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One-pot synthesis of 5,6-dihydroxylated benzo[*b*]furan derivatives

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Abstract—In the presence of sodium iodate and pyridine, several 5,6-dihydroxylated benzo[*b*]furan derivatives were synthesized via oxidation–Michael addition of β-dicarbonyl compounds with catechols in a one-pot procedure. The final products were confirmed by ESMS, NMR, and single-crystal X-ray diffraction study. The mechanism different from that of electrochemical methods was proposed based on DFT calculation.

Hydroxylated benzo[*b*]furan moiety constitutes a major group of natural biologically active heterocycle compounds,[1–5] which have attracted much attention owing to their wide range of biological activities, such as acting as antioxidant agents, antifungal agents, modulators of estrogen receptor, 5-lipoxygenase inhibitors, cyclooxygenase-2 inhibitors, and Na^+, K^+-ATPase inhibitors.[6–11] They can also be employed as the key intermediate in the synthesis of quinone type natural products such as tanshinone or mansonone F. In recent years, we have focused on the studies of bioactivities and chemical properties of tanshinones[12–14] isolated from *Salvia miltiorrhiza Bunge*, a well-known traditional Chinese medicinal herb. As part of the projects, synthesis of polyhydroxylated benzo[*b*]furan derivatives was proposed.

Many documents on the preparation of benzo[*b*]furan derivatives have been reported. These works generally involve the intramolecular cyclization of a suitable substituted benzene ring.[3,15–18] These strategies involve either multi-steps, rigorous reaction conditions, or expensive reagents, and the synthesis of polyhydroxylated benzo[*b*]furan derivatives have not been reported using these methods. Nematollahi et al. reported[19–24] the synthesis of polyhydroxylated benzo[*b*]furans by electrochemical oxidation of catechols in the presence of 1,3-dicarbonyl compounds such as β-diketones, β-ketoesters, coumarins and 4-hydroxy-6-methyl-2-pyrone. Wanzlick et al.[25] and Darbarwar et al.[26] found that the oxidative coupling of catechol with 4-hydroxy-coumarins in the presence of potassium ferricyanide led to 11,12-oxygenated coumestan derivatives. Nevertheless, the chemical access to polyhydroxylated benzo[*b*]furans still remain scarce. Herein we described a facile chemical method for the synthesis of 5,6-dihydroxylated benzo[*b*]furan derivatives by oxidation–Michael addition of catechol and substituted catechols with β-dicarbonyl compounds (Scheme 1) and studied a possible reaction mechanism.

Our initial attempt to synthesize 5,6-dihydroxyl benzo[*b*]furans via oxidation–addition reaction of catechols[27] with acetylacetone or ethyl acetylacetate was based on Wanzlick's[25] and Darbarwar's[26] methods by using potassium ferricyanide as oxidant in aq acetone solution of sodium acetate. However, the reaction failed to give the desired products.

After extensive study, we found that sodium iodate and pyridine in aq ethanol worked well at room temperature. The final products were purified easily by column chromatography. In this procedure, it was found that the amount of water used was very critical, small proportion of water could enhance the solubility of sodium iodate in ethanol and then would benefit the reaction, while too much water could lead to none of the products

Keywords: Catechol; Oxidation addition; β-Dicarbonyl compounds; 5,6-Dihydroxylated benzo[*b*]furan.
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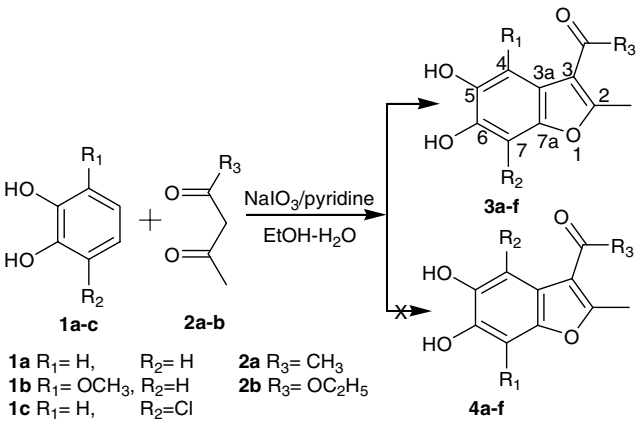


