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Regiospecific Michael reaction of (+)-euryfuran with activated 1,4-benzoquinones

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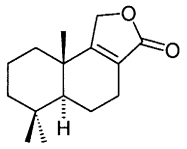
Abstract

(+)-Euryfuran cycloadds regiospecifically to activated monosubstituted 1,4-benzoquinones under mild conditions to give the corresponding Michael adducts which, depending on the quinone substituent, undergo in situ redox reactions to the respective euryfurylbenzoquinones. One of the reported Michael adducts undergoes a facile stereoselective cyclisation under oxidant conditions to afford a naphthofuro[4,3-*c*]benzopyran derivative. The regiospecificity of the Michael and cyclisation reactions are discussed.

Keywords: activated quinones; terpenes; Michael reaction; regiospecificity; redox reactions; cyclisation.

Several drimane-related natural products exhibit important biological activity including insect antifeedant, plant growth regulation, cytotoxic, antimicrobial, molluscicidal, and anticomplemental properties.[1] Our interest to develop new cytotoxic quinones[2–4] led us to study reactions to link (+)-euryfuran (**2**), an antitumoral drimane[5] having the 3,4-fused furan skeleton, to quinonoid compounds. We report here preliminary results on the Michael reaction of (+)-euryfuran (**2**) with the highly reactive 1,4-benzoquinones **3a**–**c** which provides a regiospecific access to euryfuran derivatives containing a quinone fragment bonded to the 12-position.



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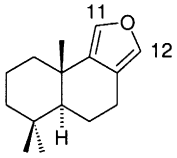

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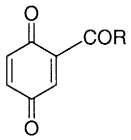

3a. R = H
b. R = Me
c. R = OMe

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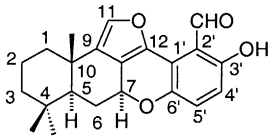
(+)-Euryfuran (**2**) was prepared via a two-step sequence from natural (+)-confertifolin (**1**) according to our previously published procedure.[6] The 1,4-benzoquinones **3a**–**c** were selected as Michael acceptors due to precedent reactions of quinone **3b** with furans that provide access to furylbenzoquinones.[7]

The reaction of furan **2** and the unstable quinone **3a** was firstly examined by in situ generation of **3a** from 2,5-dihydroxybenzaldehyde (1 equiv.) and silver(I) oxide in dichloromethane at room temperature. The reaction proceeded rapidly (<1 min) to afford two products which were isolated by flash chromatography. The major product was characterised as adduct **5a** (35%)[8] and the minor product demonstrated spectral properties[9] in accord with compound **4** (20%). However, when quinone **3a** prepared from 2,5-dihydroxybenzaldehyde and silver(I) oxide in a separate procedure was treated with 1 equiv. of euryfuran (**2**) in benzene at room temperature, compound **5a** was obtained as the sole product in 90% yield.



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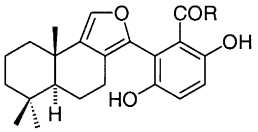
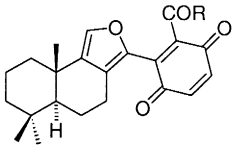


