Communication

Atom-Economic Synthesis of 4-Pyrones from Diynones and Water

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Abstract: Transition-metal-free synthesis of 4-pyrones via TfOH-promoted nucleophilic addition/cyclization of diynones and water has been developed. This transformation is simple, atom economical and environmentally benign, providing rapid and efficient access to substituted 4-pyriones.

Keywords: 4-pyrones; diynones; water; transition-metal-free

1. Introduction

Water (H2O) is inexpensive, safe, and environmentally friendly [1]. It is the most economic and eco-friendly solvent available in Nature and therefore highly desirable for chemical reactions [2]. Generally, water offers several “green chemistry” benefits as a solvent in organic transformations, including high efficiency, lower cost, ease of process, green and environmental protection [3,4]. Recently, there are many reports of clean transformations in water medium [5–19], such as coupling reactions [20–30], cyclizations [31–34], Michael additions [35–39], and condensations [40,41]. Additionally, H2O also participates in organic reactions as a nucleophile [42,43] to provide various kinds of functional compounds such as imidazo[1,2-a]pyridines [44], amino acid salts [45], α-amino ketones [46], and 1,3-oxazinan-2-ones [47]. Thus, the studies of organic reactions in aqueous solvents or H2O-participating reactions are attractive in synthetic chemistry.

4-Pyriones are heterocycles with multiple biological activities [48–50], which are widely found in biologically active natural products and functional chemicals [51–59]. Particularly, phenoxans, funicones and rapicones possess potent anti-HIV activity (Figure 1) [60–62]. In general, 4-pyriones are prepared via the well-known condensation cyclization reaction of carbonyl compounds with polystep reactions [63–67]. Additionally, a transformation of isoxazoles to substituted pyran-4-ones in the presence of Mo(CO)6 and HCO2H in a two-step procedure was established [68]. Although these reported methods have made significant contributions to the applications of 4-pyriones in pharmacology and food manufacture [69], the development of efficient and practical synthetic methods for 4-pyriones from easily accessible starting materials is still highly desirable. Continuing our interest in the conversion of alkynes to heterocycles [70–77], herein, we would like to describe an efficient, transition-metal-free synthesis of 4-pyriones through TfOH-promoted cyclization of diynones. Water acts as both the substrate and solvent, obviating the need for an organic co-solvent. Overall, the reaction is atom-economical and environmentally benign.
2. Results and Discussion

1,5-Diphenylpenta-1,4-diyn-3-one (1a) was chosen as model substrate to identify the optimal conditions for this reaction (Table 1). Originally, the reaction was carried out in the presence of 1 equiv. TfOH for 24 h to afford the desired product 2a in 70% yield (Table 1, entry 1). When other acid catalysts such as CH₃COOH, PTSA, HCl, H₃PO₄ and PhCOOH were screened, the yield of 2a decreased (Table 1, entries 2–6). Further experiments demonstrated that decreasing the amount of TfOH was detrimental to the yield of 2a (Table 1, entries 7 and 8), and no obvious improvement of yield was noted by using 2 equiv. of TfOH (Table 1, entry 9). Poor yield of 2a was obtained when the reaction was performed at 80 °C, while not much change was noted between 100 °C and 130 °C (Table 1, entries 10 and 11). In addition, an 83% yield was achieved when the reaction time was extended to 36 h (Table 1, entry 12). Thus, the best conditions for this transformation involved 1 equiv. of TfOH in H₂O at 100 °C for 36 h.

Table 1. Optimization of reaction conditions [a].

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Time (h)</th>
<th>Yield (%) [b]</th>
</tr>
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<tr>
<td>1</td>
<td>TfOH</td>
<td>24</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>CH₃COOH</td>
<td>24</td>
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<td>3</td>
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<tr>
<td>6</td>
<td>PhCOOH</td>
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<td>10</td>
</tr>
<tr>
<td>7 [c]</td>
<td>TfOH</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>8 [d]</td>
<td>TfOH</td>
<td>24</td>
<td>50</td>
</tr>
<tr>
<td>9 [e]</td>
<td>TfOH</td>
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<td>80</td>
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<tr>
<td>10 [f]</td>
<td>TfOH</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>11 [g]</td>
<td>TfOH</td>
<td>24</td>
<td>75</td>
</tr>
<tr>
<td>12</td>
<td>TfOH</td>
<td>36</td>
<td>83</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 1a (0.5 mmol), catalyst (1 equiv.), H₂O (1 mL), at 100 °C; [b] Isolated yields; [c] TfOH (0.2 equiv.); [d] TfOH (0.5 equiv.); [e] TfOH (2 equiv.); [f] At 80 °C; [g] The reaction was carried out in a sealed tube at 130 °C.

