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Simple and Convenient Synthesis of 4-Unsubstituted-3-(3-Oxoalkyl)isocoumarins

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Abstract: A simple transformation of 2-alkylfurans and 2-formylbenzoic acids into 4-unsubstituted 3-(3-oxoalkyl)isocoumarins is described. It is based on the synthesis of 2-(2-carboxybenzyl)furans followed by their acid-catalyzed recyclization to the target isocoumarins.

Keywords: Furans, isocoumarins, ring closure, ring opening

Isocoumarins are class of natural products with a broad spectrum of biological activity.[1] 4-Unsubstituted 3-alkylisocoumarins have been isolated from fungi,[2] lichens,[3] and high plants.[4] They showed antifungal,[4g,5] antibacterial,[6] antitumor,[7] anti-angiogenic,[8] antidiabetic,[9] phytotoxic,[10] and other kinds of physiological activity; synthetic isocoumarins being at least equipotent to natural ones. For example, 2-(8-hydroxy-6-methoxy-1-oxo-1*H*-2-benzopyran-3-yl)propionic acid is a synthetic isocoumarin that is currently entering phase II clinical trials.[7e] These and other data stimulate the

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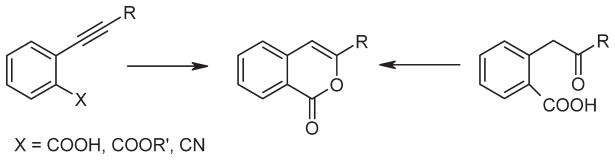


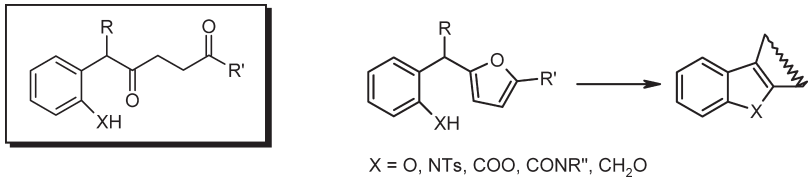
Scheme 1.

interest in the development of new approaches to the synthesis of 4-unsubstituted 3-alkylisocoumarins.

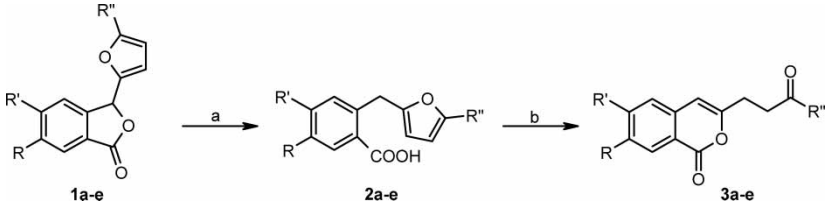
At present, some ways to 3-alkylisocoumarins are known. Two of them (Scheme 1) have the largest scope of applicability. The first method is based on the electrophilic or transition metal–mediated cyclization of the alkynes possessing a carboxylate or an equivalent group in proximity to the triple bond.[11] The second one is the intramolecular cyclization of *ortho*-(2-oxoalkyl)benzoic acids that can be prepared by different methods. The last way is the general approach to construction of the isocoumarin framework. It has been successfully applied to the synthesis of 3-alkylisocoumarins.[12]

It is well known that under acidic condtions alkylfurans undergo a ring opening with formation of 1,4-dicarbonyl compounds.[13] It means that benzylfurans can be considered as synthons of benzyl alkyl ketones. Based on this fact, for the past decade we have developed the general method of synthesis of benzannelated heterocycles by recyclization of *ortho*-substituted benzylfurans (Scheme 2). By varying *ortho*-substituent in the benzyl fragment, we have synthesized the different heterocycles including benzofurans, indoles, isochromenes, and isoquinolones.[14] In this work, we applied this methodology to the synthesis of 4-unsubstituted 3-alkylisocoumarins.

As starting compounds we used available 3-(2-furyl)phthalides **1** (Scheme 3), which are usually synthesized by *ortho*-lithiation of benzoic acid derivatives followed by treatment of organolithium intermediates with the corresponding aldehydes.[15] Here, we applied an alternative method, acid-catalyzed condensation of 2-formylbenzoic acid with 2-alkylfurans.[14e,16] In spite of lower yields, this method is more convenient because of its simplicity and the absence of any precautions that are needed during the work with organolithium compounds.



Scheme 2.



Scheme 3. a) Zn, NH_4OH, reflux; b) HCl, EtOH, reflux.