5a. R = H
b. R = Me
c. R = OMe



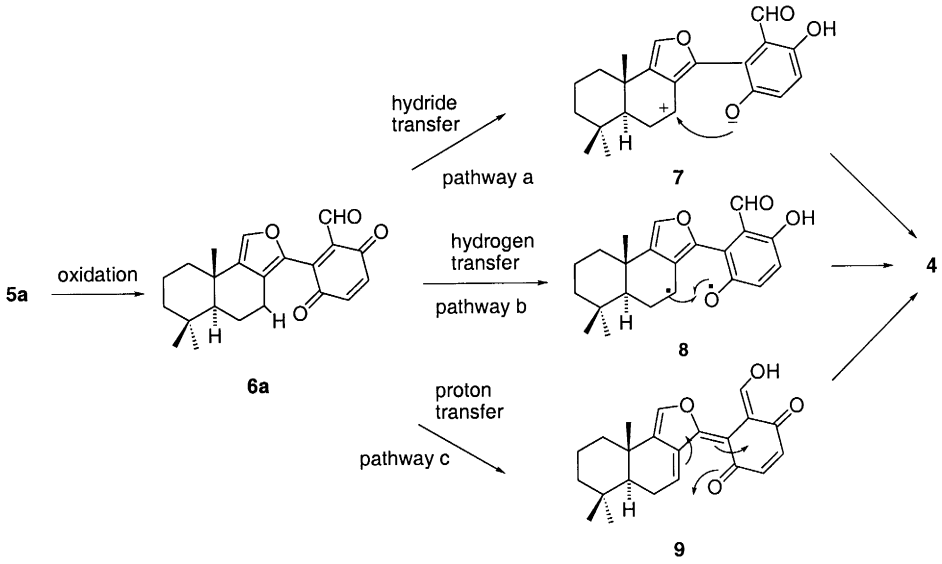
6a. R = H
b. R = Me
c. R = OMe

Next, we examined the reaction of euryfuran (**2**) with 1 equiv. of 2-acetyl-1,4-benzoquinone (**3b**) in dichloromethane at room temperature. The reaction afforded after 5 hours a mixture of 2,5-dihydroxyacetophenone along with two products which were isolated by flash cromatography. The less polar compound was characterised as adduct **5b** (17%) and the more polar product displayed spectral properties in accordance with quinone **6b** (51% based on **3b**). The presence of 2,5-dihydroxyacetophenone, detected by ^{1}H NMR and TLC analysis in the reaction mixture, indicated that **6b** arose from a redox reaction between adduct **5b** and quinone **3b**.

We studied the reaction of furan **2** with 1 equiv. of 2-methoxycarbonyl-1,4-benzoquinone (**3c**) in dichloromethane at room temperature. In this case the reaction occurred slowly (20 h) affording a mixture of quinone **6c** (74% based on **3c**) and methyl 2,5-dihydroxybenzoate. The absence of Michael adduct **5c** can be attributed to a slow addition of nucleophile **2** to quinone **3c**, followed by a fast redox reaction between the nascent Michael adduct **5c** and quinone **3c**.

The absence of quinone **6a** in the reaction of furan **2** and quinone **3a** could be explained assuming its participation in the formation of furopyran **4**. Apparently, compound **4** could arise from **6a** via cyclisation of zwitterion intermediate **7** formed through an intramolecular hydride ion transfer process[10] (pathway a), by intramolecular reaction of biradical intermediate **8** (pathway b) generated by hydrogen abstraction,[11] or by cyclisation of intermediate **9** formed by proton transfer (pathway c, Scheme 1). In order to shed some light on the course of the formation of **4**, compound **5a** was allowed to react with 1 equiv. of DDQ in anhydrous dioxane under nitrogen atmosphere at room temperature, and the reaction progress was monitored by TLC analysis using compound **4** as reference. The reaction proceeded rapidly (<1 min) to give furopyran **4** as the sole product. The same result was obtained when the reaction was carried out in darkness. These experiments support a stepwise ionic mechanism where compound **4** arises from the cyclisation of intermediates **7** or **9**.

Taking into account that the reaction of compound **2** with quinones **3a**–**c** were performed using the same conditions, it is reasonable to deduce that the absence of products type **4** in the reactions of **2** with **3b** and **3c** could be attributed to the redox potential of the quinone fragment in **6b** and **6c** which does not facilitate an intramolecular hydride transfer reaction. This assumption was verified through an



Scheme 1.

experiment where furylquinone **6c** was recovered after being treated with DDQ in boiling toluene for 6 hours. This result does not disregard the fact that formation of **4a** could proceed through a proton transfer process. The reluctance towards cyclisation of **6b** and **6c** through this mechanism probably is related to the less electrophilic character of the acetyl and metoxycarbonyl groups than the formyl group.

