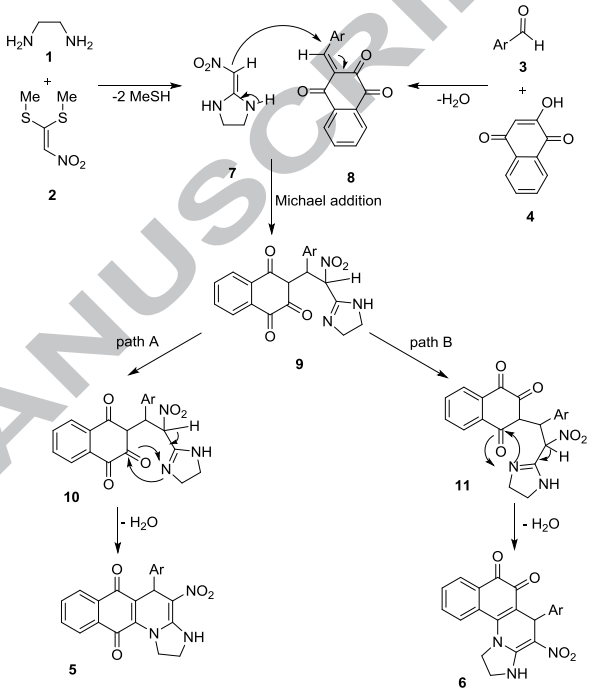


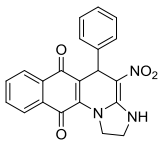
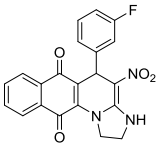
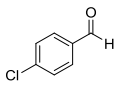
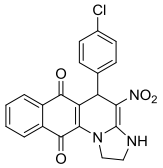
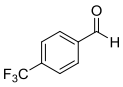
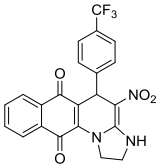
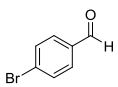
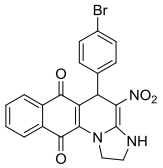
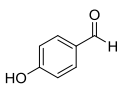
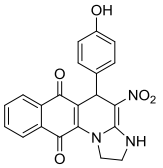
Figure 2. ORTEP diagram of **5b**. Thermal ellipsoids are at the 30% probability level.

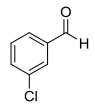
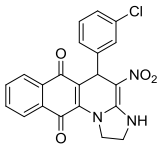
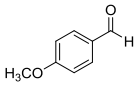
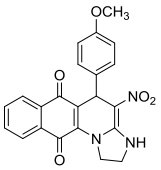
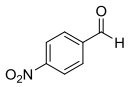
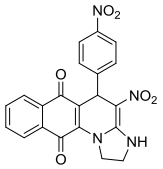
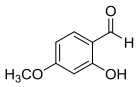
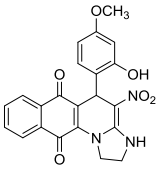
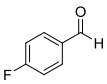
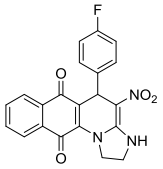
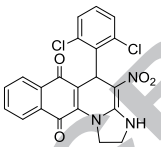
A proposed mechanism for product formation is shown in Scheme 2. Firstly, addition of ethylenediamine to 1,1-bis(methylthio)-2-nitroethene leads to the formation of ketene aminal **7** while Knoevenagel condensation between the aldehyde and 2-hydroxy-1,4-naphthoquinone would give intermediate **8**. The ketene aminal **7** then adds to the Knoevenagel adduct **8** to give intermediate **9**, which undergoes successive imine-enamine tautomerization, followed by nucleophilic addition of the secondary amino group to the more reactive carbonyl group, to give product **5**. Intermediate **9** can potentially cyclize by two paths. The spectral data analyses showed that product **6** of path B was not formed (chemical shift of carbonyl carbons for **6** are specially deshielded more than 190 ppm) and the four-component reaction described, shows high regioselectivity for the formation of product **5**.



Scheme 2. Proposed mechanism for the formation of benzo[*g*]imidazo[1,2-*a*]quinolinedione **5**.

