Tetrahedron Letters 53 (2012) 7085–7087

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A novel one-pot pseudo five-component isocyanide-based reaction: synthesis of 2,6-bis(alkylamino)-benzofuro[5,6-*b*]furan-4,8-dione derivatives

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ARTICLE INFO

Article history:
Received 21 April 2012
Revised 5 October 2012
Accepted 18 October 2012
Available online 27 October 2012

Keywords:
Isocyanide
Benzofuran
Quinone
Multi-component

ABSTRACT

A novel one-pot pseudo five-component reaction of isocyanides with 2,5-dihydroxycyclohexa-2,5-diene-1,4-dione and various aliphatic and aromatic aldehydes in ethanol at room temperature has been studied. 2,6-Bis(alkylamino)-benzofuro[5,6-*b*]furan-4,8-dione derivatives were isolated as the products in good yields after 24 h.

Natural and synthetic quinonoid compounds are well known. They continue to demand attention by virtue of their presence in antitumor quinone natural products such as (−)-saframycin[1] and *rac*-mitomycin.[2,3] This category of compounds has a variety of biological properties such as antibacterial, antifungal, antiprotozoal, inhibition of the human immunodeficiency virus (HIV)-1 reverse transcriptase, and antitumor activity.[4–9] Kendomycin [(−)-TAN 2162] **A**, a novel ansamycin compound has been shown to be a potent endothelin receptor antagonist and an anti-osteoporotic compound with remarkable antibacterial and cytostatic activity.[10] Balsaminones A (**B**) and B (**C**) were isolated from the pericarp of fruit of *Impatiens balsamina* L. and have significant antipruritic activity[11] (Fig. 1). Some of these pharmacological effects have been attributed to the formation of DNA-damaging anion-radical intermediates formed by bioreduction of the quinone nucleus.[12]

Furans are useful synthetic intermediates[13–15] finding utility as masked α,β-unsaturated esters,[16] and as precursors to hydroxypyranones[17] and polyoxygenated natural products[18] as well as to mono- and oligosaccharides.[19] Furan substructures are an important motif in materials chemistry providing promising plastics derived from renewable sources,[20] self-healing macromolecular materials,[21] conducting polymers,[22] and photovoltaics.[23] Hence, the synthesis of furans has attracted considerable attention.[24–26]

As part of our continuing interest in the development of new synthetic methods in heterocyclic chemistry and our interest in isocyanide-based multi-component reactions (IMCRs),[27] we describe an efficient synthesis of fully substituted 2,6-bis(alkylamino)-benzofuro[5,6-*b*]furan-4,8-dione derivatives **4a**–**m** in high yields via the reaction of 2,5-dihydroxycyclohexa-2,5-diene-1,4-dione (**1**), aldehydes **2**, and isocyanides **3** in EtOH as the solvent at room temperature (Scheme 1).

This chemistry permits us to introduce molecular diversity under mild reaction conditions and to synthesize a large number of 2,6-bis(alkylamino)-benzofuro[5,6-*b*]furan-4,8-dione derivatives **4a**–**m**.[28] The reaction is straightforward and treatment of 2,5-dihydroxycyclohexa-2,5-diene-1,4-dione (**1**) (1 mmol) and various aldehydes **2** (2 mmol) with isocyanides **3** (2 mmol) in EtOH (10 mL) led to the formation of **4a**–**m** (Fig. 2).

The structures of compounds **4a**–**m** were deduced from their IR, mass, elemental analyses, and ^{1}H NMR spectral data. For example, the ^{1}H NMR spectrum of **4a** consisted of a multiplet for the cyclohexyl ring protons (δ = 1.02–1.98), a broad signal for the NH–*CH* cyclohexyl protons (δ = 2.86), a broad singlet for the NH (δ = 6.45) protons, and two broad resonances for the aromatic protons (δ = 7.74 and 8.16). It is noteworthy that the ^{13}C NMR spectra of

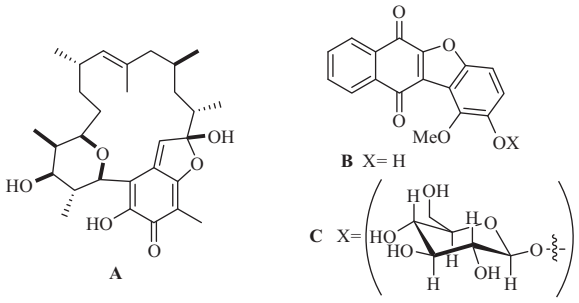

Figure 1. Some biologically active quinones.

