



InCl₃-catalyzed three-component reaction: a novel synthesis of dihydropyrano[3,2-*b*]chromenediones under solvent-free conditions

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ABSTRACT

Three-component coupling (3CC) of kojic acid, aldehyde and 1,3-dione has been achieved in the presence of 10 mol% InCl₃ under solvent-free conditions to afford the corresponding dihydropyrano[3,2-*b*]chromenedione derivatives in good yields. This is the first example of the condensation of kojic acid, aldehyde and 1,3-diones to provide a novel series of kojic acid derivatives.

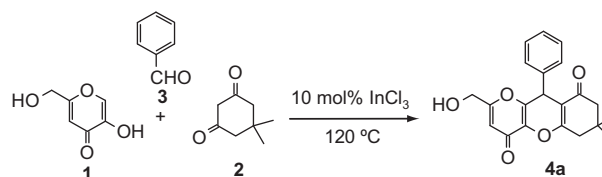
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Multi-component, one-pot synthesis has received considerable attention because of its wide range of applications in pharmaceutical chemistry for the creation of structural diversity and combinatorial libraries for drug discovery.¹ MCRs are extremely convergent, producing a remarkably high increase of molecular complexity in just one step.² The ready availability, potential biological activity and high reactivity of kojic acid makes it an attractive molecule in pharmaceutical chemistry.^{3,4} Consequently, a large number of kojic acid derivatives have been prepared for biological evaluation.^{5,6} Recently, indium trichloride has evolved as a mild and water-tolerant Lewis acid imparting high regio-, chemo- and diastereoselectivity in various organic transformations.⁷ Compared to conventional Lewis acids, indium trichloride in particular has advantages of low catalyst loading, moisture stability and catalyst recycling. However, to the best of our knowledge, there are no reports on three-component coupling of aldehyde, kojic acid and 1,3-diketone to produce a new class of kojic acid derivatives.

In continuation of our interest in exploring the synthetic utility of indium(III) chloride,⁸ we herein disclose a novel three-component reaction for the direct synthesis of dihydropyrano[3,2-*b*]chromenedione derivatives from kojic acid, 1,3-diones and aldehydes. We initially attempted a three-component reaction of kojic acid (**1**), dimedone (**2**) and benzaldehyde (**3**) in the presence of 10 mol% InCl₃. The reaction proceeded well under neat conditions at 120 °C and the corresponding product, 2-(hydroxymethyl-7,7-dimethyl-10-phenyl-7,8-di-hydroxypyran[3,2-*b*]chromene-4,9-(6*H*,10*H*)-dione **4a** was obtained in 90% yield (Scheme 1).

This result provided the incentive for further study of the reaction with various aldehydes and 1,3-diketones. Interestingly, a variety of aldehydes including *ortho*-, *meta*-, and *para*-substituted aryl aldehydes participated well in this reaction (Table 1). As seen from Table 1, halo-substituted aromatic aldehydes gave comparatively higher yields than methoxy and methyl-substituted aromatic aldehydes (Table 1, entries b–d, and j). Aliphatic aldehyde, for example, *n*-propanaldehyde also participated in this reaction under similar conditions (Table 1, entry l). Both cyclic and acyclic 1,3-diketones worked well in this reaction. Interestingly, curcumin was also effective for this three-component reaction (Table 1, entry h). However, the reaction did not proceed with β-ketoesters such as ethyl or methyl acetoacetate under similar conditions due to the transesterification of β-ketoester with the primary hydroxyl group of kojic acid.

Mechanistically, we suggest that the reaction proceeds through a domino Knoevenagel-hetero Diels–Alder reaction to give a tricyclic intermediate which on dehydration leads to the desired product (Scheme 2).



Scheme 1. Reaction between kojic acid, dimedone and benzaldehyde.

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Table 1
Three-component reaction for the synthesis of dihydropyrano[3,2-*b*]chromenediones

Entry	Kojic acid	Diketone	Aldehyde	Product ^a	Time (min)	Yield ^b (%)
a					90	90
b					95	85
c					90	95
d					95	85
e					80	95
f					80	95
g					85	95
h					120	65
i					85	85
j					75	85
k					70	90
l					70	85

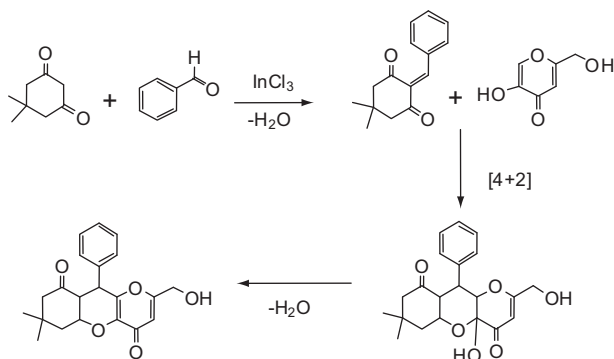
^a All products were characterized by ¹H NMR, IR and mass spectroscopy.

^b Yield refers to pure products after chromatography.

The effects of various indium(III) reagents such as InF₃, InCl₃, In(ClO₄)₃ and In(OTf)₃ were tested. Of these, indium trichloride was found to be an effective catalyst in terms of conversion. Though, the reaction proceeds even with 10 mol % of *p*-TSA, the products were obtained in low yields (30–40% over 6–8 h). Next, we have studied the effect of the solvent for this conversion. The reactions were sluggish and the corresponding products were obtained in low yields when solvents such as toluene, acetonitrile,

ethanol and 1,2-dichloroethane were used. The best results were obtained under solvent-free conditions. The scope and generality of this process is illustrated with respect to various aldehydes and 1,3-diones and the results are presented in Table 1.⁹

In summary, we have developed a novel method for the synthesis of dihydropyrano[3,2-*b*]chromenedione derivatives by means of a three-component reaction between kojic acid, aldehyde and 1,3-dione using a catalytic amount of InCl₃ under neat conditions. This



Scheme 2. A plausible reaction mechanism.

method is simple and is convenient to prepare a wide range of kojic acid derivatives in a single-step operation.

