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Article

Acid-catalyzed chemoselective *C*- and *O*-prenylation of cyclic 1,3-diketones

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ABSTRACT

The chemoselective *C*- and *O*-prenylation of cyclic 1,3-diketones was achieved by tuning the prenyl source and catalyst. In the presence of the solid acid Nafion, the coupling of 1,3-cyclohexanediones with isoprene gave *C*-prenylated 5-chromenones. Alternatively, using prenol as the substrate with the Lewis acid $AlCl_3$ as the catalyst resulted in the exclusive *O*-prenylation of 1,3-cyclohexanediones. Notably, the resulting products could easily undergo aromatization to deliver prenylated resorcinols that are otherwise difficult to prepare. Our methodology is highly selective, atom-economical, operationally simple, easily scalable, and has potential applications throughout organic synthesis.

1. Introduction

Derivatives of 5-chromenone are common among natural products, particularly in medicinal plants [1–4]. For example, tomentodiones H and J, which are two syncarpic acid-conjugated terpenoids (SACTs) isolated from the traditional Chinese medicinal plant *Rhodomyrtus tomentosa*, contain multi-substituted 5-chromenone scaffolds (Scheme 1) [5]. *Perhydro*-tetrahydrocannabinol (THC) and -cannabichromene (CBC), constituents of marijuana (*Cannabis sativa*), also possess such important cores [6]. Owing to their occurrence in medicinal compounds, intense efforts have focused on the synthesis of 5-chromenone derivatives.

The synthesis of 5-chromenone derivatives is generally achieved using the cost-effective and commercially available 1,3-cyclohexanedione as the starting material (Scheme 2). Only a two-step procedure is required to prepare 5-chromenone derivatives from 1,3-cyclohexanedione and either prenyl bromide [7–9] or bromo-substituted benzyl bromide [10]. Owing to its atom- and step-economy, the [3+3] annulation of 1,3-cyclohexanedione with unsaturated precursors represents a more convenient and straightforward strategy. In the presence of acids or water, α,β-unsaturated aldehydes [11–15] and propargylic alcohols [16–21] are suitable coupling partners in this process. Despite these advances, exploiting new [3+3] annulation reactions to access 5-chromenone frameworks from

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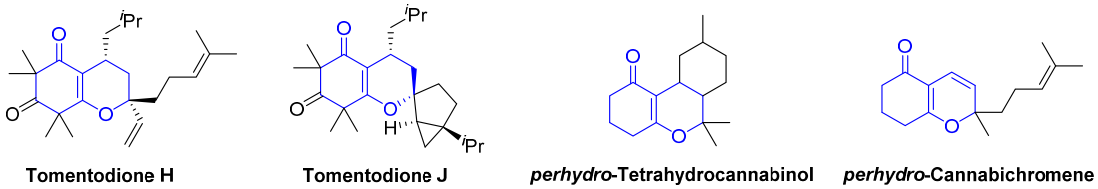


Scheme 1. Representative natural products containing 5-chromenone derivatives.

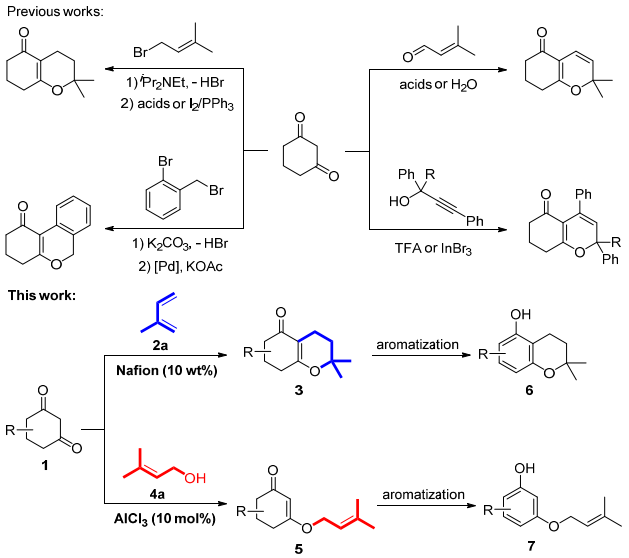
other easily accessible and low-cost chemicals is still in high demand.

Isoprene is an important bulk chemical in industry with an annual capacity of up to 800,000 metric tons. Expanding on our continuing interest in exploring the diverse reactivity of isoprene [22–25], we have developed an efficient alternative for the synthesis of 5-chromenone derivatives 3 via [3+3] annulation of isoprene 2a and 1,3-cyclohexanediones 1 using the solid acid Nafion as a catalyst (Scheme 2, this work). The pathway for this process involves a domino *C*-prenylation and intramolecular cyclization. Using prenol 4a as the coupling partner in the presence of $AlCl_3$ catalyst resulted in the chemoselectivity of the reaction switching exclusively to *O*-prenylation [26–33]. Notably, both products 3 and 5 could be aromatized to the corresponding prenylated resorcinols that are otherwise difficult to synthesize [34–39].

2. Experimental

2.1. General information

Reagents were purchased from commercial sources and used without further purification. Solvents were treated prior to use following standard procedures. Unless otherwise stated, all reactions were conducted under inert conditions. All reactions were monitored by TLC, GC-FID, or NMR analysis. Flash column chromatography was performed on silica gel (200–300 mesh) using a forced flow of eluent at 0.3–0.5 bar pressure. Silica gel GF254 was used for TLC analysis and products were visualized by fluorescence quenching under UV light. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz instrument at room temperature in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard. HRMS data were obtained with a Micromass HPLC-Q-TOF mass spectrometer (ESI) or Agilent 6540 Accurate-MS spectrometer (Q-TOF).



