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Synthesis of novel dihydrofuro[*b*]-pyridinone derivatives: oxidation coupling of 3-hydroxy-4(1*H*)-pyridinone with β-dicarbonyl compounds

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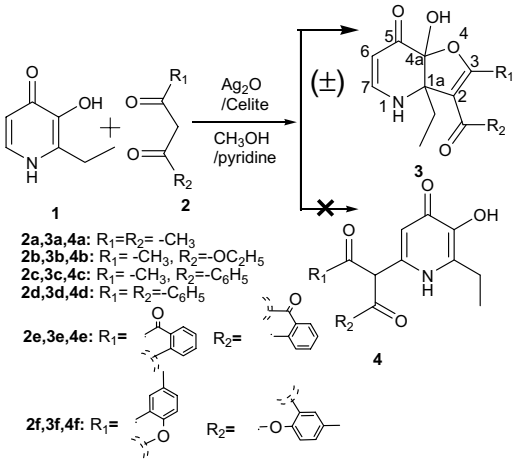
Abstract—Oxidation coupling of 3-hydroxy-4(1*H*)-pyridinone with β-dicarbonyl compounds led to unexpected dihydrofuro[*b*]-pyridinone derivatives, indicating an alternative pathway other than that with anilines or thiols. By this strategy, six novel dihydrofuro[*b*]-pyridinone derivatives were synthesized.

4(1*H*)-Pyridinone derivatives have attracted more and more attention due to their interesting pharmacological properties.[1–11] The preparation of compounds with 4(1*H*)-pyridinone moiety has widely been reported.[12–15] We have reported the synthesis of 6-substituted 3-hydroxy-4(1*H*)-pyridinones via oxidation–Michael addition of 3-hydroxy-4(1*H*)-pyridinone **1** with anilines or thiols.[16,17] Compared to many reports on oxidation–Michael addition of catechols with various nucleophiles such as ammonia, coumarins, 4-hydroxy-methyl-2-pyrone, β-diketone, and β-ketonester yielding *o*-quinone derivatives and benzofurans,[18–21] oxidation–Michael addition of *ortho*-hydroxy-pyridinones with nucleophiles has been less well studied.[16,17] Herein, we first described the unexpected preparation of dihydrofuro[*b*]-pyridinone derivatives from the oxidation coupling of 3-hydroxy-4(1*H*)-pyridinone with β-dicarbonyl compounds, as partial results of our further projects.

The procedure is similar to our previous reports: β-dicarbonyl compounds were used as nucleophiles instead of anilines or thiols, and the oxidation and coupling were processed in one-pot procedure in the presence of Ag_2O/Celite[22] and pyridine at 40 °C in methanol.[23] The reaction of **1** and acetylacetone **2a**, following by recrystallization from ethanol, yielded a colorless powder (Scheme 1).



Scheme 1.

Keywords: Pyridinone; Oxidation coupling; β-Dicarbonyl compounds; Dihydrofuro[*b*]-pyridinone.
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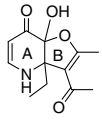
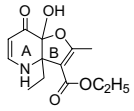
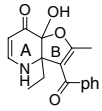
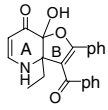
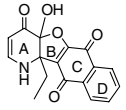
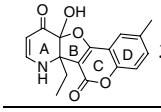
Table 1. The important ^{1}H and ^{13}C NMR data of **3a–f** in DMSO-d_6[a]

Products **3**	FAB-MS (M+1)	3	5	6		7		1a	4a
		δ_C	δ_C	δ_H	δ_C	δ_H	δ_C	δ_C	δ_C
 **3a**	238	169.0	181.5	4.56	88.8	7.25	152.1	71.3	102.5
 **3b**	268	164.7	182.2	4.57	89.6	7.28	153.1	71.0	103.7
 **3c**	300	169.3	182.1	4.62	89.8	7.35	153.3	72.8	103.5
 **3d**	362	165.7	183.1	4.68	90.8	7.37	153.3	73.9	103.6
 **3e**	312	161.4	179.5	4.80	92.2	7.41	153.2	70.8	107.7
 **3f**	314	166.9	180.9	4.69	90.3	7.38	153.1	69.4	106.2

[a] All carbon and hydrogen atoms are assigned according to ^{1}H NMR, ^{13}C NMR, DEPT, and HMQC.

