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An efficient route for commercially viable syntheses of furan- and thiophene-anellated β-hydroxychalcones ☆

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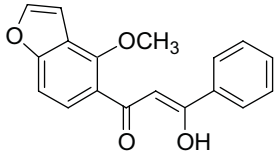
Abstract—An efficient route for the syntheses of β-hydroxychalcones containing benzofuran and benzothiophene rings is described. Isoxazolines obtained from oxime–olefin cycloadditions were reduced under pressure to a mixture of products. Isoxazoles obtained from Claisen aroylation of an ester and subsequent acid cyclization, or from isoxazolines via DDQ-mediated dehydrogenation, were subjected to catalytic hydrogenation followed by hydrolysis to afford 1-phenyl-3-(benzofuran-5-yl)-1,3-diketone and 1-phenyl-3-(benzothiophene-5-yl)-1,3-diketones in very good yields.

1. Introduction

The development of new methods for the syntheses of heterocycles is important in organic chemistry. Synthetic interest in pongamol and its derivatives has increased due to its antimicrobial,[1] quinone reductase,[2] soothex and questice[3] activities. It is used commercially in cosmetic and sun-screen preparations for protection from UV radiation.[4] The active ingredients are usually obtained from natural sources.[3–5] Despite their simple structural framework they have not been prepared commercially in efficient quantities. As a part of our ongoing interest in the study of furanoflavonoids[6] and their heterocyclic analogues, we have previously reported syntheses of nitrogen and sulfur heterocyclic analogues and their antimicrobial activities.[7] We now describe an easy and efficient approach towards commercially viable syntheses of β-hydroxychalcones from isoxazolines and isoxazoles as masked 1,3-bifunctional compounds.[8,9]



Pongamol

2. Results and discussion

A common procedure for the syntheses of furan-anellated β-hydroxychalcones is via condensation of the karanjic acid ester with the enolate of acetophenone[10,11] but the maximum overall yield of the product obtained was 41%.[11] Competing Claisen and aldol condensation lead to undesired products in these reactions which restrict these methods for commercial use. We have tried these methods but results were inconsistent with the literature reports and we obtained only poor yields of the final compounds.[7] We now report the use of isoxazolines derived from oxime–olefin cycloaddition reactions and their hydrogenolysis to afford β-hydroxyketones which can be oxidized easily to the β-hydroxychalcones with mild oxidizing agents (Scheme 1, route 1).

Key ester **1** was obtained from methylation of karanjic acid (a degradation product of karanjin)[12] and also via a three step sequence starting from cyclohexane-1,3-dione.[11] Ester **2** was obtained from thiophene as described previously by us.[7] LAH reduction followed by PCC oxidation of the esters **1** and **2** yielded aldehydes which were converted to oximes **3** and **4** by heating with hydroxylamine hydrochloride in aqueous ethanol in

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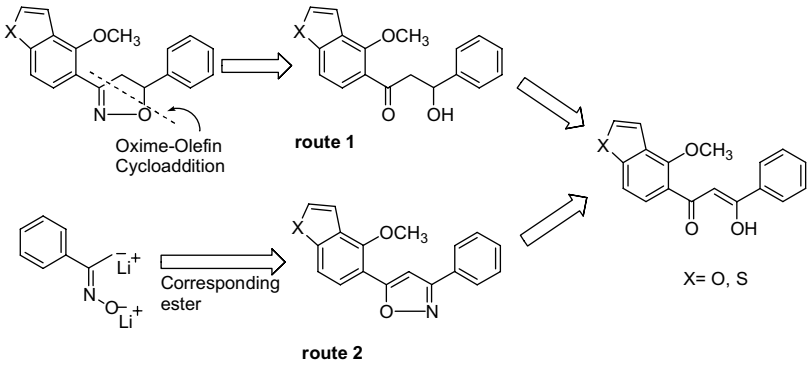
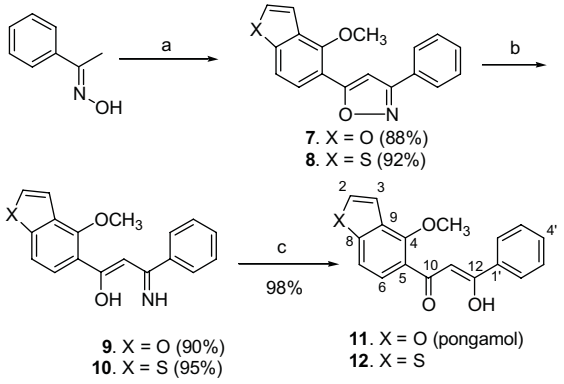


Scheme 1. Possible routes for the syntheses.