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- General procedure*: A mixture of aldehyde (1 mmol), kojic acid (1.0 mmol), 1,3-dicarbonyl compound (1.1 mmol) and InCl₃ (10 mol %) was stirred at 120 °C for a specified time (Table 1). After complete conversion, as indicated by TLC, the reaction mixture was diluted with water and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 60–120 mesh, ethyl acetate–hexane, 7:3) to afford the pure substituted dihydropyrano[3,2-*b*]chromenedione. Compound **4a**: Solid, mp 186–188 °C; IR (KBr): ν_{\max} 3361, 3081, 2955, 2892, 1669, 1624, 1443, 1377, 1284, 1219, 1147, 1076, 991, 953, 712 cm⁻¹; ¹H NMR (300 MHz, CDCl₃ + DMSO-*d*₆): δ 7.33–7.16 (m, 5H), 6.37 (s, 1H), 5.48–5.38 (br s, 1H), 4.82 (s, 1H), 4.20 (dd, *J* = 5.8, 11.7 Hz, 2H), 2.64 (d, *J* = 5.2 Hz, 2H), 2.20 (d, *J* = 6.0 Hz, 2H), 1.14 (s, 3H), 1.06 (s, 3H); ¹³C NMR (75 MHz, DMSO-*d*₆): δ 195.4, 169.6, 168.3, 163.6, 150.9, 140.9, 136.5, 128.5, 127.8, 127.3, 111.4, 111.2, 59.0, 49.6, 37.7, 31.8, 28.2, 26.7; ESI-MS: *m/z*: 352 (M⁺). HRMS calcd for C₂₁H₂₀O₅: 352.1388, found: 352.1399. Compound **4b**: Solid, mp 180–182 °C; IR (KBr): ν_{\max} 3361, 2955, 1670, 1628, 1512, 1445, 1376, 1261, 1219, 1183, 1075, 952, 824, 777 cm⁻¹; ¹H NMR (300 MHz, CDCl₃ + DMSO-*d*₆): δ 7.14 (d, *J* = 8.6 Hz, 2H), 6.80 (d, *J* = 8.4 Hz, 2H), 6.32 (s, 1H), 5.57–5.48 (m, 1H), 4.75 (s, 1H), 4.29–4.11 (m, 2H), 3.74 (s, 3H), 2.63 (d, *J* = 3.4 Hz, 2H), 2.19 (d, *J* = 10.0 Hz, 2H), 1.13 (s, 3H), 1.05 (s, 3H). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 195.9, 170.2, 168.8, 163.9, 158.9, 151.7, 136.9, 133.5, 129.4, 114.4, 111.8, 59.6, 55.5, 50.2, 37.3, 32.3, 28.8, 27.2. ESI-MS: *m/z*: 382 (M⁺). HRMS calcd for C₂₂H₂₂O₆: 382.1414, found: 382.1419. Compound **4f**: Solid, mp 160–164 °C; IR (KBr): ν_{\max} 3363, 2960, 2927, 1639, 1600, 1507, 1376, 1221, 1191, 1073, 955, 844 cm⁻¹; ¹H NMR (500 MHz, CDCl₃ + DMSO-*d*₆): δ 7.28–7.20 (m, 2H), 7.03–6.94 (m, 2H), 6.37 (s, 1H), 5.51–5.39 (br s, 1H), 4.29–4.12 (m, 2H), 2.64 (q, *J* = 17.8 Hz, 2H), 2.20 (q, *J* = 16.7 Hz, 2H), 1.14 (s, 3H), 1.06 (s, 3H). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 195.4, 169.6, 168.3, 163.6, 162.8, 159.6, 150.5, 136.5, 137.1, 137.0, 129.8, 129.7, 115.4, 115.1, 111.4, 111.1, 59.0, 49.6, 37.0, 31.8, 26.8. ESI-MS: *m/z*: 370 (M⁺). HRMS calcd for C₂₁H₁₉O₅F: 370.1214, found: 370.1208. Compound **4g**: Solid, mp 198–200 °C; IR (KBr): ν_{\max} 3282, 2954, 2871, 1668, 1633, 1595, 1443, 1376, 1221, 1193, 1145, 1039, 952, 753 cm⁻¹; ¹H NMR (500 MHz, CDCl₃ + DMSO-*d*₆): δ 7.35 (d, *J* = 7.3 Hz, 1H), 7.24–7.15 (m, 3H), 6.38 (s, 1H), 5.36 (s, 1H), 4.30–4.12 (m, 2H), 2.66 (q, *J* = 17.8 Hz, 2H), 2.20 (q, *J* = 15.7 Hz, 2H), 1.14 (s, 3H), 1.10 (s, 3H); ¹³C NMR (75 MHz, DMSO-*d*₆): δ 195.2, 169.5, 168.3, 164.2, 150.0, 138.1, 136.7, 132.7, 130.2, 129.5, 129.0, 127.5, 111.4, 110.6, 59.0, 49.6, 35.1, 31.7, 28.2, 26.8. ESI-MS: *m/z*: 386 (M⁺). HRMS calcd for C₂₁H₁₉O₅Cl: 386.0999, found: 386.1005.