3-(2-Furyl)phthalides **1a**–**e** were reduced to 2-(2-carboxybenzyl)furans **2a**–**e** by a slightly modified literature procedure[15b,17] with zinc dust in refluxing aqueous ammonia (Scheme 3, Table 1). Unfortunately, this method cannot be applied to reduction of phthalides containing bromine, iodine, or nitro groups in the aromatic ring. In the last case, the complex unidentified mixture was obtained. For bromo- and iodo-substituted phthalides, dehalogenation products were formed.

The synthesized 2-(2-carboxybenzyl)furans **2a**–**e** were known to transform into naphtho[2,3-b]furans by treatment with trifluoroacetic anhydride[18] or with acetic anhydride and acetic acid in the presence of $ZnCl_2$.[15b,17b,19] Under these aprotic conditions, furan is stable to ring opening. However, it can be expected that attack on the α-position of 2,5-disubstituted furans should be much faster by Brønsted acids than by bulky electrophilic species in acylation reaction. Indeed, we found that heating of **2a**–**e** in ethanolic hydrogen chloride yielded isochromones **3a**–**e** in good yields (Scheme 3, Table 1).

In conclusion, we have developed a simple and convenient method of synthesis of 4-unsubstituted-3-(3-oxoalkyl)isocoumarins. The presence of the carbonyl group in the alkyl substituent allows the further modification of synthesized isocoumarins. For example, isocoumarin **3a** can straightforwardly be transformed into an efficient antifungal agent (E)-3′-oxoartemidin[5c] and its analogs, including capillarin, which has also been used for treatment of hepatocellular jaundice[20] and showed insect antifeeding activity.[21] Then, this simple method can be useful for the synthesis of the broad scope of isocoumarins followed by screening of the synthesized compounds on different kinds of biological activity.

Table I. Yields of 2-(2-carboxybenzyl)furans **2** and isocoumarins **3**

Compound	R	R′	R″	Yield **2** (%)	Yield **3** (%)
a	H	H	Me	51	70
b	Cl	H	Me	46	72
c	MeO	MeO	Me	58	75
d	H	H	tBu	55	65
e	Cl	H	tBu	48	68

EXPERIMENTAL

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AC 200 and Bruker DPX 300 spectrometers. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane as an internal standard, and coupling constants (J) are given in Hertz. Mass spectra were recorded on a Kratos MS-30 instrument with 70 eV electron impact ionization at 200 °C. IR spectra were measured as KBr plates on InfraLUM FT-02 and InfraLUM FT-801 instruments. Compounds **3** were purified by column chromatography using silica gel KSK (5–40 μm), manufactured by LTD Sorbpolymer.

General procedure for the synthesis of compounds **1a–e** was reported earlier.[16] Analytical data of compounds **1a**,**b**,**d**,**e** were given in previous publications.[14e,16]

5,6-Dimethoxy-3-(5-methyl-2-furyl)-1,3-dihydro-1-isobenzofuranone (1c). Mp 163–164 °C (CH_2Cl_2/petroleum ether). IR (KBr): 1758, 1605, 1503, 1461, 1325, 1274, 1220, 1123, 1052, 936, 872, 811, 762 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.23 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 5.93 (d, $J = 3.3$ Hz, 1H, H_{Fur}), 6.21 (d, $J = 3.3$ Hz, 1H, H_{Fur}), 6.27 (s, 1H, CH), 6.81 (s, 1H, H_{Ar}), 7.30 (s, 1H, H_{Ar}). Anal. calcd. for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15; found: C, 65.78; H, 5.19.

General Procedure for the Synthesis of Compounds 2a–e

The mixture of phthalide **1** (0.01 mol), zinc dust (30 g), and $CuSO_4 \cdot 5H_2O$ (1 g) in aqueous ammonia (300 ml) was refluxed under stirring for 6–10 h until reaction was complete (thin-layer chromatography, TLC, monitoring). Hot solution was filtered off; filtrate was cooled and neutralized with conc. hydrochloric acid to pH 5–6. The product was extracted with AcOEt (3 × 20 ml). Extract was heated with activated charcoal, filtered, and evaporated to dryness. The residue was recrystallized from CH_2Cl_2/petroleum ether.

2-[(5-Methyl-2-furyl)methyl]benzoic acid (2a). Yield 51%. White solid. Mp 99–100 °C. IR (KBr): 1682, 1573, 1312, 1293, 1273, 1080, 1018, 924, 780, 735 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 2.26 (s, 3H, CH_3), 4.23 (s, 2H, CH_2), 5.87 (s, 2H, H_{Fur}), 7.28–7.37 (m, 2H, H_{Ar}), 7.47–7.55 (m, 1H, H_{Ar}), 8.06–8.10 (m, 1H, H_{Ar}). Anal. calcd. for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59; found: C, 72.31; H, 5.68.