In view of the recent reported results[12] on the conversion of Diels–Alder adducts of furans into Michael adducts, we decided to monitor the reaction of **2** with **3c** in order to have evidence on the participation of possible Diels–Alder adduct intermediates on the formation of the Michael adducts. The reaction progress was followed by ^{1}H NMR analysis in $CDCl_3$ at room temperature. The signals of Diels–Alder adducts were not detected during the early stage of the reaction and after 90 minutes, increasing production of furylquinone **6c** and methyl gentisate were found. These results indicate that the reaction of **2** with quinones **3a**–**c** is initiated by a Michael addition to give the corresponding adducts **5a**–**c** which, depending on the formation rate, undergo dehydrogenation reaction with the activated 1,4-benzoquinone **3a**–**c** to give the corresponding furylquinones **6a**–**c**. It is reasonable to assume that regiospecific formation of the Michael adducts **5** is controlled by the nucleophilic attack of **2** to the activated quinones **3a**–**c** through the less hindered 12-position.

In summary, we report three examples on the regiospecific Michael reaction of (+)-euryfuran (**2**) with activated 1,4-benzoquinones **3a**–**c** that offer interesting possibilities to prepare a wide range of new quinone-containing (+)-euryfuran derivatives for cytotoxic activity assays. Furthermore, the cyclisation found on adduct **5a** can be extended to the synthesis of new members of the furo[3,2-*c*]benzopyrans series. Efforts along these lines are currently under way.

Acknowledgements

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8. Selected data for compound **5a**: yellow crystals mp 104–104.5°C; $[\alpha]_D^{22}$=+102.4 (c, 2.1; $CHCl_3$); IR ν_{max} (cm^{-1}) 3423 (O-H), 2927 (C-H), 1650 (C=O); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 11.36 (s, 1H, 3′-OH), 9.60 (s, 1H, CHO), 7.30 (s, 1H, H-11), 7.20 (d, 1H, *J*=9, 1 Hz, H-5′), 6.94 (d, 1H, *J*=9.1 Hz, H-4′), 5.72 (s, 1H, 6′-OH), 2.70 (ddd: *J*=1.6, 6.5, 17.0 Hz, 1H, H-7_{eq}), 2.42 (ddd: *J*=7.2, 11.3, 17.0 Hz, 1H, H-7_{ax}), 2.01 (dd, 1H, *J*=10.8 Hz, H-1_{eq}), 1.90–1.31 (m, 9H), 1.25 (s, 3H, 10-Me), 0.95 (s, 3H, 4α-Me), 0.92 (s, 3H, 4β-Me); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.79, 18.94, 21.59, 21.59, 25.04, 33.16, 33.49, 34.07, 39.24, 41.86, 51.23, 117.21, 118.51, 119.44, 123.32, 126.06, 136.76, 138.90, 139.34, 149.94, 156.74, 196.66; elemental analysis $C_{22}H_{26}O_4$ (354.44); calcd: C, 74.55; H, 7.39; found: C, 75.02; H, 7.67.
9. Satisfactory spectroscopic and microanalytical data were obtained for all new compounds. Selected data for compound **4**: yellow crystals mp 143.5–144.5°C; $[\alpha]_D^{22}$=−18.1 (c, 16; $CHCl_3$); IR ν_{max} (cm^{-1}) 3146 (O-H), 2864 (C-H), 1646 (C=O); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 11.47 (s, 1H, 3′-OH), 10.64 (s, 1H, CHO), 7.26 (s, 1H, H-11), 7.14 (d, 1H, *J*=8.9 Hz, H-5′), 6.72 (d, 1H, *J*=8.9 Hz, H-4′), 5.47 (d, 1H, *J*=7.6 Hz, H-7_{ax}), 2.40–2.04 (m, 3H, H-6+H-1); 1.81–1.26 (m, 6H), 1.18 (s, 3H, 10-Me), 1.01 (s, 3H, 4α-Me), 0.97 (s, 3H, 4β-Me); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.46, 21.39, 22.00, 26.97, 33.29, 33.43, 34.34, 37.43, 42.48, 49.63, 69.35, 113.90, 116.67, 119.71, 120.95, 126.47, 136.29, 137.33, 143.47, 146.50, 157.17, 196.91; elemental analysis $C_{22}H_{24}O_4$ (352.42); calcd: C, 74.98; H, 6.86; found: C, 75.23; H, 7.32.
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