Scheme 2. Synthesis of 5-chromenone derivatives from 1,3-cyclohexanedione.

2.2. General procedure for the annulation of cyclic 1,3-diketones with isoprene

Isoprene (120 μL, 1.20 mmol) was added to a mixture of cyclic 1,3-diketones 1 (0.40 mmol) and Nafion (10 wt%) in 1,2-dichloroethane (DCE, 1.0 mL) in a sealed tube and stirred at 110 °C for 24 h. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel using petroleum ether and ethyl acetate to give the desired 5-chromenones 3.

2,2-Dimethyl-7-phenyl-2,3,4,6,7,8-hexahydro-5*H*-chromen-5-one (3a). Light yellow solid, mp 60–61 °C, 84.1 mg, 82% yield, R_f = 0.60 (petroleum ether/EtOAc 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.29 (m, 2H), 7.27–7.21 (m, 3H), 3.39–3.27 (m, 1H), 2.74–2.49 (m, 4H), 2.40–2.14 (m, 2H), 1.75–1.62 (m, 2H), 1.34 (s, 3H), 1.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.2, 169.7, 143.1, 128.7, 126.9, 126.7, 109.8, 77.5, 43.8, 39.1, 36.6, 32.2, 27.7, 25.5, 15.7. HRMS calculated for $C_{17}H_{21}O_2$ $[M+H]^+$ 257.1536, found 257.1543.

2,2-Dimethyl-2,3,4,6,7,8-hexahydro-5*H*-chromen-5-one (3b). Colorless oil, 53.1 mg, 74% yield, R_f = 0.60 (petroleum ether/EtOAc 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33–2.24 (m, 4H), 2.20–2.16 (m, 2H), 1.92–1.85 (m, 2H), 1.62–1.58 (m, 2H), 1.22 (s, 3H), 1.21 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 170.6, 110.0, 77.0, 36.7, 32.3, 29.2, 26.6, 21.0, 15.7. HRMS calculated for $C_{11}H_{17}O_2$ $[M+H]^+$ 181.1223, found 181.1225.

2,2,7-Trimethyl-2,3,4,6,7,8-hexahydro-5*H*-chromen-5-one (3c). White solid, mp 68–69 °C, 62.9 mg, 81% yield, R_f = 0.60 (petroleum ether/EtOAc 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43–2.33 (m, 1H), 2.36–2.25 (m, 1H), 2.26–2.10 (m, 3H), 2.10–1.96 (m, 2H), 1.69–1.55 (m, 2H), 1.28 (s, 3H), 1.21 (s, 3H), 1.02 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 170.0, 109.5, 77.1, 45.1, 37.3, 32.2, 28.6, 27.5, 25.7, 21.1, 15.6. HRMS calculated for $C_{12}H_{19}O_2$ $[M+H]^+$ 195.1380, found 195.1385.

2,2,7,7-Tetramethyl-2,3,4,6,7,8-hexahydro-5*H*-chromen-5-one (3d). White solid, mp 70–71 °C, 69.6 mg, 84% yield, R_f = 0.70 (petroleum ether/EtOAc 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23–2.13 (m, 6H), 1.60 (t, J = 6.6 Hz, 2H), 1.22 (s, 6H), 0.99 (s,

6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 168.9, 108.7, 77.1, 50.7, 43.0, 32.3, 32.2, 28.4, 26.6, 15.5. HRMS calculated for $C_{13}H_{21}O_2$ $[M+H]^+$ 209.1536, found 209.1531.

2,2,6,6-Tetramethyl-2,3,4,6,7,8-hexahydro-5*H*-chromen-5-one (3e). Colorless oil, 25.7 mg, 31% yield, R_f = 0.70 (petroleum ether/EtOAc 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (tt, J = 6.4, 1.7 Hz, 2H), 2.20 (tt, J = 6.6, 1.8 Hz, 2H), 1.77 (q, J = 6.4 Hz, 2H), 1.63 (t, J = 6.6 Hz, 2H), 1.25 (s, 6H), 1.09 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.1, 168.4, 108.1, 76.7, 39.9, 34.8, 32.4, 26.7, 26.2, 25.0, 16.2. HRMS calculated for $C_{13}H_{21}O_2$ $[M+H]^+$ 209.1536, found 209.1538.

2,2,8,8-Tetramethyl-2,3,4,6,7,8-hexahydro-5*H*-chromen-5-one (3e'). Colorless oil, 41.8 mg, 50% yield, R_f = 0.60 (petroleum ether/EtOAc 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40–2.34 (m, 2H), 2.19 (t, J = 6.7 Hz, 2H), 1.78–1.72 (m, 2H), 1.59 (t, J = 6.7 Hz, 2H), 1.22 (s, 6H), 1.12 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.0, 175.8, 108.4, 76.4, 35.7, 35.2, 33.6, 32.0, 26.4, 25.6, 16.1. HRMS calculated for $C_{13}H_{21}O_2$ $[M+H]^+$ 209.1536, found 209.1538.

2,2,6,6,8,8-Hexamethyl-2,3,4,8-tetrahydro-5*H*-chromene-5,7(6*H*)-dione (3f). Light yellow solid, mp 58–59 °C, 32.0 mg, 32% yield, R_f = 0.70 (petroleum ether/EtOAc 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (t, J = 6.7 Hz, 2H), 1.69 (t, J = 6.7 Hz, 2H), 1.34 (s, 6H), 1.31 (s, 6H), 1.30 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.9, 198.3, 170.9, 106.7, 77.7, 55.1, 47.7, 31.9, 26.5, 25.1, 24.7, 16.7. HRMS calculated for $C_{15}H_{23}O_3$ $[M+H]^+$ 251.1642, found 251.1646.