5-Chloro-2-[(5-methyl-2-furyl)methyl]benzoic acid (2b). Yield 46%. White solid. Mp 113–114 °C. IR (KBr): 1684, 1570, 1302, 1250, 1021, 909, 868, 778, 705 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 2.25 (s, 3H, CH_3), 4.38 (s, 2H, CH_2), 5.88 (s, 2H, H_{Fur}), 7.25 (d, $J = 8.4$ Hz, 1H, H_{Ar}), 7.46 (dd, $J = 2.3$, 8.4 Hz, 1H, H_{Ar}), 8.05 (d, $J = 2.3$ Hz, 1H, H_{Ar}). Anal. calcd. for $C_{13}H_{11}ClO_3$: C, 62.29; H, 4.42; found: C, 62.33; H, 4.40.

4,5-Dimethoxy-2-[(5-methyl-2-furyl)methyl]benzoic acid (2c). Yield 58%. White solid. Mp 139–140 °C. IR (KBr): 1686, 1573, 1523, 1459, 1415, 1354, 1299, 1270, 1221, 1170, 1073, 931, 879, 772 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ_H 2.24 (s, 3H, CH_3), 3.88 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.38 (s, 2H, CH_2), 5.84 (s, 2H, H_{Fur}), 6.74 (s, 1H, H_{Ar}), 7.63 (s, 1H, H_{Ar}). Anal. calcd. for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84; found: C, 65.23; H, 5.86.

2-[(5-*tert*-Butyl-2-furyl)methyl]benzoic acid (2d). Yield 55%. White solid. Mp 108–109 °C. IR (KBr): 1696, 1572, 1486, 1410, 1306, 1257, 1167, 1124, 1078, 1013, 933, 829, 794, 732 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ_H 1.26 (s, 9H, *t*-Bu), 4.44 (s, 2H, CH_2), 5.85 (s, 2H, H_{Fur}), 7.25–7.37 (m, 2H, H_{Ar}), 7.46–7.54 (m, 1H, H_{Ar}), 8.06–8.10 (m, 1H, H_{Ar}). Anal. calcd. for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02; found: C, 74.47; H, 6.98.

5-Chloro-2-[(5-*tert*-butyl-2-furyl)methyl]benzoic acid (2e). Yield 48%. White solid. Mp 103–104 °C. IR (KBr): 1692, 1558, 1483, 1401, 1300, 1243, 1014, 868, 772, 706 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ_H 1.25 (s, 9H, *t*-Bu), 4.38 (s, 2H, CH_2), 5.84 (d, $J = 3.2$ Hz, 1H, H_{Fur}), 5.87 (d, $J = 3.2$ Hz, 1H, H_{Fur}), 7.20 (d, $J = 8.3$ Hz, 1H, H_{Ar}), 7.45 (dd, 1H, $J = 2.2$, 8.3 Hz, 1H, H_{Ar}), 8.05 (d, $J = 2.2$ Hz, 1H, H_{Ar}). Anal. calcd. for $C_{16}H_{17}ClO_3$: C, 65.64; H, 5.85; found: C, 65.75; H, 5.91.

General Procedure for the Synthesis of Compounds 3a–e

Compound **2** (0.01 mol) was refluxed for 5 min in ethanolic hydrogen chloride (50 ml, 30% by weight). The solution was poured into H_2O. The mixture was extracted with CH_2Cl_2 (2 × 20 ml). The combined extract was washed with H_2O and dried (Na_2SO_4). Petroleum ether was added to the extract, and the mixture was filtered through small pad of silica gel. The purified solution was evaporated to dryness. Residue was recrystallized from CH_2Cl_2/petroleum ether.

3-(3-Oxobutyl)-1*H*-1-isochromenone (3a). Yield 70%. White solid. Mp 83–84 °C. IR (KBr): 1717, 1164, 855, 767, 689 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ_H 2.17 (s, 1H, CH_3), 2.75–2.80 (m, 2H, CH_2), 2.85–2.90 (m, 2H, CH_2), 6.30 (s, 1H, H_{Het}), 7.31–7.34 (m, 1H, H_{Ar}), 7.40–7.46 (m, 1H, H_{Ar}), 7.62–7.68 (m, 1H, H_{Ar}), 8.19–8.22 (m, 1H, H_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 27.4, 30.0, 40.2, 103.7, 120.0, 125.2, 127.8, 129.4, 134.8, 137.3, 156.2, 162.8, 206.5. MS (IE): m/z 216 (24, M^+), 174 (25), 173 (100), 155 (25), 145 (31), 131 (38), 127 (33), 117 (67), 103 (27), 91 (28), 89 (72), 77 (45), 63 (38), 59 (44), 55 (47), 43 (45). Anal. calcd. for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59; found: C, 72.31; H, 5.64.