	R_1	R_2	R_3
3a	H	H	CH_3
3b	H	H	OC_2H_5
3c, 4c	OCH_3	H	CH_3
3d, 4d	OCH_3	H	OC_2H_5
3e, 4e	H	Cl	CH_3
3f, 4f	H	Cl	OC_2H_5

Scheme 1.

except the tarred polymer. The possible reason was that final products were easy to be oxidized. Besides, 1.0 equiv of pyridine was required as the catalyst.

According to the above procedure, six 5,6-dihydroxylated benzo[*b*]furans were obtained successfully via reaction of catechols with β-dicarbonyl compounds in moderate isolated yields (ca. 30–50%), and their structures were confirmed by NMR and ESMS.[28]

Generally, it is considered that the presence of a methoxy or chlorine group at the C-3 position of **1b** and **1c** would yield two types of products **3** and **4** in each case. However, the ^{1}H NMR and ^{13}C NMR spectra suggested that compounds **3c–f** were obtained as essentially the only isomer, **4c–f** were undetectable. The structure of **3c** was further confirmed by the HMBC correlations (Table 1) of H-7 (*δ*, 7.11) with C-6 (*δ*, 139.4), C-7a (*δ*, 144.5), C-3a (*δ*, 117.4), and C-5 (*δ*, 132.7). Compound **3e** was also confirmed by HMBC (Table 1) and single-crystal X-ray diffraction study (shown as Fig. 1 for the ORTEP drawing of **3e**).[29] The unambiguously determined structures of **3c** and **3e** also lent support to the proposed structures of **3d** and **3f**.

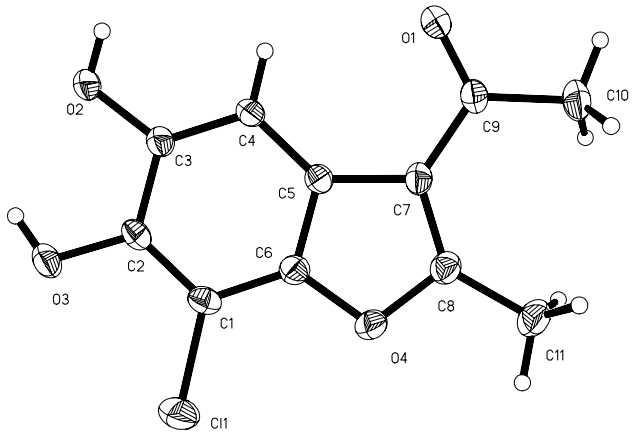


Figure 1. ORTEP drawing of compound **3e**.

As proposed by Nematollahi et al.,[20–24] the oxidation–addition reaction of **1b** with **2** proceeded via the intermolecular and intramolecular addition of *o*-quinone as the key intermediate. Compounds **4c–d** were expected to be obtained. However, NMR spectra confirmed that the obtained products were **3c–d** instead of **4c–d**. It was possible that our process followed the different pathway from that of electrochemical condition in Refs. 20–24. In order to further elucidate this hypothesis, DFT calculation on atomic charge of intermediate 3-methoxy-*o*-quinone **5** was carried out. The calculation results (Table 2) indicated that C-9 in **5** would be more easily attacked by a nucleophile than C-6 because the former (−0.12016) had less atomic charge than the latter (−0.22058) (see Fig. 2 for structures). This result was consistent with the regioselectivity reported by Nematollahi et al. Encouraged by this preliminary calculation results, we carried out another calculation on substrate **1b**. The results (Table 2) showed that H-9 (0.42263) in **1b** had more positive charge than H-14 (0.40637). It would then be possible that the oxidation of **1b** took place in a stepwise manner through single electron transfer. Therefore, a possible mechanism was proposed in Scheme 2.