90% and 95% yields, respectively. The oximes thus obtained were subjected to the oxime–olefin cycloaddition reaction with styrene in ethanol in the presence of chloramine-T[13] to produce the reactive dipolar nitrile oxide in situ and thus the product isoxazolines **5** (94%) and **6** (96%) (Scheme 2).[14] Catalytic hydrogenolysis over Raney-Ni failed under NTP conditions whilst under pressure (40 psi) a mixture of products due to hydrogenation of the furan and thiophene rings along with the isoxazoline ring was obtained. Various attempts to hydrogenate the isoxazoline ring selectively failed which led us to change our strategy to that shown in route 2 (Scheme 1), as isoxazoles are known to undergo hydrogenolysis under mild conditions.[15]

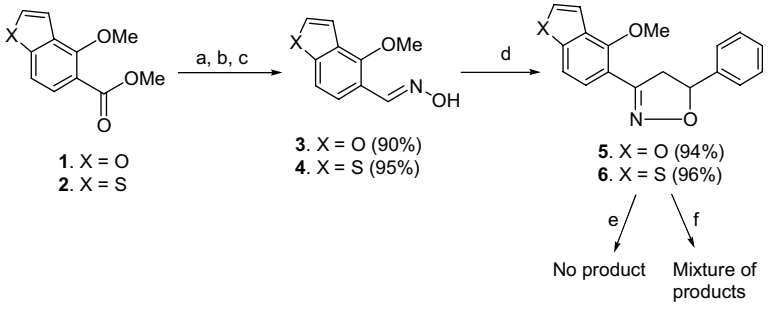
The isoxazoles **7** and **8** were synthesized from acetophenone oxime and esters **1** and **2**.[11] The acetophenone oxime was treated with two equivalents of *n*-BuLi to afford the dilithium salt of the oxime. Aroylation of the dianion with the ester was accomplished with 0.5 mol of ester **1** and **2**/mol of dianion. Aroylation occurred at the more nucleophilic carbanion site.[16] The presumed intermediate keto-oximes were not isolated but were cyclized directly under acidic conditions to give the isoxazoles **7** and **8** in 88% and 92% yields, respectively.[17]Hydrogenolysis over Raney-Ni at NTP produced imines **9** (90%) and **10** (95%) and then hydrolysis of the imines on silica gel with acetic acid afforded β-hydroxychalcones **11** (pongamol) and **12** in nearly quantitative yields (Scheme 3).



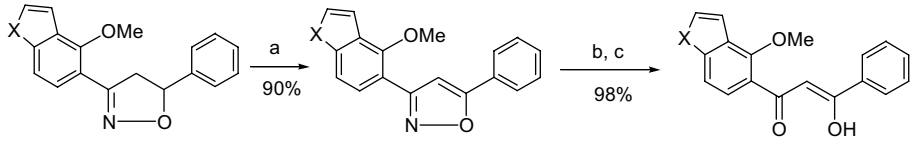
Scheme 3. Reagents and conditions: (a) *n*-BuLi (2 equiv), THF, 0 °C, 30 min, added **1**/**2** in THF, 15 min, then 3 N HCl, reflux, 1 h; (b) Raney-Ni, H_2, rt, THF–H_2O (3:1), 12–16 h; (c) silica gel, AcOH few drops, 18 h.

After successful completion of the syntheses of the desired products via isoxazoles, we have further synthesized isoxazoles **13** and **14**[18] in 90% yields via DDQ-mediated dehydrogenation of the isoxazolines **5** and **6** in order to avoid the use of butyllithium and render the process cost effective (Scheme 4). DDQ has not previously been used for dehydrogenation of isoxazolines.