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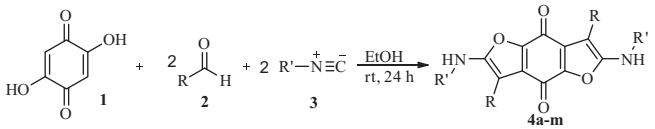
0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.10.072



R= aliphatic or aromatic
R'= cyclohexyl, 1,1,3,3-tetramethylbutyl or *tert*-butyl

Scheme 1. Synthesis of 2,6-bis(alkylamino)-benzofuro[5,6-*b*]furan-4,8-dione derivatives **4a**–**m**.

most of the products did not show any signals even after extended scanning. For products **4e**, **4g**, and **4j** signals were observed only for the non-aromatic segment of the molecule. For example, the ^{13}C NMR spectrum of **4e** exhibited four signals for the cyclohexyl rings and the signals for the other C-atoms were not evident (see supplementary data). More interestingly, the signals for the OMe groups, as substituents on the phenyl rings, were also not observed. Apparently, the presence of a free radical in the molecule and its resonance within the aromatic systems caused major portions of the ^{13}C NMR spectra associated with the aromatic systems and their substituents to collapse. Attempts to record ^{13}C NMR spectra of the products using *d*-TFA and d_5-pyridine also failed. Furthermore, attempts were made to transform the products into the corresponding alcohols via electrochemical reduction, however they were not reduced under these conditions. Such behavior has also been reported for similar compounds,[29] which are in accord with our results and conclusions.

Although no mechanistic studies have been carried out, it is conceivable that the initial event is the condensation between the 2,5-dihydroxycyclohexa-2,5-diene-1,4-dione (**1**) and the aldehyde **2** providing intermediate **5**. These are reactive species with an *o*-quinone methide (oQM) scaffold.[30] Then, on the basis of the well-established chemistry of reactions of isocyanides with electron deficient heterodienes,[31] the intermediates **5** may undergo a [1+4] cycloaddition reaction with the isocyanides to produce intermediate **6**. Imine to enamine tautomerization produces compound **7**, which then undergoes a comparable sequence to form the furan on the other side scheme 2.

In summary, we have developed an efficient and potentially useful novel reaction for the synthesis of 2,6-bis(alkylamino)-benzofuro[5,6-*b*]furan-4,8-diones **4a**–**m**. The products were formed in good yields on mixing the readily available substrates in ethanol as the solvent. The broad scope, operational simplicity, practicality, and mild reaction conditions render this an attractive