To further verify the validity of the above result, the DFT calculations of substrate **1c** and *o*-quinone **6** were also performed. As shown in Table 2, the electronic charges of H-9 and H-14 in **1c** (Fig. 2) were similar, indicating that both of the hydroxyl groups might be oxidized, and the oxidation–Michael addition reaction would proceed essentially via *o*-quinone **6** as the inter-

Table 1. Key ^{1}H and ^{13}C NMR and HMBC data for compounds **3c** and **3e** (DMSO-d_6)

Position	δ_C		δ_H		HMBC (H–C)	
	3c	**3e**	**3c**	**3e**	**3c**	**3e**
2a	15.2	15.1	2.70	2.70	2,3	2,3
3	117.2	117.5	—	—	—	—
3a	117.4	117.3	—	—	—	—
4	135.7	104.4	—	—	—	—
5	132.7	143.2	—	—	—	—
6	139.4	140.9	—	—	—	—
7	100.6	102.6	7.11	7.35	5, 6, 7a, 3a	5,6,7a, 3
7a	144.5	144.2	—	—	—	—

Table 2. Atomic charges for selected atoms in compounds **5**, **6**, **1b**, and **1c**[30]

Atom	5	1b	1c	6
O-4	−0.39902	−0.64650	−0.67277	−0.38969
O-7	−0.43239	−0.63358	−0.64698	−0.41273
C-6	−0.22058	—	—	−0.13227
C-9	−0.12016	—	—	−0.11659
H-9	—	0.42263	0.42982	—
H-14	—	0.40637	0.43057	—

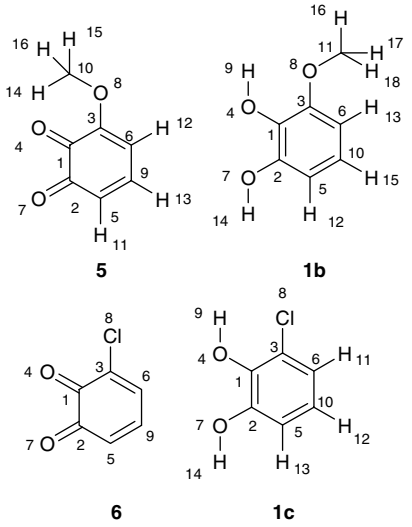
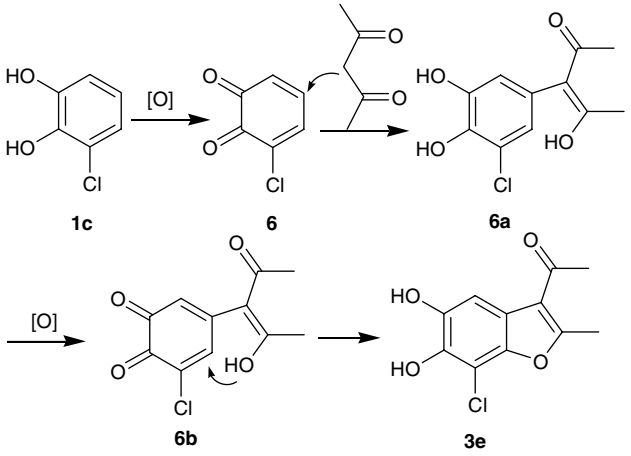


Figure 2.

mediate. The atomic charges indicated that C-9 (−0.11659) in **6** would be more easily attacked by **2** than C-6 (−0.13227), and **3e**–**f** were expected to be formed (Scheme 3). This was in agreement with our results.

In summary, we have described a facile method for synthesis of 5,6-dihydroxylated benzo[*b*]furan derivatives. The electronic effect of C-3 substituents on catechols was investigated and the different pathway from that of electrochemical method was proposed based on DFT calculation. Although the oxidation of final products in this system caused the yield decrease, the described method held promise in the synthesis of 5,6-dihydroxylated benzo[*b*]furan derivatives due to the facile procedure and the readily available material. The optimization of this method and reaction of various substituted catechols with β-dicarbonyl compounds are in progress.