In conclusion, the work described here demonstrates an easy, efficient and commercially viable synthesis of pongamol and its sulfur heterocyclic analogue. Further



Scheme 2. Reagents and conditions: (a) LAH, THF, 0 °C, rt, 2 h; (b) PCC, dry DCM, rt, 2 h; (c) $NH_2OH{\cdot}HCl$, EtOH, 10% aq NaOH, Δ, 1 h; (d) styrene, chloramine-T, EtOH, reflux, 9 h; (e) Raney-Ni, H_2, rt, THF–H_2O (3:1), 48 h; (f) Raney-Ni, H_2 40 psi, THF: H_2O (3:1), 10 h.



5. X = O
6. X = S

13. X = O
14. X = S

11. X = O (pongamol)
12. X = S

Scheme 4. Reagents and conditions: (a) DDQ, dioxane, reflux, 6–8 h; (b) Raney-Ni, H_2, rt, THF–H_2O (3:1), 12–16 h, (c) silica gel, AcOH few drops, 18 h.

studies on the syntheses and pharmacological potential of functionalized isoxazolines, isoxazoles and β-hydroxychalcones are in progress.

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14. Compound **5**: white crystals, mp 85 °C; IR (KBr) ν_{max}: 2902, 1593, 1468, 1354, 1244, 1156, 1060, 808, 977, 897, 763 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ: 7.74 (1H, d, $J = 8.6$ Hz, H-6), 7.57 (1H, d, $J = 1.4$ Hz, H-2), 7.41–7.31 (5H, m, H-2′–H-6′), 7.23 (1H, dd, $J = 8.6$, 0.6 Hz, H-7), 6.92 (1H, d, $J = 1.4$ Hz, H-3), 5.69 (1H, dd, $J = 10.6$, 8.5, H-12), 4.04 (3H, s, –OCH_3), 3.93 (1H, dd, $J = 17.2$, 10.7 Hz, H-11a), 3.48 (1H, dd, $J = 17.2$, 8.4 Hz, H-11b); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 158.2 (C-10), 156.1 (C-8), 152.5 (C-4), 144.8 (C-2), 141.6 (C-1′), 129.0 (C-3′, 5′), 128.4 (C-4′), 126.3 (C-2′, 6′), 125.9 (C-6), 119.2 (C-9), 115.5 (C-5), 107.3 (C-7), 105.3 (C-3), 82.9 (C-12), 60.9 (OCH_3), 46.2 (C-11); FAB MS (+ve): m/z 294 $[M+H]^+$. Elemental analysis calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78%. Found: C, 73.54; H, 5.26; N, 4.59%. Compound **6**: oil; IR (KBr) ν_{max}: 2928, 1638, 1493, 1453, 1364, 1331, 1216, 1047, 1013, 770 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ: 7.78 (1H, d, $J = 8.4$ Hz, H-6), 7.64 (1H, d, $J = 8.5$ Hz, H-7), 7.41–7.49 (6H, m, H-2, H-2′–H-6′), 7.36 (1H, br d, $J = 6.9$ Hz, H-3), 5.74 (1H, dd, $J = 10.7$, 8.3 Hz, H-12), 3.94 (1H, dd, $J = 17.2$, 10.7 Hz, H-11a), 3.91 (3H, s, –OCH_3), 3.53 (1H, dd, $J = 17.2$, 8.2 Hz, H-11b); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 155.6 (C-10), 154.2 (C-4), 143.8 (C-8), 141.5 (C-1′), 134.5 (C-9), 129.1 (C-3′, 5′), 128.5 (C-4′), 127.1 (C-2), 126.3 (C-2′, 6′), 125.6 (C-3), 121.1 (C-6), 119.0 (C-7), 118.3 (C-5), 83.0 (C-12), 62.9 (OCH_3), 45.8 (C-11); FAB MS (+ve): m/z 310 $[M+H]^+$. Elemental analysis calcd for $C_{18}H_{15}NO_2S$: C, 69.88; H, 4.89; N, 4.53; S, 10.36%. Found: C, 70.14; H, 4.73; N, 4.62; S, 10.49%.
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17. Compound **7**: colourless needles, mp 102–103 °C; IR (KBr) ν_{max}: 2993, 1590, 1477, 1454, 1390, 1186, 1107, 941, 904, 845, 764 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ: 7.86 (1H, d, $J = 8.5$ Hz, H-6), 7.83 (2H, m, H-2′–H-6′), 7.59 (1H, br s, H-2), 7.43–7.47 (3H, m, H-3′, 4′, 5′), 7.30 (1H, d, $J = 8.6$ Hz, H-7), 7.05 (1H, s, H-11), 6.97 (1H, br s, H-3), 4.07 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 172.3 (C-10), 161.2 (C-8), 159.0 (C-4), 154.6 (C-12), 144.9 (C-2), 130.3 (C-4′), 129.3 (C-3′, 5′), 128.2 (C-1′), 126.2 (C-2′, 6′), 126.0 (C-6), 119.6 (C-5), 115.0 (C-9), 107.4 (C-7), 105.3 (C-3), 101.0 (C-11), 60.9 (OCH_3); FAB MS (+ve): 292 $[M+H]^+$. Elemental analysis calcd for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50; N, 4.81%. Found: C, 74.08; H, 4.36; N, 4.69%. Compound **8**: white plates, mp 138–139 °C; IR (KBr) ν_{max}: 3104, 2942, 1595, 1573, 1459, 1394, 1327, 1213, 1009, 939, 761 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.97 (1H, d, $J = 8.7$ Hz, H-6), 7.93 (2H, dd, $J = 7.8$, 2.1 Hz, H-2′, 6′), 7.76 (1H, d, $J = 8.7$ Hz, H-7), 7.58 (1H, d, $J = 6.0$ Hz, H-2), 7.48–7.54 (4H, m, H-3′, 4′, 5′, 3), 7.18 (1H, s, H-11), 4.04 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 167.3 (C-10), 163.7 (C-12), 153.1