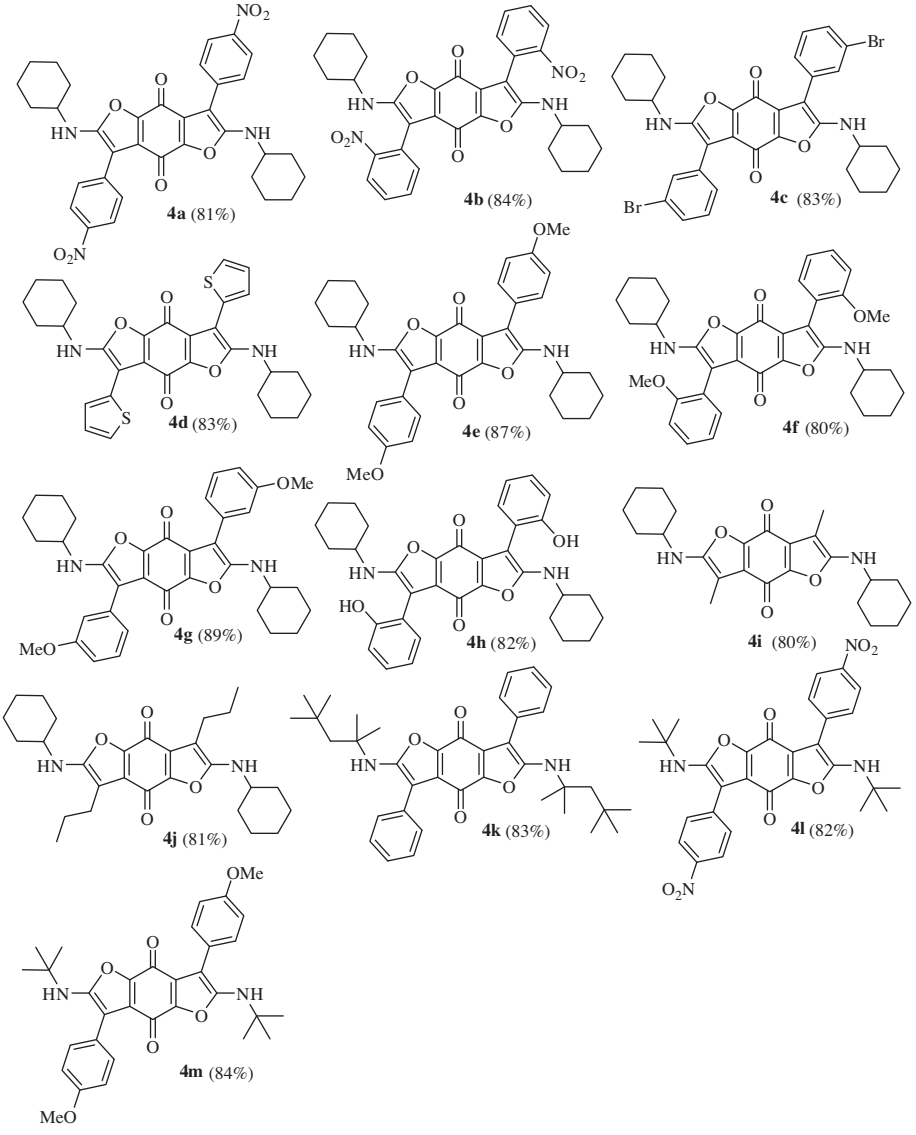
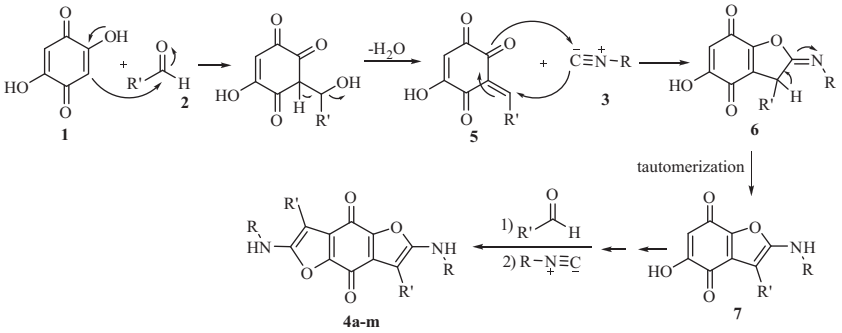


Figure 2. The structures and isolated yields of products **4a**–**m**.



Scheme 2. Proposed mechanism for the formation of compounds **4a**–**m**.

approach for the generation of different 2,6-bis(alkylamino)-benzofuro[5,6-*b*]furan-4,8-diones. This reaction may find use in diversity-oriented synthesis and for the design of pharmaceutical substance libraries.

Acknowledgments

We gratefully acknowledge financial support from the Iran National Science Foundation (INSF) and the Research Council of Shahid Beheshti University.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.072.

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28. Typical procedure illustrated by the synthesis of 2,6-bis(cyclohexylamino)-3,7-bis(4-nitrophenyl)benzofuro[5,6-*b*]furan-4,8-dione (**4a**). To a stirred solution of 2,5-dihydroxycyclohexa-2,5-diene-1,4-dione (**1**) (1 mmol) and 4-nitrobenzaldehyde (**2**) (2.1 mmol) in EtOH (10 mL), cyclohexyl isocyanide **3** (2.1 mmol) was added. The mixture was stirred for 24 h at room temperature. After completion of the reaction (monitored by TLC), the solvent was removed under vacuum and the residue purified by column chromatography using *n*-hexane–EtOAc (1:4) as the eluant. The appropriate fractions were pooled and the solvent removed by evaporation to give the product **4a** as a black powder (0.51 g, 81%); dec. >190 °C. IR (KBr) cm^{-1}: 3319, 2930, 2855, 1700, 1669, 1516, 1347. ^1H NMR (300.13 MHz, DMSO-d_6) δ: 1.02–1.98 (20H, m, 10CH_2 of cyclohexyl), 2.86 (2H, br s, 2*CH*NH), 6.45 (2H, br s, 2NH), 7.74 (4H, br s, CH-Ar), 8.16 (4H, br s, CH-Ar). 624 (M^+, 5), 608 (5), 578 (5), 532 (5), 494 (5), 444 (10), 323 (55), 271 (60), 189 (30), 83 (70), 55 (100). Anal. Calcd for $C_{34}H_{32}N_4O_8$: C, 65.38; H, 5.16; N, 8.97. Found C, 65.39; H, 5.18; N, 8.99.
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