2,2-Dimethyl-3,4,6,7-tetrahydrocyclopenta[*b*]pyran-5(2*H*)-one (3g). Light yellow oil, 30.7 mg, 46% yield, R_f = 0.30 (petroleum ether/EtOAc 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.53–2.50 (m, 2H), 2.43–2.40 (m, 2H), 2.24–2.18 (tt, J = 6.5, 2.0 Hz, 2H), 1.67 (t, J = 6.5 Hz, 2H), 1.35 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0, 183.8, 113.1, 80.5, 33.2, 31.8, 26.8, 26.4, 14.5. HRMS calculated for $C_{10}H_{15}O_2$ $[M+H]^+$ 167.1067, found 167.1065.

2,2-Dimethyl-3,4,6,7,8,9-hexahydrocyclohepta[*b*]pyran-5(2*H*)-one (3h). Light yellow oil, 10.3 mg, 13% yield, R_f = 0.60 (petroleum ether/EtOAc 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63–2.55 (m, 2H), 2.52–2.46 (m, 2H), 2.27 (t, J = 6.8 Hz, 2H), 1.80–1.73 (m, 4H), 1.59 (t, J = 6.8 Hz, 2H), 1.25 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 170.6, 112.4, 76.5, 41.4, 33.0, 32.2, 26.5, 23.4, 21.2, 18.4. HRMS calculated for $C_{12}H_{19}O_2$ $[M+H]^+$ 195.1380, found 195.1373.

1,3,7,7-Tetramethyl-1,5,6,7-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*)-dione (3i). Light yellow solid, mp 126–127 °C, 26.0 mg, 29% yield, R_f = 0.30 (petroleum ether/EtOAc 2/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.33 (d, J = 9.5 Hz, 6H), 2.47 (t, J = 6.6 Hz, 2H), 1.78 (t, J = 6.6 Hz, 2H), 1.40 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 155.1, 151.3, 85.5, 81.3, 31.9, 28.4, 27.9, 26.5, 16.0. HRMS calculated for $C_{11}H_{17}N_2O_3$ $[M+H]^+$ 225.1234, found 225.1232.

2,2,7-Trimethyl-3,4-dihydro-2*H*,5*H*-pyrano[4,3-*b*]pyran-5-one (3j). Light yellow oil, 36.2 mg, 47% yield, R_f = 0.40 (petroleum ether/EtOAc 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 (s, 1H), 2.39 (t, J = 6.6 Hz, 2H), 2.13 (s, 3H), 1.72 (d, J = 13.3 Hz, 2H), 1.29 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 164.1, 159.8, 100.8, 96.9, 77.6, 32.0, 26.5, 19.7, 16.6. HRMS calculated for $C_{11}H_{15}O_3$ $[M+H]^+$ 195.1016, found 195.1018.

2.3. General procedure for the O-prenylation of cyclic 1,3-diketones with prenol

Prenol (125 μL, 1.20 mmol) was added to a mixture of cyclic 1,3-diketones 1 (0.40 mmol) and $AlCl_3$ (5.4 mg, 10 mol%) in DCE (1.0 mL) in a sealed tube and stirred at 70 °C for 24 h. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel using petroleum ether and ethyl acetate to give the desired *O*-prenylated cyclohexenones 5.

5-((3-Methylbut-2-en-1-yl)oxy)-1,6-dihydro-[1,1'-biphenyl]-3(2*H*)-one (5a). Light yellow oil, 65.2 mg, 64% yield, R_f = 0.50 (petroleum ether/EtOAc 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.30 (m, 2H), 7.28–7.21 (m, 3H), 5.47 (s, 1H), 5.44–5.35 (m, 1H), 4.49–4.35 (m, 2H), 3.40–3.32 (m, 1H), 2.76–2.49 (m, 4H), 1.79 (d, J = 1.4 Hz, 3H), 1.71 (d, J = 1.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 176.9, 142.8, 139.8, 128.8, 127.0, 126.7, 117.9, 102.8, 65.8, 43.9, 39.4, 36.7, 25.8, 18.3. HRMS calculated for $C_{17}H_{21}O_2$ $[M+H]^+$ 257.1536, found 257.1541.

3-((3-Methylbut-2-en-1-yl)oxy)cyclohex-2-en-1-one (5b). Light yellow oil, 55. mg, 77% yield, R_f = 0.40 (petroleum ether/EtOAc 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40–5.29 (m, 2H), 4.33 (d, J = 6.9 Hz, 2H), 2.36 (t, J = 6.3 Hz, 2H), 2.32–2.27 (m, 2H), 1.93 (p, J = 6.5 Hz, 2H), 1.74 (s, 3H), 1.66 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 177.9, 139.6, 117.9, 103.0, 65.4, 36.7, 29.2, 25.8, 21.3, 18.2. HRMS calculated for $C_{11}H_{17}O_2$ $[M+H]^+$ 181.1223, found 181.1227.

5-Methyl-3-((3-methylbut-2-en-1-yl)oxy)cyclohex-2-en-1-one (5c). Colorless oil, 53.5 mg, 69% yield, R_f = 0.50 (petroleum ether/EtOAc 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38–5.30 (m, 2H), 4.33 (d, J = 6.9 Hz, 2H), 2.44–2.32 (m, 2H), 2.25–2.06 (m, 2H), 2.04–1.94 (m, 1H), 1.74 (s, 3H), 1.66 (s, 3H), 1.03 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.8, 177.3, 139.6, 118.0, 102.6, 65.5, 45.1, 37.3, 28.9, 25.8, 20.9, 18.2. HRMS calculated for $C_{12}H_{19}O_2$ $[M+H]^+$ 195.1380, found 195.1382.

