One-Pot Synthesis of Novel Highly Functionalized Furan-Based Polyphenolics

Article in Synlett · October 2015
DO: 0.055/s0035560580

8 authors, including:

Oualid Talhi
Centre de Recherche Scientifique et Technique...
31 PUBL CA ONS 72 C A ONS
SEE PROF LE

K. Bachari
Centre de Recherche Scientifique et Technique...
125 PUBL CA ONS 460 C A ONS
SEE PROF LE

Gilbert Kirsch
University of Lorraine
354 PUBL CA ONS 3,210 C A ONS
SEE PROF LE

Artur M S Silva
University of Aveiro
802 PUBL CA ONS 8,614 C A ONS
SEE PROF LE

Some of the authors of this publication are also working on these related projects:

Valorization of Algerian vegetable waste in the wastewater treatment View project

Synthesis and reactivity of 3 acetyl 2 aminothiophenes View project
One-Pot Synthesis of Novel Highly Functionalized Furan-Based Polyphenolics


QOPNA, Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal
oualid.talhi@ua.pt
artur.silva@ua.pt

CICECO – Aveiro Institute of Materials, Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal
Centre de Recherche Scientifique et Technique en Analyses Physico-Chimiques CRAPC, BP384, Bou-Ismail, 42004, Tipaza, Algeria
Laboratoire Structure et Réactivité des Systèmes Moléculaires Complexes, UMR 7565, Université de Lorraine, Avenue du Général Delestraint, 57070 Metz, France

Received: 12.09.2015
Accepted after revision: 04.10.2015
Published online: 21.10.2015

Abstract
Novel, highly functionalized furan-based polyphenolics were prepared. The employed methodology involves a one-pot 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) catalyzed 1,4-conjugate addition of 1,3-dicarbonyl compounds on 3-bromochromones, furan heterocyclization, and chromanone ring opening.

Key words furan, polyphenols, 1,3-dicarbonyl compounds, 1,4-conjugate addition, ring transformation

The furan heterocycle is found in a variety of synthetic and natural compounds, and some of these present a myriad of biological activities, such as antitumor1 and antiviral activity,2 among others.3 The furan moiety is also considered an important structural unit in polymers.4 Furthermore, furfural and 5-hydroxymethylfurfural are basic nonpetroleum chemicals that can be transformed into numerous chemical intermediates of high industrial value.5

One of the most important methods for the synthesis of furans is the Paal–Knorr approach, which consists of the acid-catalyzed dehydrative cyclization of 1,4-dicarbonyl compounds.6 Domino and multicomponent procedures7 and transition-metal-catalyzed synthesis8 are other methods that are used for the preparation of furan-based derivatives. Nevertheless, due to the multiple operating reaction steps and chemical-consuming drawbacks associated with the currently reported methods, there remains a need to develop procedures that can be conducted under milder reaction conditions towards furan-based derivatives.

Chromones, which are an important family of oxygen-containing heterocyclic compounds,9 are desirable and versatile starting materials for the design of a variety of het-
Erocylic molecules, especially several with important biological applications. Halogen-containing chromones are a small but interesting group of compounds because of the synthetic transformations they can undergo. Iaroshenko and Langer recently reported the synthesis of functionalized 2-salicyloylfurans by reacting 3-halochromones with \( \beta \)-ketoamides using a one-pot protocol. Moreover, Gammill reported the reaction of 3-bromochromone with dialkyl \( \beta \)-diketones or \( \beta \)-ketoesters in the presence of DBN or DBU to prepare trisubstituted furans.

Following our interest in preparing oxygen-containing heterocyclic polyphenolics with potential biological properties using 3-bromochromones as starting materials, we report herein the synthesis of novel, highly functionalized polysubstituted furan derivatives. The methodology utilized involves the reaction of 3-bromochromones \( 1a,b \) with a series of substituted 1,3-dicarbonyl compounds \( 2a-h \) catalyzed by DBU (Scheme 1, Table 1).

**Table 1** Furan-Based Polyphenolics 3a–i and Starting 3-Bromochromones 1a,b and 1,3-Dicarbonyl Compounds 2a–h

<table>
<thead>
<tr>
<th>3-Bromochromone</th>
<th>1,3-Dicarbonyl compound</th>
<th>Furan product</th>
</tr>
</thead>
<tbody>
<tr>
<td>( 1a )</td>
<td>( 2a )</td>
<td>( 3a )</td>
</tr>
<tr>
<td>( 2b )</td>
<td>( 3b )</td>
<td>48</td>
</tr>
<tr>
<td>( 2c )</td>
<td>( 3c )</td>
<td>56</td>
</tr>
</tbody>
</table>

**Scheme 1** Synthetic pathway and proposed mechanism for the synthesis of furan-based polyphenolics 3a–i
Table 1 (continued)