(C-4), 143.9 (C-8), 134.4 (C-1′), 130.3 (C-4′), 129.8 (C-9), 129.3 (C-3′, 5′), 127.5 (C-2), 127.3 (C-2′, 6′), 124.0 (C-6), 121.5 (C-3), 119.3 (C-7), 116.3 (C-5), 101.1 (C-11), 61.8 (OCH_3); FAB MS (pos.): *m/z* 308 $[M+H]^+$, 615 $[2M+H]^+$. Elemental analysis calcd for $C_{18}H_{13}NO_2S$: C, 70.34; H, 4.26; N, 4.56; S, 10.43%. Found: C, 70.48; H, 4.36; N, 4.41; S, 10.54%.

18. Compound **13**: colourless needles, mp 104–105 °C; IR, ^1H and ^{13}C NMR are nearly similar to compound **7**, except for the ^{13}C NMR values for the three carbons C-12, C-10 and C-4; ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 169.8 (C-12), 162.5 (C-8), 158.1 (C-4), 152.3 (C-10), 145.2 (C-2), 130.2 (C-4′), 130.0 (C-3′, 5′), 129.0 (C-1′), 126.8 (C-2′, 6′), 126.2 (C-6), 118.8 (C-9), 114.6 (C-5), 107.4 (C-7), 105.6 (C-3), 100.7 (C-11), 60.3 (OMe-4); FAB MS (+ve): *m/z* 292 $[M+H]^+$. Elemental analysis calcd for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50; N, 4.81%. Found: C, 74.39; H, 4.59; N, 4.73%. Compound **14**: colourless needles, mp 141–143 °C; IR, ^1H and ^{13}C NMR are nearly similar to compound **8**, except for the ^{13}C NMR values for the three carbons C-4, C-10 and C-12; ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 170.3 (C-12), 160.9 (C-10), 154.1 (C-4), 143.6 (C-8), 134.8 (C-1′), 130.3 (C-4′), 129.4 (C-3′, 5′), 128.1 (C-9), 127.1 (C-2), 126.2 (C-2′, 6′), 125.7 (C-6), 121.1 (C-3), 119.2 (C-7), 117.7 (C-5), 100.8 (C-11), 62.6 (OCH_3); FAB MS (+ve): *m/z* 308 $[M+H]^+$. Elemental analysis calcd for $C_{18}H_{13}NO_2S$: C, 70.34; H, 4.26; N, 4.56; S, 10.43%; Found: C, 70.50; H, 4.41; N, 4.63; S, 10.57%.