As our primary consideration, compound **4a** was expected. However, ^{1}H NMR, ^{13}C NMR, and DEPT (Table 1) showed the presence of three methyls, one methylene, two methines (δ 4.56, dd, 1H; δ 7.25, t, 1H), two saturated quaternary carbons (δ 71.3, 102.5), two carbonyl carbons (δ 193.4, 181.5), two olefinic quaternary carbon atoms, and one enolic quaternary carbon (δ 169.0). Two saturated quaternary carbon (δ 71.3, 102.5) can be assigned to 1a-C and 4a-C, respectively. The HMQC spectrum further confirmed that two methines were assigned to pyridinone ring. Additionally, ^{1}H NMR analysis indicates that they are the mixtures of enantiomers with a ratio of 1:1 due to the presence of chiral carbon. Upon rationalizing the above data, the obtained product tended to be **3a** instead of **4a**.

The structure of compound **3a** was further confirmed by single-crystal X-ray diffraction study, shown as Figure 1.[24] Compound **3a** comprises non-planar dihydrofuran ring and pyridinone ring, where C(2)–C(3) bond [1.558(2) Å] was observed. The interplanar angle between the dihydrofuran ring and the pyridinone ring is 69.4°. The C(11)–O(4) bond length [1.232(2) Å] is slightly longer than the C=O bond length (1.209 Å) of dinone form of the acetylacetone, which may result from the formation of dihydrofuran ring.

With the similar procedure, other pyridinone derivatives **3b–f** were obtained with different β-dicarbonyl compounds, and their structures were also confirmed by MS, ^{1}H NMR, and ^{13}C NMR study (Table 1).[23]

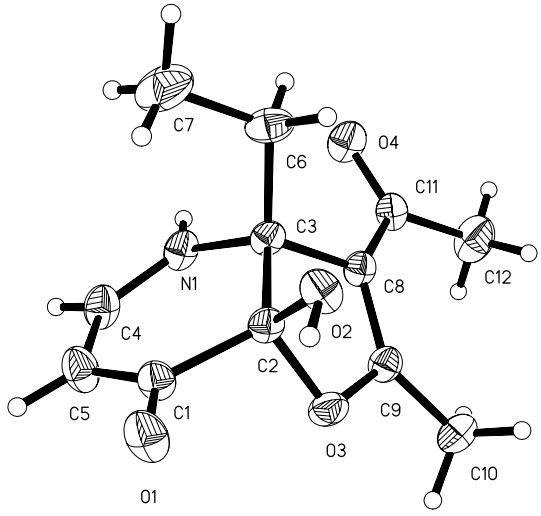


Figure 1. The molecular structure of compound **3a**.

The structures of unexpected products promote us to reconsider the mechanism of the reaction. As proposed in our previous work,[16,17] 3-hydroxy-4(1*H*)-pyridinone was first oxidized to a 2-methoxy-2-ethyl-1,2-dihydro-3,4-dinone **IIb**, and subsequent Michael-addition with thiols or anilines and aromatization gave 6-substituted-3-hydroxy-4(1*H*)-pyridinones. Obviously, the current reaction proceeded through a different pathway from that reported previously. To probe the nature of this reaction, the oxidation coupling of **1** with **2a** was monitored in protonic and aprotic solvents at 40 °C using UV