Under the optimized reaction conditions, the one-pot reaction worked well using all kinds of diynones, as shown in Table 2. Firstly, various symmetric diynones were identified as suitable substrates for the reaction and provided the desired products in moderate to good yields (Table 2, 2b–2j). Aryl groups with electron-donating groups (EDG) gave satisfactory yields (Table 2, 2b–2d and 2f–2h), whereas aryl groups with electron-withdrawing groups (EWG) afforded slightly lower yields (Table 2, 2e). Gratifyingly, aliphatic diynones worked smoothly to generate the corresponding

Figure 1. 4-Pyrones disclosed as biologically active organic molecules.
cyclization products 2i and 2j in 50% and 57%, respectively (Table 2, 2i and 2j). After exploring the reaction substrate scope of symmetric diynones, we next examined asymmetric diynones substrates. To our delight, the corresponding 4-pyrones products were obtained in moderate to good yields under the standard conditions (Table 2, 2k–2r). The desired products 2k–2q were obtained in 55%–78% yields when asymmetric diynones substrates 1k–1q (R2 = Ph, R1 = aryl- or alkyl-) were subjected to this reaction. Obviously, aryl groups with electron-donating groups gave higher yields than diynones featuring electron-withdrawing groups on the phenyl ring (Table 2, 2l and 2m vs. 2n and 2p). Notably, diynone 1p, which possess an electron-withdrawing group at the ortho-position of the phenyl ring (R1 = 2-Cl-Ph, R2 = Ph) reacted readily to afford 2p in 61% yield (Table 2, 2p). Furthermore, diynone 1q, which bear both a EDG-incorporated aryl ring and a EWG-incorporated aryl ring (R1 = 4-OMe-Ph, R2 = 4-F-Ph) also participated well in the reaction and offered 2q in 63% yield (Table 2, 2q). Finally, diynone 1r also worked smoothly to give 2r in 50% yield (Table 2, 2r).

Table 2. Synthesis of 4-pyrene derivatives [a],[b].

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>Product</th>
<th>Yield (%)</th>
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<tr>
<td>4-OMe-Ph</td>
<td>Ph</td>
<td>2q</td>
<td>63%</td>
</tr>
<tr>
<td>4-F-Ph</td>
<td>Ph</td>
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<td>63%</td>
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<td>4-F-Ph</td>
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<td>60%</td>
</tr>
<tr>
<td>4-CF3-Ph</td>
<td>Ph</td>
<td>2n</td>
<td>65%</td>
</tr>
<tr>
<td>4-Cl-Ph</td>
<td>Ph</td>
<td>2n</td>
<td>50%</td>
</tr>
<tr>
<td>2-Me-Ph</td>
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<td>50%</td>
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<td>50%</td>
</tr>
<tr>
<td>3-Cl-Ph</td>
<td>Ph</td>
<td>2n</td>
<td>50%</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 1 (0.5 mmol), TfOH (1 equiv.), H2O (1 mL), at 100 °C, 36 h; [b] Isolated yields.

To better understand the reaction mechanism, we carried out control experiments as outlined in Scheme 1. Deuterium-labeled D2O was used in the reaction with diynone 1a to give the deuterium-labeled product 2a-d in 80% yield, where over 95% of deuterium was incorporated into the cyclization product.