5,5-Dimethyl-3-((3-methylbut-2-en-1-yl)oxy)cyclohex-2-en-1-one (5d). Colorless oil, 36.5 mg, 44% yield, R_f = 0.50 (petroleum ether/EtOAc 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42–5.30 (m, 2H), 4.35 (d, J = 6.8 Hz, 2H), 2.25 (s, 2H), 2.18 (s, 2H), 1.76 (s, 3H), 1.67 (s, 3H), 1.04 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 176.2, 139.6, 118.0, 101.8, 65.6, 50.8, 43.0, 32.6, 28.4, 25.9, 18.3. HRMS calculated for $C_{13}H_{21}O_2$ $[M+H]^+$ 209.1536, found 209.1541.

6,6-Dimethyl-3-((3-methylbut-2-en-1-yl)oxy)cyclohex-2-en-1-one (5e). Colorless oil, 47.9 mg, 58% yield, R_f = 0.70 (petroleum ether/EtOAc 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39–5.34 (m, 1H), 5.24 (s, 1H), 4.32 (d, J = 6.9 Hz, 2H), 2.40 (t, J = 6.4 Hz, 2H), 1.81–1.73 (m, 5H), 1.67 (s, 3H), 1.08 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.6, 175.8, 139.5, 118.1, 101.3, 65.5, 40.2, 35.1, 26.4, 25.8, 24.6, 18.2. HRMS calculated for $C_{13}H_{21}O_2$ $[M+H]^+$ 209.1536, found 209.1530.

2,2,6,6-Tetramethyl-5-((3-methylbut-2-en-1-yl)oxy)cyclohex-4-ene-1,3-dione (5f). Light yellow solid, mp 56–57 °C, 13.2 mg, 25% yield, R_f = 0.70 (petroleum ether/EtOAc 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.49 (s, 1H), 5.43–5.35 (m, 1H), 4.45 (d, J =

6.7 Hz, 2H), 1.79 (s, 3H), 1.71 (s, 3H), 1.39 (s, 6H), 1.34 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.7, 199.5, 177.7, 140.0, 117.8, 99.9, 66.2, 55.3, 48.4, 25.9, 25.2, 24.5, 18.4. HRMS calculated for $C_{15}H_{23}O_3$ $[M+H]^+$ 251.1642, found 251.1644.

3-((3-Methylbut-2-en-1-yl)oxy)cyclopent-2-en-1-one (5g). Light yellow oil, 32.7 mg, 49% yield, R_f = 0.30 (petroleum ether/EtOAc 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42–5.36 (m, 1H), 5.28 (d, J = 1.2 Hz, 1H), 4.48 (d, J = 7.1 Hz, 2H), 2.62–2.55 (m, 2H), 2.44–2.38 (m, 2H), 1.77 (s, 3H), 1.70 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.2, 190.2, 140.6, 117.6, 105.0, 68.7, 34.1, 28.7, 25.8, 18.3. HRMS calculated for $C_{10}H_{15}O_2$ $[M+H]^+$ 167.1067, found 167.1070.

3-((3-Methylbut-2-en-1-yl)oxy)cyclohept-2-en-1-one (5h). Colorless oil, 10.7 mg, 28% yield (0.2 mmol scale), R_f = 0.60 (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 (s, 1H), 5.40–5.36 (m, 1H), 4.27 (d, J = 6.8 Hz, 2H), 2.61–2.54 (m, 4H), 1.89–1.79 (m, 4H), 1.78 (s, 3H), 1.68 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.6, 176.4, 139.3, 118.3, 106.2, 65.7, 41.8, 33.2, 25.9, 23.7, 21.4, 18.3. HRMS calculated for $C_{12}H_{19}O_2$ $[M+H]^+$ 195.1380, found 195.1377.

2.4. Procedure for the recycling experiment

In a sealed Schlenk tube (25 mL), Nafion (10 wt%, 37.7 mg), 5-phenyl-1,3-cyclohexanedione 1a (2.00 mmol, 376.5 mg), DCE (5.0 mL), and isoprene (0.60 mL, 6.00 mmol) were added in sequence. The resulting mixture was stirred at 110 °C for 24 h. Upon completion, Nafion was filtered, washed with ethyl acetate, and dried by vacuum pump for 1 h prior to use in the next cycle. The collected solution was analyzed by GC-FID using 1,3,5-trimethoxybenzene as an internal standard.

2.5. General procedure for the aromatization of 3a and 5a

An oven-dried Schlenk flask equipped with a magnetic stirrer was sealed with a rubber plug and then evacuated and back-filled with nitrogen. The flask was charged with a solution of LiHMDS (1.0 mol/L in THF, 1.5 mL, 3.0 equiv), dry THF (1.0 mL), and dry pentane (2.0 mL) and cooled to −78 °C. After stirring for 10 min, a solution of substrate 3a or 5a (128.1 mg, 0.5 mmol, 1.0 equiv) in THF (1.0 mL) was added dropwise over 3 min and stirred at −78 °C for an additional 30 min. A solution of tosyl chloride (209.7 mg, 1.1 mmol, 2.1 equiv) in THF (1.5 mL) was then added dropwise over 10 min and further stirred at −78 °C for 30 min. A solution of LiHMDS (1.0 mol/L in THF, 0.5 mL, 1.0 equiv) was then added dropwise over 1 min. The mixture was subsequently warmed to room temperature over 20 min and then stirred at room temperature for an additional 30 min. The reaction was quenched by 1.0 mol/L HCl (aq, 5 mL) and diluted with EtOAc (20 mL). The aqueous phase was then extracted with EtOAc and the combined organic phases were washed with brine (1 × 10 mL), dried over anhydrous Na_2SO_4, filtered through Celite, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to afford the desired aromatized product 6a or 7a.