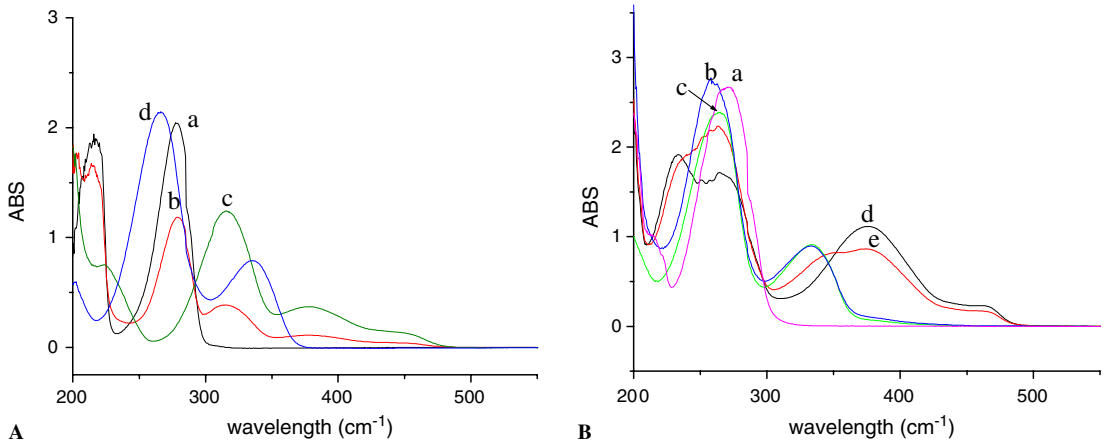


Figure 2. A: a, **1** in methanol; b–c, **1** with oxidant in methanol, b: 1 h, c: 2 h, show **1** disappeared and intermediate (**II$_b$**) formed; d, **3a** in methanol; B: a–b, **1** with **2a** and oxidant in CH_3CN, a: 0 h, b: 5 h; c, **3a** in CH_3CN; d, **II$_b$** in CH_3CN; e, **II$_b$** with **2a** in CH_3CN (3 h).

technique (Fig. 2). In the case of no acetylacetone **2a**, an intermediate **IIb** formed clearly (315 nm) in methanol,[25] which is consistent with our previous observation.[16,17] When **IIb** (374 nm in CH_3CN) was treated with **2a** in CH_3CN/pyridine, the peak corresponding to **3a** (345 nm) was observed, indicating a substitution occurred at 2-position. To further confirm this result, the reaction of **1** with **2a** was also investigated in CH_3CN, **3a** was obtained as expected, and the yield (50%) was even higher than that in methanol (40%). These results indicate that there is a competition between methanol and **2a** in the system.

According to the above experimental results, the proposed mechanism can be best described in Scheme 2. Briefly, **1** was first oxidized to an active intermediate **I**, which was attacked competitively by acetylacetone and methanol leading to intermediate **II$_a$** and minor **II$_b$**, the intermediate **II$_a$** subsequently underwent fast intramolecular addition to produce the cyclized product **3a**. In the case of pre-isolated **II$_b$** reacting with acetylacetone, the methoxy in 2-C position was substituted by **2a** due to the predominant nucleophilicity of the latter and led to **II$_a$**, which underwent fast intramolecular addition to yield **3a**.

It is noticeable that when the intermediate **II$_b$** was treated with aniline or thiol in the absence of any base, the Michael addition products (6-position) were obtained instead of 2-substituted products. We reasoned that in the absence of strong base such as NaH or BuLi, the aniline or thiol derivatives exhibit mainly the properties of an addition reagent. Usually, it is possible to get Michael addition products during the reaction of the intermediate **II$_b$** and β-diketone derivatives in the presence of pyridine, however we failed to do so. It seems that the subsequent cyclization plays an important role in the reaction direction.

In summary, Ag_2O/Celite-mediated oxidative coupling of 3-hydroxy-4(1*H*)-pyridinone with β-dicarbonyl compounds give six new dihydrofuro[*b*]-pyridinone derivatives. The whole procedure was investigated and the possible mechanism was proposed. The preliminary bioactive screening suggested that these compounds showed good antioxidant activity. The detailed bioactive test is ongoing.