Scheme 1. Control experiments.
This result demonstrated that H2O was introduced into the 4-pyrone. Moreover, an O18-labeled experiment further showed that H2O reacted with diynones to form 4-pyrone. On the basis of the above results and existing literature [78], a plausible mechanistic description of the nucleophilic addition and cyclization reaction is shown in Scheme 2. First, the carbonyl of the diynone substrate was activated by TfOH, followed by nucleophilic addition of H2O to the carbon–carbon triple bond of diynone and keto–enol tautomerization [79,80] to form intermediate A. Then intermediate A was converted to B through protonation and C–C bond rotation, which was promoted by elevated temperature. Subsequently, an intramolecular nucleophilic attack of the oxhydryl group to the carbon–carbon triple bond of B lead to a cyclization intermediate C. Finally, deprotonation of C gave the desired 4-pyrene 2.

Scheme 2. Proposed mechanism.

The treatment of 1,5-diphenylpenta-1,4-diyn-3-one 1a in H2O at 100 °C for 36 h in the presence of TfOH afforded the corresponding cyclization product 2a in 83% yield. The preparation of this compound 2a on gram-scale afforded 53% of the isolated product (Scheme 3).

Scheme 3. Gram-scale synthesis.

3. Materials and Methods

3.1. General Information

All manipulations were performed under an air atmosphere unless otherwise stated. Column chromatography was performed on silica gel (300–400 mesh). NMR spectra were obtained using an Avance 500 spectrometer (1H at 500 MHz and 13C at 125 MHz) or an Avance 400 spectrometer (1H at 400 MHz and 13C at 100 MHz) (Bruker). IR spectra were recorded on a model? FT-IR spectrometer (manufacturer) and only major peaks are reported in cm−1. High resolution mass spectra (HRMS) were recorded on the a Exactive Mass Spectrometer (Thermo Scientific, USA) equipped with ESI or APCI ionization sources. Unless stated otherwise, commercial reagents were used without further purification. All reagents were weighed and handled at room temperature. Compounds 1a–1r were prepared by the reported methods [78,81].
3.2. General Procedure for the Synthesis of Compounds 2 (Scheme 4)

The reaction mixture of 1 (0.5 mmol), TfOH (1 equiv.) and H2O (1 mL) in a 15 mL test tube was stirred at 100 °C for 36 h, and monitored periodically by TLC. Upon completion, the reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with water and brine, dried over MgSO4 and filtered. The solvent was removed under vacuum. The residue was purified by flash column chromatography (petroleum ether and ethyl acetate, 1:1) to afford 4-pyrones 2.  

2,6-Diphenyl-4H-pyran-4-one (2a) [82]. The general procedure was used with 1,5-diphenylpenta-1,4-diyne-3-one (115.04 mg, 0.5 mmol, 1 equiv.) and TfOH (1 equiv.) and H2O (1 mL) in a 15 mL test tube was stirred at 100 °C for 36 h, and monitored periodically by TLC. Upon completion, the reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with water and brine, dried over MgSO4 and filtered. The solvent was removed under vacuum. The residue was purified by flash column chromatography (petroleum ether and ethyl acetate, 1:1) to afford the product as a yellow solid (124.78 mg, 81%); m.p. 190–193.8 °C (lit: 189–191 °C); 1H-NMR (500 MHz, CDCl3) δ 7.79 (d, J = 8.0 Hz, 4H), 6.76 (s, 2H), 2.43 (s, 6H) ppm; 13C-NMR (125 MHz, CDCl3) δ 180.2, 163.4, 141.9, 129.8, 128.7, 125.8, 110.7, 21.5 ppm; IR (KBr): 3066, 1646, 1605, 1507, 1413, 1383, 942, 819, 478 cm−1; HRMS (m/z) (APCI): calcd for C18H16O2 271.1222 [M + H+]; found 271.1219.

2,6-Di-p-tolyl-4H-pyran-4-one (2b) [78]. The general procedure was used with 1,5-di-p-tolylpenta-1,4-diyne-3-one (129.05 mg, 0.5 mmol, 1 equiv.) and water (1 mL). The crude obtained was purified by column chromatography (petroleum ether/ethyl acetate = 5:1 to 2:1) to afford the product as a yellow solid (129.05 mg, 85%); m.p. 135.3–136.2 °C (lit: 139–140 °C); 1H-NMR (500 MHz, CDCl3) δ 7.84 (dd, J = 8.5, 5.2 Hz, 4H), 7.22 (t, J = 8.4 Hz, 4H), 6.75 (s, 2H) ppm; 13C-NMR (125 MHz, CDCl3) δ 179.9, 164.6 (d, J = 253.4 Hz), 162.5, 128.1 (d, J = 8.8 Hz), 127.6 (d, J = 3.3 Hz), 116.5(d, J = 3.4 Hz) ppm; IR (KBr): 3022, 2925, 2872, 1637, 1450, 1335, 770, 683 cm−1; HRMS (m/z) (APCI): calcd for C16H14O2 263.1070 [M + H+]; found 263.1071.