7-Chloro-3-(3-oxobutyl)-1*H*-1-isochromenone (3b). Yield 72%. White solid. Mp 87–88 °C. IR (KBr): 1718, 1651, 1484, 1390, 1354, 1319, 1252, 1153, 1045, 953, 894, 867, 795, 695 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ_H 2.17 (s, 3H, CH_3), 2.75–2.80 (m, 2H, CH_2), 2.84–2.89 (m, 2H, CH_2),

6.29 (s, 1H, H_{Het}), 7.29 (d, $J = 8.4$ Hz, 1H, H_{Ar}), 7.59 (dd, $J = 2.1$, 8.4 Hz, 1H, H_{Ar}), 8.16 (d, $J = 2.1$ Hz, 1H, H_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 27.3, 29.9, 40.0, 103.1, 121.2, 126.7, 128.9, 133.4, 135.1, 135.7, 156.6, 161.6, 206.3. MS (IE): m/z 250 (24, M^+), 209 (22), 207 (100), 189 (14), 179 (14), 165 (18), 151 (24), 123 (41), 55 (22), 43 (42). Anal. calcd. for $C_{13}H_{11}ClO_3$: C, 62.29; H, 4.42; found: C, 62.24; H, 4.45.

6,7-Dimethoxy-3-(3-oxobutyl)-1*H*-1-isochromenone (3c). Yield 75%. White solid. Mp 167–168 °C. IR (KBr): 1711, 1654, 1608, 1508, 1470, 1393, 1269, 1237, 1044, 871, 777 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.14 (s, 3H, CH_3), 2.72–2.77 (m, 2H, CH_2), 2.82–2.87 (m, 2H, CH_2), 3.92 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 6.21 (s, 1H, H_{Het}), 6.69 (s, 1H, H_{Ar}), 7.55 (s, 1H, H_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 27.3, 30.0, 40.3, 56.2 (2C), 103.4, 105.8, 109.2, 113.0, 133.0, 149.3, 155.0, 155.1, 162.7, 206.6. MS (IE): m/z 276 (21, M^+), 233 (52), 149 (11), 119 (12), 63 (36), 43 (100). Anal. calcd. for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84; found: C, 65.28; H, 5.88.

3-(4,4-Dimethyl-3-oxopentyl)-1*H*-1-isochromenone (3d). Yield 65%. White solid. Mp 77–78 °C. IR (KBr): 1729, 1659, 1480, 1389, 1166, 1099, 997, 963, 759, 688 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.12 (s, 9H, *t*-Bu), 2.75–2.81 (m, 2H, CH_2), 2.88–2.94 (m, 2H, CH_2), 6.30 (s, 1H, H_{Het}), 7.31–7.34 (m, 1H, H_{Ar}), 7.40–7.46 (m, 1H, H_{Ar}), 7.62–7.68 (m, 1H, H_{Ar}), 8.20–8.23 (m, 1H, H_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 26.3 (3C), 27.9, 33.8, 44.1, 103.7, 120.0, 125.1, 127.7, 129.4, 134.8, 137.4, 156.7, 162.9, 214.0. MS (IE): m/z 258 (37, M^+), 201 (17), 174 (81), 173 (100), 159 (76), 131 (44), 129 (31), 117 (24), 115 (29), 103 (29), 89 (43), 57 (70). Anal. calcd. for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02; found: C, 74.52; H, 7.07.

7-Chloro-3-(4,4-dimethyl-3-oxopentyl)-1*H*-1-isochromenone (3e). Yield 68%. White solid. Mp 91–92 °C. IR (KBr): 1723, 1656, 1481, 1153, 1098, 968, 871, 780, 694 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.13 (s, 9H, *t*-Bu), 2.76–2.80 (m, 2H, CH_2), 2.90–2.94 (m, 2H, CH_2), 6.30 (s, 1H, H_{Het}), 7.30 (d, $J = 8.4$ Hz, 1H, H_{Ar}), 7.61 (dd, $J = 2.1$, 8.4 Hz, 1H, H_{Ar}), 8.19 (d, $J = 2.1$ Hz, 1H, H_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 26.3 (3C), 27.9, 33.6, 44.1, 103.1, 121.3, 126.7, 129.0, 133.4, 135.1 (2C), 135.8, 157.1, 214.1. MS (IE): m/z 292 (40, M^+), 209 (36), 207 (100), 192 (19), 173 (22), 165 (35), 145 (16), 101 (22), 89 (20), 86 (31), 59 (32), 57 (86). Anal. calcd. for $C_{16}H_{17}ClO_3$: C, 65.64; H, 5.85; found: C, 65.73; H, 5.91.

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