<table>
<thead>
<tr>
<th>3-Bromochromone</th>
<th>1,3-Dicarbonyl compound</th>
<th>Furan product</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>Br</td>
<td>MeO</td>
<td>76</td>
</tr>
<tr>
<td>2a</td>
<td></td>
<td>MeO</td>
<td>52</td>
</tr>
<tr>
<td>2f</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2g</td>
<td>Cl</td>
<td>MeO</td>
<td>38</td>
</tr>
<tr>
<td>2h</td>
<td>MeO, OMe</td>
<td>MeO, OMe, OMe</td>
<td>30</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yield after chromatographic purification and recrystallization.
The best results were achieved when a catalytic amount of base (1 drop) was used in THF heated to reflux for 48 hours, with furans 3a–i being obtained in moderate to good yields (30–76%). Given that, under these conditions, furan derivative 3d was obtained in moderate yield (36%) and some unreacted 3-bromochromone 1a and 1,3-dicarbonyl compound 2d remained, we examined the use of longer reaction times and increased quantities of base. However, under these conditions, the formation of the desired furan derivative was not favored; instead, increasing amounts of degradation products were observed. Although unsuccessful, the same study was performed for the derivatives obtained in lower yields.

The results seem to indicate that the reaction is favored by the use of less substituted 1,3-dicarbonyl reagents, which permits access to the corresponding furans 3a, 3e, and 3f in good yields (60–76%). The use of 1,3-dicarbonyl compounds with a styryl group as substituent leads to the corresponding 5-styryl substituted furan derivatives 3b and 3c (48 and 56%, respectively) in better yields than those of 3d and 3h, bearing the 5-phenyl group (36 and 38%, respectively). The synthetic procedure described herein possesses several advantages, including mild conditions and a one-pot protocol, and it is suitable for the construction of a library of important furan-based polyphenolic compounds (Table 1).16

As proposed by Gammill,13 the reaction presumably follows a tandem process that is initiated by an organobase-promoted 1,4-conjugate addition of 2 to 1, leading to intermediate I, which is in equilibrium with the corresponding enolic tautomer in the attached 1,3-dicarbonyl moiety II.17 This enolic form readily undergoes intramolecular heterocyclization, involving nucleophilic substitution of the bromo leaving group, affording a fused dihydrofuran-chromane intermediate III. Finally, this intermediate goes through a chromanone ring opening, and is converted into polysubstituted furan 3 (Scheme 1).

The most important structural features revealed from analysis of the 1H NMR spectra of furans 3a–i are the singlet corresponding to the resonance of the H-3 proton at δ = 7.35–7.61 ppm. However, the furan ring of derivative 3e displays two doublets at δ = 7.71 (H-3) and 8.20 (H-5) ppm as a result of the small coupling between protons H-3 and H-5 (JH3–H5 = 0.8 Hz). The 3′-OH and 3″-OH protons of the 2,4-benzoyl substituents appear at high frequency (δ = 11.88–12.80 and 11.86–12.03 ppm, respectively), due to intramolecular hydrogen bonding with the carbonyl groups. Furans 3b, 3c, and 3i, bearing a 5-styryl group, were mainly characterized by the presence of the CH=CH− double bond, which resonates as two doublets at δ = 7.22–7.37 (Hα) and 7.52–7.57 (Hβ) ppm, and exhibits a mutual coupling constant Jαα,Hβ of approximately 16 Hz, typical of the trans-conformation.

The structure of furans 3a–i was further confirmed by their 13C NMR spectra and by analysis of their HSQC and HMBC spectra (Figure 1 shows the main HMBC correlations for 3a). Differentiation between quaternary carbons C-2 (δ = 148.5–152.0 ppm) and C-4 (δ = 121.1–127.3 ppm) was achieved by examining the HMBC correlations that were established with the neighboring protons H-3, 5-CH3 and Hα in the 5-styryl substituted furans (Figure 1). Moreover, in all cases, the 4-C=O (δ = 190.1–195.8 ppm) was found to be more deshielded than the 2-C=O (δ = 182.6–184.8 ppm).

The structural features of furans 3a–i were further investigated by single-crystal X-ray diffraction analysis of compound 3a. This compound produced good-quality single crystals from a (1:1) mixture of hexane and dichloromethane by slow evaporation at 6 °C. Crystallographic studies show that 3a crystallizes in the centrosymmetric monoclinic P21/n space group,18 with the molecular unit present in the crystal structure confirming the structure previously indicated by NMR studies (Figure 2).

In summary, we have reported the preparation of furan-based polyphenolic derivatives by a one-pot synthetic methodology. This procedure starts with an organobase-catalyzed 1,4-conjugate addition of 1,3-dicarbonyl compounds onto 3-bromochromones and follows a tandem process of furan heterocyclization and chromanone ring open-
ing. The biological properties of these novel, highly functionalized furan-based polyphenolics will be investigated in due course.

Acknowledgment

Thanks are due to FCT/MEC for the financial support of the QOPNA research Unit (FCT UID/QUI/00062/2013) and CICECO–Aveiro Institute of Materials (FCT UID/CTM/50011/2013), through national funds and, where applicable, co-financed by the FEDER, within the PT2020 Program. Further thanks are due to CICECO for funding the purchase of a single-crystal X-ray diffractometer. J.L.C.S. is grateful to FCT for her PhD grant (SFRH/BD/76407/2011).