2,6-Bis(4-methoxyphenyl)-4H-pyran-4-one (2c) [82]. The general procedure was used with 1,5-bis(4-methoxyphenyl)penta-1,4-diyne-3-one (145.05 mg, 0.5 mmol, 1 equiv.) and water (1 mL). The crude obtained was purified by column chromatography (petroleum ether/ethyl acetate = 5:1 to 2:1) to afford the product as a yellow solid (145.05 mg, 80%); m.p. 160–161.3 °C (lit: 167–170 °C); 1H-NMR (125 MHz, CDCl3) δ 7.74 (d, J = 8.9 Hz, 4H), 6.70 (s, 2H), 3.88 (s, 6H) ppm; 13C-NMR (125 MHz, CDCl3) δ 134.4, 127.5, 123.9, 114.5, 109.7, 55.5 ppm; IR (KBr): 3064, 3003, 2930, 1715, 1667, 1650, 1450, 1340, 1250, 910 cm−1; HRMS (m/z) (APCI): calcd for C25H26O3 389.1857 [M + H+]; found 389.1856.

2,6-Bis(4-(tert-butyl)phenyl)-4H-pyran-4-one (2d) [82]. The general procedure was used with 1,5-bis(4-(tert-butyl)phenyl)penta-1,4-diyne-3-one (171.10 mg, 0.5 mmol, 1 equiv.) and water (1 mL). The crude obtained was purified by column chromatography (petroleum ether/ethyl acetate = 5:1 to 2:1) to afford the product as a yellow solid (171.10 mg, 86%); m.p. 192–194 °C (lit: 192–194 °C); 1H-NMR (500 MHz, CDCl3) δ 7.79 (d, J = 8.9 Hz, 4H), 6.77 (s, 2H), 3.88 (s, 6H) ppm; 13C-NMR (125 MHz, CDCl3) δ 180.5, 163.5, 155.0, 128.6, 126.0, 125.7, 34.9, 31.0 ppm; IR (KBr): 3064, 3003, 2998, 2970, 2868, 1715, 1667, 1650, 1450, 1340, 1250, 910 cm−1; HRMS (m/z) (APCI): calcd for C31H32O2 474.2169 [M + H+]; found 474.2157.

2,6-Bis(4-fluorophenyl)-4H-pyran-4-one (2e) [82]. The general procedure was used with 1,5-bis(4-fluorophenyl)penta-1,4-diyne-3-one (133.12 mg, 0.5 mmol, 1 equiv.) and water (1 mL). The crude obtained was purified by column chromatography (petroleum ether/ethyl acetate = 5:1 to 2:1) to afford the product as a white solid (85.22 mg, 60%); m.p. 160–161.3 °C (lit: 167–170 °C); 1H-NMR (500 MHz, CDCl3) δ 7.84 (dd, J = 8.5, 5.2 Hz, 4H), 7.22 (t, J = 8.4 Hz, 4H), 6.75 (s, 2H) ppm; 13C-NMR (125 MHz, CDCl3) δ 179.9, 164.6 (d, J = 253.4 Hz), 162.5, 128.1 (d, J = 8.8 Hz), 127.6 (d, J = 3.3 Hz), 116.5(d, J = 3.4 Hz) ppm; IR (KBr): 3064, 2925, 2875, 1631, 1450, 1340, 1250, 910 cm−1; HRMS (m/z) (APCI): calcd for C18H14F2O2 321.0714 [M + H+]; found 321.0714.
2.6-Bis(4-pentylyphenyl)-4H-pyran-4-one (2f). The general procedure was used with 1,5-bis(4-pentylyphenyl)penta-1,4-diyn-3-one (185.11 mg, 0.5 mmol, 1 equiv.) and water (1 mL). The crude obtained was purified by column chromatography (petroleum ether/ethyl acetate = 5:1 to 2:1) to afford the product as a yellow solid (163.06 mg, 84%); m.p. 66.7–67.9 °C; 1H-NMR (500 MHz, CDCl3) δ 7.76 (d, J = 8.1 Hz, 4H), 7.32 (d, J = 8.1 Hz, 4H), 6.77 (s, 2H), 2.70–2.66 (m, 4H), 1.69–1.61 (m, 4H), 1.36–1.33 (m, 8H), 0.90 (t, J = 6.9 Hz, 6H) ppm; 13C-NMR (125 MHz, CDCl3) δ 180.1, 168.8, 163.6, 131.5, 131.3, 129.0, 125.8, 114.0, 111.1, 35.6, 20.3, 13.9 ppm; IR (KBr): 3032, 2956, 2929, 2857, 1717, 1649, 1609, 1485, 1384, 1260, 1075, 929, 784, 435 cm⁻¹; HRMS (m/z) (APCI): calcd for C26H24O5: 442.1572 [M + H⁺]; found 442.1569.