6-Chloro-2,2-dimethyl-7-phenylchroman-5-ol (6a). Brown oil, 120.5 mg, 83% yield, R_f = 0.50 (petroleum ether/EtOAc 8/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.35 (m, 5H), 6.47 (s, 1H), 5.85 (s, 1H), 2.78 (t, J = 6.8 Hz, 2H), 1.84 (t, J = 6.8 Hz, 2H), 1.36 (s, 6H).

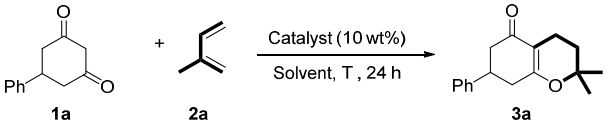
^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 149.7, 139.3, 138.8, 129.4, 128.1, 127.7, 111.8, 109.0, 108.8, 74.6, 32.1, 26.8, 17.8. HRMS calculated for $C_{17}H_{18}ClO_2$ $[M+H]^+$ 289.0990, found 289.0986.

2-Chloro-5-((3-methylbut-2-en-1-yl)oxy)-[1,1'-biphenyl]-3-ol (7a). Yellow oil, 111.5 mg, 77% yield, R_f = 0.30 (petroleum ether/EtOAc 30/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.34 (m, 5H), 6.64 (d, J = 2.8 Hz, 1H), 6.53 (d, J = 2.9 Hz, 1H), 5.78 (s, 1H), 5.49 (t, J = 7.0 Hz, 1H), 4.50 (d, J = 6.8 Hz, 2H), 1.81 (s, 3H), 1.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 152.5, 141.5, 139.3, 138.7, 129.3, 128.2, 127.9, 119.3, 110.5, 110.1, 101.5, 65.2, 25.9, 18.3. HRMS calculated for $C_{17}H_{18}ClO_2$ $[M+H]^+$ 289.0990, found 289.0999.

3. Results and discussion

In previous works, the annulations of 1,3-cyclohexanediones were often performed in the presence of various homogeneous acids. In comparison, we began our investigation by employing solid acids to catalyze the [3+3] annulation of 5-phenyl-1,3-cyclohexanedione 1a and isoprene 2a (Table 1). To our delight, when Nafion was subjected to the mixture of 1a, 2a, and dioxane at 110 °C, the anticipated [3+3] adduct 3a was afforded in 76% yield (entry 1). Other heterogeneous acids, such as H-MOR (Si/Al = 24) and H-USY (Si/Al = 3), showed no catalytic activity, while Amberlyst-15 was able to promote the annulation, albeit with decreased yield (entries 2–4). Temperature-programmed desorption of ammonia (NH_3-TPD) experiments revealed the sequence of acid amount of the catalysts as Amberlyst-15 (3.397 mmol/g) > H-USY (1.318 mmol/g) > H-MOR (0.876 mmol/g), which is

Table 1
Solid acid-catalyzed [3+3] annulation of 1,3-cyclohexanedione 1a with isoprene 2a.



1a 2a 3a

Entry	Catalyst (10 wt%)	Solvent	Temperature (°C)	Yield of 3a [a] (%)
1	Nafion	Dioxane	110	76
2	H-USY	Dioxane	110	Trace
3	H-MOR	Dioxane	110	N.R.
4	Amberlyst-15	Dioxane	110	44
5	Nafion	DCE	110	92
6	Nafion	Toluene	110	64
7	Nafion	DCE	80	10
8	Nafion	DCE	90	44
9	Nafion	DCE	100	53
10	Nafion	DCE	120	88

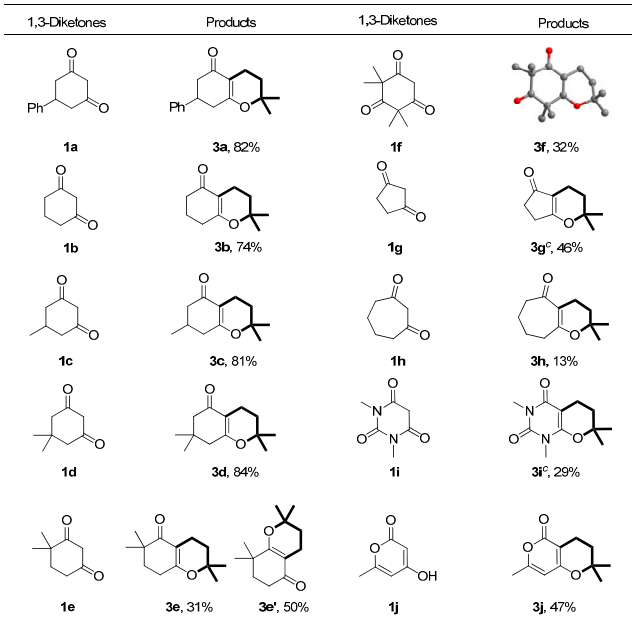
Reaction conditions: 1a (0.20 mmol), 2a (0.60 mmol), catalyst (10 wt%, based on the quantity of 1a), solvent (0.5 mL), T °C, 24 h. [a] Yield was determined by GC-FID using 1,3,5-trimethoxybenzene as an internal standard. N.R. = no reaction.

consistent with their catalytic performances [40]. An exception to this sequence was Nafion (2.123 mmol/g), which gave the highest yield of 3a (entry 1), presumably due to the strong, electron-deficient polyfluoro-substituted sulfonic group on Nafion making it more acidic than Amberlyst-15. These results suggested that both acid amount and strength of the catalyst contribute to its reactivity. A survey of the solvents demonstrated that the annulation in DCE furnished the product 3a in 92% yield, while the non-polar solvent toluene gave an inferior result (entries 5 and 6). The temperature exerted a remarkable influence on the reaction outcome. The yield of 3a increased dramatically with increasing temperatures in the range of 80 to 110 °C, at which temperature the productivity plateaued (entries 7–10).