Acknowledgements

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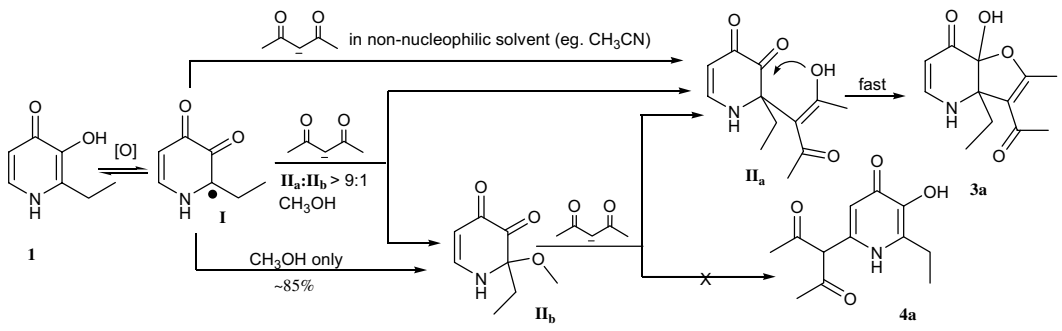

Scheme 2.

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22. Ag_2O/Celite was prepared according to the known procedure, see: Balogh, V.; Retizon, M.; Golfer, M. *J. Org. Chem.* **1972**, *36*, 1339–1341.
23. General procedure for the synthesis of **3a**–**f**: A mixture of 3-hydroxy-4(1*H*)-pyridinone (0.695 g, 5 mmol), β-dicarbonyl compounds **2** (5 mmol), pyridine (0.395 g, 5 mmol), and Ag_2O/Celite (3 g, containing 6 mmol Ag_2O) in methanol (50 mL) was magnetically stirred at 40 °C for 8 h. The reaction mixture was filtered to afford a yellow solution that was concentrated. The residue was purified by recrystallization from ethanol to give the desired products. Spectral and analytic data for **3a**. White solid. FAB: *m*/*z* 238 (M+1). ^{1}H NMR, δ (ppm) (DMSO-d_6, 300 MHz): 0.81 (t, J = 7.2 Hz, 3H, methyl), 1.65–1.78 (m, 2H, CH_2), 2.23 (s, 3H, methyl), 2.27 (s, 3H, methyl), 4.56 (dd, J = 7.2, 0.9 Hz, 1H, ring A), 7.25 (t, J = 7.2 Hz, 1H, ring A), 7.38 (s, 1H, OH), 7.93 (d, J = 7.2 Hz, 1H, NH). ^{13}C NMR, δ (ppm) (DMSO-d_6, 75 MHz): 8.6, 15.7, 25.6, 29.9, 71.3, 88.8, 102.5, 117.8, 152.1, 169.0, 181.5, 193.4.
Compound **3b**. Colorless solid. FAB: *m*/*z* 268 (M+1). ^{1}H NMR, δ (ppm) (DMSO-d_6, 300 MHz): 0.83 (t, J = 7.2 Hz, 3H, methyl), 1.25 (t, J = 7.2 Hz, 3H, methyl), 1.83–2.45 (m, 2H, CH_2), 2.15 (s, 3H, methyl), 4.12 (q, J = 7.2, 2H, CH_2), 4.57 (dd, J = 7.2, 0.9 Hz, 1H, ring A), 7.28 (t, J = 7.2 Hz, 1H, ring A), 7.47 (s, 1H, OH), 7.95 (d, J = 7.2 Hz, 1H, NH). ^{13}C NMR, δ (ppm) (DMSO-d_6, 75 MHz): 9.5, 15.0, 15.5, 27.0, 60.3, 71.0, 89.6, 103.7, 107.9, 153.1, 164.7, 170.2, 182.2.
Compound **3c**. Colorless solid. FAB: *m*/*z* 300 (M+1). ^{1}H NMR, δ (ppm) (DMSO-d_6, 300 MHz): 0.87 (t, J = 7.2 Hz, 3H, methyl), 1.61 (s, 3H, methyl), 1.94–2.14 (m, 2H, CH_2), 4.62 (dd, J = 7.2, 0.9 Hz, 1H, ring A), 7.35 (t, J = 7.2 Hz, 1H, ring A), 7.51–7.61 (m, 5H, ph), 8.11 (d, J = 7.2 Hz, 1H, NH). ^{13}C NMR, δ (ppm) (DMSO-d_6, 75 MHz): 9.4, 16.5, 26.3, 72.8, 89.8, 103.5, 117.1, 129.0, 129.4, 133.0, 140.4, 153.3, 169.3, 182.1, 192.9.