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560580.

References and Notes


Synlett

J. L. C. Sousa et al.

1.6 Hz, 1 H, H-5'), 7.22 (d, J = 16.5 Hz, 1 H, H-α), 7.16 (dd, J = 8.4, 1.9 Hz, 1 H, H-6'), 7.10 (dd, J = 8.4, 1.0 Hz, 1 H, H-4), 7.08 (dd, J = 8.4, 1.9 Hz, 1 H, H-2'), 7.02 (dd, J = 8.2, 7.2, 1.0 Hz, 1 H, H-6), 6.89 (d, J = 8.4 Hz, 1 H, H-5'), 6.54 (d, J = 2.5 Hz, 1 H, H-4'), 6.49 (dd, J = 9.0, 2.5 Hz, 1 H, H-6'), 5.95 (s, 3 H, 3''-OCH3), 3.93 (s, 3 H, 4''-OCH3), 3.89 (s, 3 H, 5''-OCH3). 13C NMR (125.77 MHz, CDCl3): δ = 191.9 (C-1”), 184.3 (C-1’), 166.6 (C-5”), 166.2 (C-3’), 163.3 (C-3”), 159.6 (C-5), 158.8 (C-4’), 149.3 (C-3’’), 148.9 (C-2’), 136.6 (C-β), 136.4 (C-5’), 133.7 (C-7’), 131.0 (C-7’’), 128.6 (C-1”), 123.0 (C-3’), 122.0 (C-6’’), 121.9 (C-4’), 119.3 (C-6’), 118.8 (C-2’), 118.7 (C-4’’), 114.0 (C-2’’’), 112.1 (C-α), 111.2 (C-5’’’), 109.3 (C-2’’’), 108.0 (C-6’’’), 101.3 (C-4’’’), 56.02, 56.00 (3’’’-OCH3), 55.77 (5”-OCH3). HRMS (ESI+): m/z calc’d for [C35H22O3ClHN+Na]+: 523.1363; found: 523.1344.

(E)-[5-(4-Chlorostyryl)furan-2,4-diyl]bis[(2-hydroxyphenyl)methanone] (3c): Yield: 249 mg (56%); yellow solid; mp 193-194 °C. 1H NMR (300.13 MHz, CDCl3): δ = 1.90 (s, 1 H, 3’-OH), 11.86 (s, 1 H, 3’’-OH), 8.21 (dd, J = 8.2, 1.5 Hz, 1 H, H-7’’), 7.72 (dd, J = 8.1, 1.6 Hz, 1 H, H-7’), 7.61 (s, 1 H, H-3’), 7.60-7.49 (m, 4 H, H-5’’’, 5”’, 3’’’’, 5’’’’), 7.53 (d, J = 16.3 Hz, 1 H, H-β), 7.38 (d, J = 8.6 Hz, 2 H, H-2’’, 6’’), 7.37 (d, J = 16.3 Hz, 1 H, H-α), 7.12-7.09 (m, 2 H, H-4’’, 4’’’), 7.03 (ddd, J = 8.1, 7.2, 1.2 Hz, 1 H, H-6’’), 6.96 (ddd, J = 8.2, 7.3, 1.1 Hz, 1 H, H-6’’’), 13C NMR (75.47 MHz, CDCl3): δ = 193.5 (C-1”), 184.4 (C-1’), 163.4 (C-3’), 163.0 (C-3’’), 159.2 (C-5’), 149.3 (C-2’), 137.0 (C-5’’), 136.6 (C-5’’’), 135.6 (C-1’’’), 135.5 (C-β), 133.9 (C-4’’’), 131.9 (C-7’’), 131.0 (C-7’’’), 129.3 (C-2’’’’, 6’’’), 128.8 (C-3’’’’, 5’’’’), 122.7 (C-3’), 122.5 (C-4’), 119.9 (C-2’), 119.4 (C-6’), 119.3 (C-6’’’), 118.8 (C-4’’’), 118.7 (C-2’’’), 114.5 (C-α). HRMS (ESI+): m/z calc’d for [C35H22O3ClHN+Na]+: 545.0837; found: 545.0833.


(18) Crystal Data for 3a: C17H12O2; M = 244.24: monoclinic; space group P21/n; Z = 4; a = 7.3330(9) Å, b = 10.5928(14) Å, c = 15.0866(19) Å, β = 90.62(4)°; V = 1171.7(3) Å³; μ(Mo-Kα) = 0.102 mm⁻¹; Dc = 1.385 g cm⁻³; colorless needle: crystal size 0.28 × 0.10 × 0.08 mm³. Of a total of 8785 reflections collected, 2126 were independent (Rint = 0.0685). Final R1 = 0.0494 [I > 2σ(I)] and wR2 = 0.1286 (all data). Data completeness to θ = 25.24°, 99.2%. Crystallographic data for 3a has been deposited into the Cambridge Crystallographic Data Centre with the deposition number CCDC 1409624.