It is worthwhile to mention that prenol 4a and 1,3-cyclohexanedione 1a could also undergo the [3+3] annulation efficiently under the standard conditions (Table 2, entry 1). Surprisingly, when this reaction was performed at 70 °C, a small amount of 5a was detected along with 3a (entry 2). Compound 3a was the cyclized *C*-prenylated product, while 5a was formed by *O*-prenylation of 1a. Considering that direct *O*-prenylation of 1,3-cyclohexanedione is rare [41], additional efforts were devoted to increasing the selectivity of 5a. Happily, *O*-prenylated product 5a was afforded exclusively using Lewis acid $AlCl_3$ (entry 4). Other Lewis acids, such as $InCl_3$, $GaCl_3$, and $Zn(OTf)_2$, furnished 3a as the main product, while in the presence of YCl_3, 5a predominated, but with a lower yield (entries 5–8). Utilizing dioxane/toluene as the solvent diminished the yield of 5a (entries 9 and 10). Increasing the temperature increased the formation of 3a (entry 12).

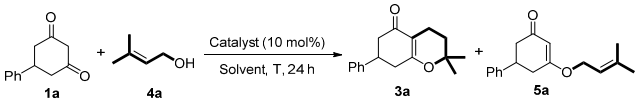
Having established the optimal conditions, we next explored the generality of the [3+3] annulation of cyclic 1,3-diketones with isoprene. The expected adduct 3a was isolated in 82% yield after subjecting 5-phenyl-1,3-cyclohexanedione 1a to the standard conditions (Table 3). Using this procedure, 1,3-cyclohexanedione 1b was readily converted to 5-chromenone 3b in 74% yield. Other suitable substrates for the reaction were 5-methyl- and 5,5-dimethyl-substituted 1,3-cyclohexanediones, which provided the corresponding products 3c and 3d in 81% and 84% yield, respectively. In the case of 4,4-dimethyl-1,3-cyclohexanedione 1e, the reaction gave a mixture of 5-chromenones 3e and 3e' in 81% yield with moderate regioselectivity. Gratifyingly, sterically hindered,

Table 3
Nafion-catalyzed [3+3] annulation of cyclic 1,3-diketones with isoprene.



Conditions: 1 (0.40 mmol), 2a (1.20 mmol), Nafion (10 wt%, based on 1), DCE (1.0 mL), 110 °C, 24 h. [a] Isolated yields. [b] 150 °C.

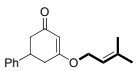
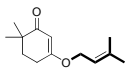
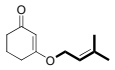
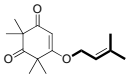
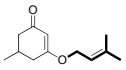
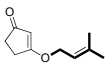
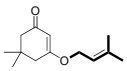
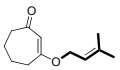
Table 2
Lewis acid-catalyzed *O*-prenylation of 1,3-cyclohexanedione 1a with prenol 4a.



Entry	Catalyst (10 mol%)	Solvent	Temperature (°C)	Yield of 3a [a] (%)	Yield of 5a [a] (%)
1 [b]	Nafion	DCE	110	62	0
2 [b]	Nafion	DCE	70	24	Trace
3	$FeCl_3$	DCE	70	N.D. [c]	N.D. [c]
4	$AlCl_3$	DCE	70	0	60
5	$InCl_3$	DCE	70	12	Trace
6	$GaCl_3$	DCE	70	20	0
7	YCl_3	DCE	70	0	30
8	$Zn(OTf)_2$	DCE	70	25	Trace
9	$AlCl_3$	Dioxane	70	0	46
10	$AlCl_3$	Toluene	70	0	58
11	$AlCl_3$	DCE	80	0	50
12	$AlCl_3$	DCE	90	4	38

Reaction conditions: 1a (0.20 mmol), 4a (0.60 mmol), catalyst (10 mol%, based on the quantity of 1a), solvent (0.5 mL), *T* °C, 24 h. [a] Yield was determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard. [b] Nafion (10 wt%, based on the amount of 1a). [c] A complex mixture was afforded. N.D. = not detected.

Table 4
$AlCl_3$-catalyzed *O*-prenylation of cyclic 1,3-diketones with prenol.

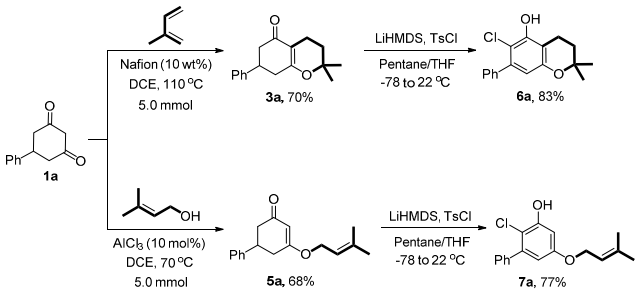
1,3-Diketones	Products [a]	1,3-Diketones	Products [a]
 **1a**	 **5a**, 64%	 **1e**	 **5e**, 58%
 **1b**	 **5b**, 77%	 **1f**	 **5f**, 25%
 **1c**	 **5c**, 69%	 **1g**	 **5g**, 49%
 **1d**	 **5d**, 44%	 **1h**	 **5h**, 28%

Conditions: 1 (0.40 mmol), 4a (1.20 mmol), $AlCl_3$ (10 mol%, based on 1) DCE (1.0 mL), 70 °C, 24 h. [a] Isolated yields.

tetramethyl-substituted 1,3,5-cyclohexanetrione 1f (syncarpic acid) [42–44] was also tolerated in this process, providing the target product 3f in an acceptable yield. The structure of 3f was unambiguously confirmed by X-ray crystallography [45]. Notably, the transformation could be successfully extended to 1,3-cyclopentanedione 1g and 1,3-cycloheptanedione 1h, albeit with decreased yields. Moreover, this protocol was also applicable to heterocyclic 1,3-dicarbonyls, such as *N*-methyl barbituric acid 1i and 4-hydroxy-6-methyl-2*H*-pyran-2-one 1j.