Table 1. Synthesis of compounds **5a-l**

Entry	ArCHO	Product	Time (h)	Yield (%)	Entry	ArCHO	Product	Time (h)	Yield (%)
5a			1.5	82	**5g**			1.5	62
5b			1	86	**5h**			2	68
5c			1	89	**5i**			4	77

5d			1	85	**5j**			1.5	82
5e			1.5	91	**5k**			4	74
5f			2	74	**5l**			2	70

[a] Reagents and conditions: **1-4** (1 mmol), EtOH, 80 ºC.

In conclusion we have successfully synthesised various benzo[*g*]imidazo[1,2-*a*]quinolinedione derivatives in excellent yields *via* a catalyst free, four component reaction between 1,1-bis(methylthio)-2-nitro ethylene, ethylenediamine, 1,3-indandione and aromatic aldehydes.

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19. Chen, X.; Zhu, L.; Fang, L.; Yan, S.; Lin, J. *RSC Adv.* **2014**, *4*, 9926–9934.
20. ***4-nitro-5-phenyl-2,3-dihydrobenzo[g]imidazo[1,2-a]quinoline-6,11(1H,5H)-dione (5a):*** Red powder: mp 238-240 °C (dec.), 0.306 g, yield: 82%. IR (KBr) (ν_{max} /cm^{-1}): 3320 (NH), 1641 (C=O), 1480 (Ar), 1438 and 1357 (NO_2), 1252 (C-N). MS (EI, 70 eV): m/z (%) = 373 (M^+, 13), 340 (23), 327 (48), 296 (100), 250 (41), 193 (14), 139 (21), 105 (23), 77 (58), 51 (33), 41 (18). ^{1}H NMR (300 MHz, DMSO): δ 3.83-3.89 (2H, m, CH_2), 4.42-4.52 (1H, m, CH), 4.62-4.68 (1H, m, CH), 5.45 (1H, s, CH), 7.09-7.1 (1H, m, 1CH of Ar), 7.18-7.23 (2H, m, 2CH of Ar), 7.32 (2H, d, $^3J_{HH}$=7.5 Hz, 2CH of Ar), 7.78-8.01 (4H, m, 4CH of Naph.), 9.67 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO): δ 38.3 (CH), 44.6 (CH_2NH), 48.6 (CH_2N), 106.6 (C-NO_2), 122.9, 125.7, 126.7, 127.1, 128.5, 128.7, 131.3, 131.4, 134.1, 135.0, 139.0, 143.6, 152.7 (C=C-NO_2), 180.1 (C=O), 181.3 (C=O).
21. Single crystal X-ray data for **5b**: $C_{22}H_{15}Cl_4N_3O_4$, M = 527.17, monoclinic system, space group $P2_1/c$, a = 11.309(2), b = 16.327(3), c = 12.264(3) Å; β = 106.41(3) º; V = 2172.2(8) Å^3, Z = 4, D_{calcd} = 1.612 g cm^{-3}, μ (Mo-Kα)= 0.376 mm^{-1}, crystal dimension of 0.35×0.25×0.20 mm. The X-ray diffraction measurement was made on a STOE IPDS-II diffractometer with graphite monochromated Mo-Kα radiation. The structure was solved by using SHELXS. The Data reduction and structure refinement was carried out with SHELXL using the X-STEP32 crystallographic software package.[BB] The non-hydrogen atoms were refined anisotropically by full matrix least-squares on F^2 values to final R_1 = 0.0907, wR_2 = 0.1495 and S = 0.965 with 302 parameters using 3823 independent reflection (θ range = 2.49-24.99º). The crystallographic information file has been deposited with the Cambridge Data Centre, CCDC 1509896. *X-STEP32 Version 1.07b, Crystallographic Package*; Stoe & Cie GmbH: Darmstadt, Germany, 2000.

Supplementary Material

Experimental procedure and spectral data (copies of ^{1}H, ^{13}C NMR, IR and mass spectra of products, and crystallographic data for **5b**) can be found at http://.

The advantages of the presented procedure are as following:

The catalyst-free reactions carried out in EtOH are considerably safer, nontoxic, environmentally friendly, and inexpensive. The absence of a catalyst for the reaction avoids the use of moisture sensitive and heavy metal such as Lewis acids. This method is applicable to the synthesis of different types of benzo[g]imidazo[1,2-a]quinolinediones.

Graphical Abstract

Simple Synthesis of Benzo[*g*]imidazo [1,2-*a*]quinolinedione Derivatives *via* a One-Pot, Four-Component Reaction

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