Scheme 3.

Acknowledgements

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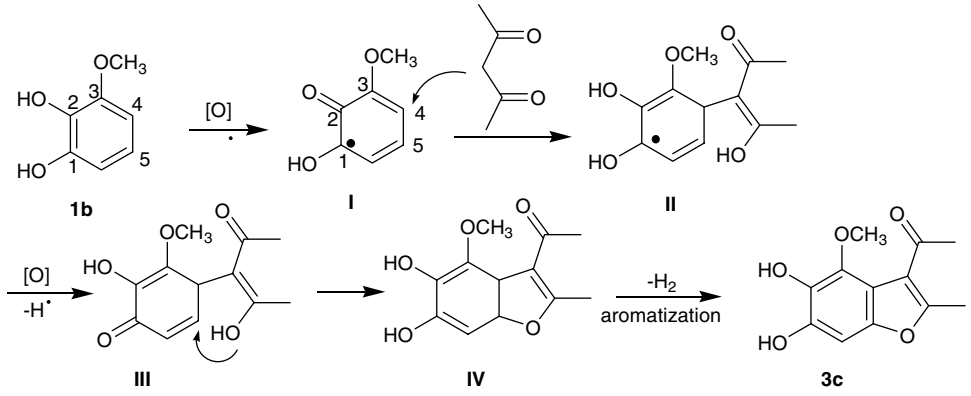
References and notes

1. Cagniant, P.; Carniant, D. *Adv. Hetercycl. Chem.* **1975**, *18*, 337–360.
2. Donnelly, D. M. X.; Meegan, M. J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Pergamon Press: New York, 1984; Vol. 4, pp 657–712.
3. (a) Takasugi, M.; Nagao, S.; Masamune, T.; Shirats, A.; Takahashi, K. *Tetrahedron Lett.* **1978**, *9*, 797–798; (b) Ward, R. S. *Nat. Prod. Rep.* **1999**, *16*, 75–96; (c) Takasugi, M.; Nagao, S.; Ueno, S.; Masamune, T.; Shirata, A.; Takahashi, K. *Chem. Lett.* **1978**, 1239–1241.



Scheme 2.