The scope of cyclic 1,3-diketone *O*-prenylation was further examined (Table 4). In the presence of $AlCl_3$, the coupling of 5-phenyl-1,3-cyclohexanedione 1a and prenol 4a furnished the desired product 5a in 64% isolated yield. The simple 1,3-cyclohexanedione 1b underwent the process efficiently to produce *O*-prenylated cyclohexenone 5b in 77% yield. The 5-methyl-substituted 1,3-cyclohexanediones 1c and 1d were compatible with the transformation, producing the target *O*-prenylated products 5c and 5d in acceptable yields. Surprisingly, when 4,4-dimethyl-1,3-cyclohexanedione 1e was employed as the substrate, the reaction afforded 5e in high selectivity. *O*-prenylation of syncarpic acid 1f generated 5f in a decreased yield, which is likely due to its large steric hindrance. Five- and seven-membered cyclic 1,3-ketones 1g and 1h could also be employed in this process.

To demonstrate the potential applications of this methodology in organic synthesis, gram-scale experiments and



Scheme 3. Gram-scale reactions and synthetic transformations.

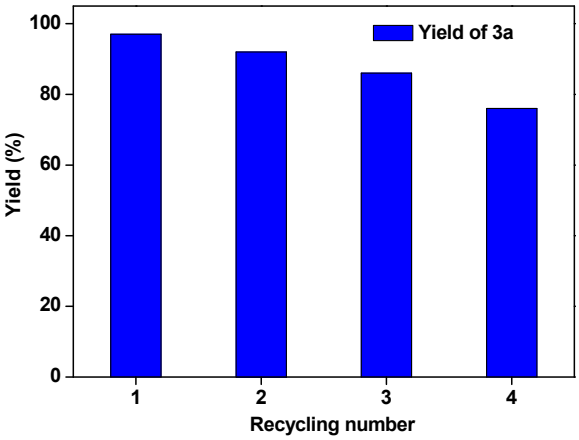
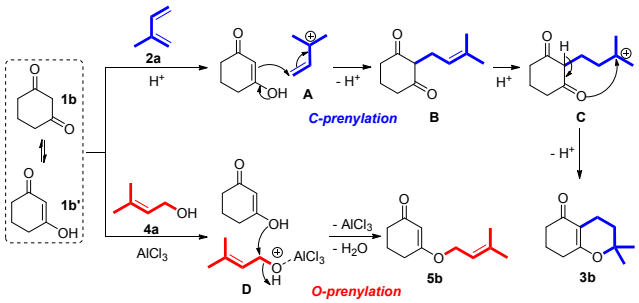


Fig. 1. Yield of 3a in recycling experiments. Reaction conditions: 5-phenyl-1,3-cyclohexanedione 1a (2.00 mmol, 376.5 mg), isoprene 2a (6.00 mmol, 0.60 mL), Nafion (10 wt%, 37.7 mg), DCE (5.0 mL), 110 °C, 24 h.

derivatizations of the resulting products were performed (Scheme 3). Both transformations could be easily scaled up to 5.0 mmol, leading to the formation of cyclized *C*-prenylated product 3a and *O*-prenylated cyclohexenone 5a in 70% and 68% yield, respectively. Treatment of 3a with lithium hexamethyldisilazide (LiHMDS) and tosyl chloride (TsCl) provided the aromatized chloro-substituted resorcinol 6a product in 83% yield [46]. Following the same procedure, 5a could be converted to *O*-prenylated resorcinol 7a in 77% yield. It should be noted that prenylated resorcinols are also important scaffolds that can be found in diverse natural products [47–52]. However, conventional catalytic prenylation of resorcinols often displays poor selectivity and does not yield the *O*-prenylated product [34–39]. Thus, our approach provides an expedient alternative to construct *C*- and *O*-prenylated resorcinols with high selectivity.

The reusability of the Nafion catalyst for the [3+3] annulation of 5-phenyl-1,3-cyclohexanedione 1a and isoprene 2a was examined (Fig. 1). Unfortunately, the yield of 3a gradually decreased after each cycle. The polymerization of isoprene could not be avoided in the presence of the strong acid at high temperatures [53–57]. Thus, after several runs under the optimized conditions, the accumulated coke on the surface of Nafion led to its diminished catalytic activity.

The coupling of 1,3-cyclohexanedione 1b with isoprene/prenol was used to illustrate the mechanism for the



Scheme 4. Proposed mechanism for *C*- and *O*-prenylation of 1,3-cyclohexanedione.

Graphical Abstract

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Acid-catalyzed chemoselective *C*- and *O*-prenylation of cyclic 1,3-diketones

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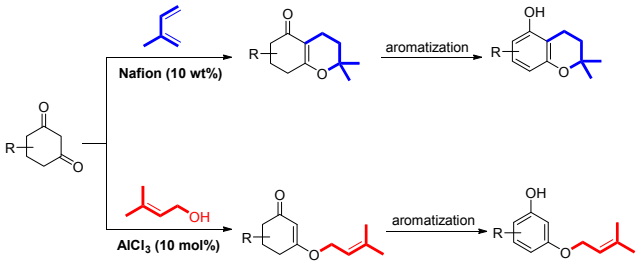
Dalian Institute of Chemical Physics, Chinese Academy of Sciences; Liaoning Shihua University



The coupling of 1,3-cyclohexanediones with isoprene produced *C*-prenylated product 5-chromenones in the presence of solid acid Nafion, while *O*-prenylation turned out to be exclusive when using prenol as substrate and Lewis acid $AlCl_3$ as catalyst.

two catalytic processes (Scheme 4). Initially, 1,3-cyclohexanedione 1b can tautomerize into its enol form 1b'. In the presence of the solid acid Nafion, isoprene 2a is protonated to yield the active isopentenyl cation A. The subsequent nucleophilic attack by the enol moiety of 1b' furnishes the *C*-prenylated diketone B, which further undergoes acid-catalyzed intramolecular cyclization to afford [3+3] adduct 3b. For Lewis acid catalysis, prenol 4a is activated by $AlCl_3$ to give intermediate D, followed by the nucleophilic S_N2 substitution of the hydroxyl group of enol isomer 1b to generate *O*-prenylated product 5b.