Compound **3d**. Colorless solid. FAB: *m*/*z* 362 (M+1). ^{1}H NMR, δ (ppm) (DMSO-d_6, 300 MHz): 0.93 (t, J = 7.2 Hz, 3H, methyl), 1.99–2.07 (m, 2H, CH_2), 4.68 (dd, J = 7.2, 0.9 Hz, 1H, ring A), 7.12–7.47 (m, 11H, ph, ring A), 7.92 (s, 1H, OH), 8.24 (d, J = 7.2 Hz, 1H, NH). ^{13}C NMR, δ (ppm) (DMSO-d_6, 75 MHz): 9.4, 26.6, 73.9, 90.8, 103.6, 115.0, 128.7, 129.5, 131.4, 133.0, 138.9,153.3, 165.7, 183.1, 193.0.
Compound **3e**. Orange solid. FAB: *m*/*z* 312 (M+1). ^{1}H NMR, δ (ppm) (DMSO-d_6, 300 MHz): 0.89 (t, J = 7.2 Hz, 3H, methyl), 2.12–2.59 (m, 2H, CH_2), 4.80 (d, J = 7.2 Hz, 1H, ring A), 7.41 (d, J = 7.2 Hz, 1H, ring A), 7.76–7.96 (m, 4H, ring D), 8.67 (s, 1H, NH). ^{13}C NMR, δ (ppm) (DMSO-d_6, 75 MHz): 9.3, 27.8, 70.8, 92.2, 107.7, 123.9, 126.3, 126.8, 131.2, 132.6, 134.1, 135.5, 153.2, 161.4, 179.5.
Compound **3f**. Colorless solid. FAB: *m*/*z* 314 (M+1). ^{1}H NMR, δ (ppm) (DMSO-d_6, 300 MHz): 0.91 (t, J = 7.2 Hz, 3H, methyl), 2.02–2.47 (m, 2H, CH_2), 2.37 (s, 3H, methyl), 4.69 (d, J = 7.2 Hz, 1H, ring A), 7.36–7.54 (m, 4H, ring A and ring D), 8.68 (d, J = 7.2 Hz, 1H, NH). ^{13}C NMR, δ (ppm) (DMSO-d_6, 75 MHz): 9.1, 21.0, 26.4, 69.4, 90.3, 106.2, 112.2, 117.2, 123.4, 134.8, 135.4, 153.1, 153.4, 158.8, 166.9, 180.9.
24. Crystal data for **3a**: $C_{12}H_{15}NO_4$, M = 237.25, triclinic, space group P-1, a = 7.499(3) Å, b = 7.742(4) Å, c = 10.042(5) Å, α = 87.105(9)°, β = 86.757(8)°, γ = 89.397 (8)°, V = 581.3(5) Å^3, Z = 2, D_c = 1.355 g/m^3, F(000) = 252, 2.03° < θ < 27.06°, $-9 \leqslant h \leqslant 9$, $-9 \leqslant k \leqslant 9$, $-8 \leqslant l \leqslant 12$, T = 293 K, colorless block, 0.48 × 0.45 × 0.43. R_1 = 0.0429 ([$I > 2\sigma(I)$]), 0.0495 (all data), wR_2 = 0.1193 ([$I > 2\sigma(I)$]), 0.1267 (all data). Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 262726. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
25. Spectral data of compound **IIb**: ^{1}H NMR, δ (ppm) (DMSO-d_6, 300 MHz): 0.78 (t, J = 7.2 Hz, 3H, CH_3), 1.65–1.90 (m, 2H, CH_2), 3.12 (s, 3H, OCH_3), 5.24 (dd, J = 7.5 1.5 Hz, 1H, pyridinone ring), 7.74 (t, J = 7.2 Hz, 1H, pyridinone ring), 9.12 (br, 1H, NH).