4. (a) Gangiant, A.; Devrahm, R.; McGuire, J.; Kiskuyjm, R. L. *J. Med. Chem.* **1995**, *38*, 3798–3805; (b) Malamas, M. S.; Sredy, J.; Moxham, C.; Katz, A.; Xu, W.; McDevitt, R.; Adebayo, F. O.; Sawickim, D. R.; Seestakkerm, L.; Sullivan, D.; Taylor, J. R. *J. Med. Chem.* **2000**, *43*, 1293–1310.
5. Teo, C. C.; Kon, O. L.; Sim, K. Y.; Ng, S. C. *J. Med. Chem.* **1992**, *35*, 1330–1339.
6. Maeda, S.; Masuda, H.; Tokoroyama, T. *Chem. Pharm. Bull.* **1994**, *42*, 2536–2545.
7. McAllister, G. D.; Hartley, R. C.; Dawson, M. J.; Knaggs, A. R. *J. Chem. Soc., Perkin. Trans. 1* **1998**, 3453–3458.
8. Alcides, J. M.; da Silva, M. P. A.; Silva, N. M. V.; Brito, F. V.; Buarque, C. D.; de Souza, D. V.; Rodrigues, V. P.; Pocas, E. S. C.; Noël, F.; Albuquerque, E. X.; Costa, P. R. R. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 283–286.
9. McCallion, G. D. *Curr. Org. Chem.* **1999**, *3*, 67–76.
10. Huang, H. C.; Chamberlain, T. S.; Serbert, K.; Koboldt, C. M.; Isakson, P. C.; Reitzm, D. B. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2377–2380.
11. Smith, R. A.; Chem, J.; Mader, M. M.; Muegge, I.; Moehler, U.; Katti, S.; Marrero, D.; Stirtan, W. G.; Weaver, D. R.; Xiao, H.; Carley, W. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2875–2878.
12. Bu, X. Z.; Huang, Z. S.; Zhang, M.; Ma, L.; Xiao, G. W.; Gu, L. Q. *Tetrahedron Lett.* **2001**, *42*, 5737–5740.
13. Gu, L. Q.; Bu, X. Z.; Ma, L. PCT CN 0100861, 24 May 2001.
14. An, L. K.; Bu, X. Z.; Wu, H. Q.; Guo, X. D.; Ma, L.; Gu, L. Q. *Tetrahedron* **2002**, *58*, 10315–10321.
15. Xie, X. G.; Chen, B.; Lu, J. P.; Han, J. J.; She, X. G.; Pan, X. F. *Tetrahedron Lett.* **2004**, *45*, 6235–6237.
16. Yang, Z.; Liu, H. B.; Lee, C. M.; Chang, H. M.; Wong, H. N. C. *J. Org. Chem.* **1992**, *57*, 7248–7257.
17. Katritzky, A. R.; Ji, Y.; Fang, Y.; Prakash, I. *J. Org. Chem.* **2001**, *66*, 5613–5615.
18. (a) Dupont, R.; Cotelie, P. *Tetrahedron* **2001**, *57*, 5585–5589; (b) Nan, Y.; Miao, H.; Yang, Z. *Org. Lett.* **2000**, *2*, 297–299.
19. Golabi, S. M.; Nematollahi, D. *J. Electroanal. Chem.* **1997**, *420*, 127–137.
20. Nematollahi, D.; Forooghi, Z. *Tetrahedron* **2002**, *58*, 4949–4953.
21. Golabi, S. M.; Nematollahi, D. *J. Electroanal. Chem.* **1997**, *430*, 141–146.
22. Nematollahi, D.; Habibi, D. *J. Org. Chem.* **2004**, *69*, 2637–2640.
23. Nematollahi, D.; Rafiee, M. *J. Electroanal. Chem.* **2004**, *566*, 31–37.
24. Nematollahi, D.; Rafiee, M. *Green. Chem.* **2005**, *7*, 638–644.
25. Wanzlick, H. W.; Gritzky, R.; Heidpreim, H. *Chem. Ber.* **1963**, *96*, 305–306.
26. Darbarwar, M.; Sundaramurthy, V.; Subba Rao, N. V. *Indian J. Chem.* **1973**, *11*, 115–116.
27. 3-Methoxylcatechol was prepared according to the known procedure, see: (a) Rond, H. *Acta Chem. Scand.* **1966**, *20*, 1182; (b) 3-Chlorcatechol was prepared by chlorination of 2-methoxyphenol and subsequent demethylation.