4. Conclusions

We have developed an efficient strategy for achieving *C*- and *O*-prenylation of cyclic 1,3-diketones. Using the solid acid Nafion as a catalyst, 1,3-cyclohexanediones and isoprene could undergo [3+3] annulation to yield cyclized *C*-prenylated 5-chromenone products. Alternatively, the $AlCl_3$-catalyzed coupling of 1,3-cyclohexanediones and prenol exclusively resulted in the formation of *O*-prenylated cyclohexenones. Notably, both products could be easily transformed into the corresponding prenylated resorcinols that are otherwise difficult to prepare. The advantages of our methodology include excellent selectivity, high atom-economy, simple operation, and easy scale-up. These attributes impart great potential for its use in organic synthesis.

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酸催化1,3-环二酮的选择性*C*-, *O*-异戊烯基化反应

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摘要: 5-色烯酮类衍生物广泛分布于自然界中, 特别是各种天然药材中. 例如, 传统药材桃金娘和大麻的活性成分都含有这类骨架. 因此, 发展高效的策略来合成5-色烯酮一直受到科研工作者的关注. 传统的方法主要是以1,3-环己二酮与异戊烯基溴或卤代苄溴为原料, 经过取代和分子内环化两步反应合成得到. 最近, 1,3-环己二酮与不饱和分子的形式[3+3]环加成反应, 由于其独特的原子和步骤经济性, 已被用于构建色烯酮骨架. 但这类不饱和分子仅限于α,β-不饱和醛与炔丙基醇. 因此, 发展新的、简单易得的合成子仍具有很大的吸引力.

本文采用廉价易得的工业化学品异戊二烯作为简单高效的合成子, 用于构建5-色烯酮骨架. 首先, 以5-苯基-1,3-环己二酮和异戊二烯为模板底物, 通过对固体酸催化剂、溶剂及反应温度等筛选发现, 在固体酸Nafion (10 wt%)催化下, 以DCE为溶剂, 110 °C反应24 h, 5-苯基-1,3-环己二酮会经过*C*-异戊烯基化和分子内环化的串联过程, 一步生成[3+3]产物5-色烯酮, 分离收率达到82%. 该反应具有高的区域和化学选择性, 以及原子经济性. 若以异戊烯基醇为原料, 在最优条件下, 也可以顺利得到5-色烯酮产物. 令人意外的是, 当温度降低到70 °C时, 除了主产物5-色烯酮, 还可以检测到少量*O*-异戊烯基化产物. 由于1,3-环己二酮的直接*O*-异戊烯基化反应至今未有报道, 我们对该选择性进行了优化. 通过对酸催化剂种类、溶剂和温度等调控发现, 以Lewis酸$AlCl_3$为催化剂, 在DCE中, 70 °C反应24 h, 5-苯基-1,3-环己二酮可以只发生*O*-异戊烯基化反应, 具有专一的选择性.

随后, 对两种催化体系分别进行了底物普适性考察. 在固体酸Nafion催化体系下, 未取代和5-取代的1,3-环己二酮都能很好地参与反应. 4,4-二甲基-1,3-环己二酮由于其非对称的结构, 可以得到两种环化产物. 2,2,4,4-四甲基-1,3,5-环己三酮(syncarpic acid)是很多天然产物分子的前体, 其也可以和异戊二烯发生环化反应, 所得产物结构得到了单晶衍射的确定. 此外, 该反应还适用于1,3-环戊二酮、1,3-环庚二酮以及巴比妥酸等底物. 对于$AlCl_3$催化体系, 五元、六元和七元环状二酮都

能顺利地发生*O*-异戊烯基化反应. 特别是, 在该体系中, 非对称的4,4-二甲基-1,3-环己二酮也只得到一种*O*-异戊烯基化产物, 具有优异的区域选择性.

最后, 在两种催化体系下, 1,3-环己二酮的*C*-和*O*-异戊烯基化反应能够很容易放大到克级规模, 并且所得到的两类产物在LiHMDS/TsCl作用下会发生芳构化过程, 得到异戊烯基化的间苯二酚, 该结构也是很多具有药理活性分子的核心单元.

因此, 通过对催化剂种类和异戊烯基源的调节, 首次实现了1,3-环二酮的选择性*C*-、*O*-异戊烯基化反应. 在固体酸Nafion催化下, 1,3-环己二酮和异戊二烯经过*C*-异戊烯基化和分子内环化的串联过程, 生成[3+3]产物5-色烯酮. 而以异戊烯基醇为原料时, 在$AlCl_3$催化下, 1,3-环己二酮可以专一地进行*O*-异戊烯基化反应. 这种利用廉价易得的原材料合成具有高附加值的结构骨架在有机合成及工业生产中具有潜在的应用价值.

关键词: 5-色烯酮; 1,3-环己二酮; *O*-异戊烯基化; [3+3]环化反应; 异戊二烯; 异戊烯基醇

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