28. General procedure for the preparation of benzo[*b*]furans: to a solution of catechols (5 mmol) in a mixture of ethanol and water (9:1, 50 mL) was added β-dicarbonyl compounds (5 mmol) and pyridine (5 mmol). To the stirring mixture was added sodium iodate (6 mmol) at room temperature and the stirring was maintained for the specified time. The progress of the reaction was monitored by TLC. After the reaction, the mixture was filtered, and then the filtrate was concentrated. The residue was extracted with ethyl acetate, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography (petroleum ether–EtOAc) to afford the desired products. Spectral and analytic data for **3a**: white solid, isolated yield, 47%. ESMS: *m*/*z* 205 (M−1). ^{1}H NMR (DMSO-d_6, 500 MHz): 2.51 (s, 3H, methyl), 2.67 (s, 3H, methyl), 6.91 (s, 1H, aromatic), 7.33 (s, 1H, aromatic), 8.89 (br, 1H, hydroxy), 9.01 (br, 1H, hydroxy). ^{13}C NMR (DMSO-d_6, 125 MHz): 15.1, 30.6, 97.6, 106.3, 117.1, 117.2, 143.2, 143.9, 146.9, 160.6, 193.8.
Compound **3b**. white solid, isolated yield, 43%. ESMS: *m*/*z* 235 (M−1). ^{1}H NMR (DMSO-d_6, 300 MHz): 1.35 (t, $J = 7.2$ Hz, 3H, methyl), 2.63 (s, 3H, methyl), 4.27 (q, $J = 7.2$ Hz, 2H, CH_2), 6.89 (s, 1H, aromatic), 7.20 (s, 1H, aromatic), 8.99 (br, 2H, hydroxy). ^{13}C NMR (DMSO-d_6, 75 MHz): 14.1, 14.3, 59.7, 97.6, 105.7, 107.9, 116.7, 143.1, 144.0, 146.8, 160.8, 163.5.
Compound **3c**. white solid, isolated yield, 41%. ESMS: *m*/*z* 235 (M−1). ^{1}H NMR (DMSO-d_6, 500 MHz): 2.50 (s, 3H, methyl), 2.70 (s, 3H, methyl), 3.94 (s, 3H, methoxy), 7.11 (s, 1H, aromatic), 8.58 (br, 1H, hydroxy), 9.07 (br, 1H, hydroxy). ^{13}C NMR (DMSO-d_6, 125 MHz): 15.2, 30.5, 60.4, 100.6, 117.2, 117.4, 132.7, 135.7, 139.4, 144.5, 160.7, 193.6.
Compound **3d**. white solid, isolated yield, 35%. ESMS: *m*/*z* 265 (M−1). ^{1}H NMR (DMSO-d_6, 300 MHz): 1.35 (t, $J = 7.2$ Hz, 3H, methyl), 2.66 (s, 3H, methyl), 3.92 (s, 3H, methoxy), 4.28 (q, $J = 7.2$ Hz, 2H, CH_2), 6.97 (s, 1H, aromatic), 8.58 (br, 1H, hydroxy), 9.09 (s, 1H, hydroxy). ^{13}C NMR (DMSO-d_6, 75 MHz): 14.0, 14.2, 60.2, 60.4, 100.7, 109.3, 118.6, 132.8, 135.5, 140.2, 144.2, 161.8, 164.2.
Compound **3e**. white solid, isolated yield, 38%. ESMS: *m*/*z* 239 (M−1). ^{1}H NMR (DMSO-d_6, 500 MHz): 2.52 (s, 3H, methyl), 2.72 (s, 3H, methyl), 7.35 (s, 1H, aromatic), 9.32 (br, 1H, hydroxy), 9.72 (br, 1H, hydroxy). ^{13}C NMR (DMSO-d_6, 125 MHz): 15.1, 30.5, 102.6, 104.4, 117.3, 117.5, 140.9, 143.2, 144.2, 161.5, 193.5.
Compound **3f**. white solid, isolated yield, 32%. ESMS: *m*/*z* 269 (M−1). ^{1}H NMR (DMSO-d_6, 300 MHz): 1.34 (t, $J = 7.2$ Hz, 3H, methyl), 2.66 (s, 3H, methyl), 4.29 (q, $J = 7.2$ Hz, 2H, CH_2), 7.20 (s, 1H, aromatic), 9.33 (br, 1H, hydroxy), 9.76 (br, 1H, hydroxy). ^{13}C NMR (DMSO-d_6, 75 MHz): 14.1, 14.3, 60.0, 102.6, 103.9, 108.5, 116.8, 140.8, 143.2, 143.9, 161.6, 163.1.
29. Crystallographic data for the structure in this paper have been deposited with Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 264239. Copies of the data can be obtained, free of charge, on application to CCDC, 12 UnionRoad, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or e-mail: deposit@ccd.cam.ac.uk].
30. All the geometry optimizations were carried out at b3lyp/6-31G* level, using the GAUSSIAN 98 package of programs until the stationary points were found. Gaussian 98, revision A11.3; Gaussian: Pittsburgh, PA, 2002.