2.6-Bis(4-ethylphenyl)-4H-pyran-4-one (2g) [78]. The general procedure was used with 1,5-bis(4-ethylphenyl)penta-1,4-diyn-3-one (143.07 mg, 0.5 mmol, 1 equiv.) and water (1 mL). The crude obtained was purified by column chromatography (petroleum ether/ethyl acetate = 5:1 to 2:1) to afford the product as a brown solid (124.70 mg, 82%); m.p. 119.5–121.5 °C; 1H-NMR (500 MHz, CDCl3) δ 7.07–7.02 (m, 4H), 6.94–6.91 (m, 4H), 6.78 (s, 2H), 2.66–2.61 (m, 8H), 1.69–1.61 (m, 4H), 0.95 (td, J = 7.4, 1.1 Hz, 6H) ppm; 13C-NMR (125 MHz, CDCl3) δ 163.6, 138.9, 132.1, 131.4, 129.0, 126.5, 123.1, 111.3, 21.5 ppm; IR (KBr): 3063, 2923, 1646, 1611, 1485, 1384, 1260, 1075, 928, 784, 694, 435 cm⁻¹; HRMS (m/z) (APCI): calcd for C26H23O5: 440.1494 [M + H⁺]; found 440.1491.

2.6-Di-m-tolyl-4H-pyran-4-one (2h) [78]. The general procedure was used with 1,5-di-m-tolylpenta-1,4-diyn-3-one (129.05 mg, 0.5 mmol, 1 equiv.) and water (1 mL). The crude obtained was purified by column chromatography (petroleum ether/ethyl acetate = 5:1 to 2:1) to afford the product as a brown oil (45.03 mg, 50%); 1H-NMR (500 MHz, CDCl 3) δ 7.51–7.46 (m, 1H), 6.72 (s, 1H), 6.19 (s, 1H), 2.60 (t, J = 7.5 Hz, 1H), 1.82–1.73 (m, 1H), 1.03 (t, J = 7.4 Hz, 3H) ppm; 13C-NMR (125 MHz, CDCl3) δ 180.1, 168.8, 163.6, 131.5, 131.3, 129.0, 125.8, 114.0, 111.1, 35.6, 20.3, 13.9 ppm; IR (KBr): 3060, 2926, 1653, 1617, 1493, 1450, 1409, 1061, 937, 866, 772, 691 cm⁻¹; HRMS (m/z) (APCI): calcd for C17H15O2: 277.1230 [M + H⁺]; found 277.1219.

2.6-Dipropyl-4H-pyran-4-one (2i) [78]. The general procedure was used with undeca-4,7-diyn-6-one (81.05 mg, 0.5 mmol, 1 equiv.) and water (1 mL). The crude obtained was purified by column chromatography (petroleum ether/ethyl acetate = 5:1 to 2:1) to afford the product as a brown oil (45.03 mg, 50%); 1H-NMR (500 MHz, CDCl3) δ 6.04 (s, 1H), 2.44 (t, J = 7.5 Hz, 4H), 1.69–1.61 (m, 4H), 0.95 (td, J = 7.4, 1.1 Hz, 6H) ppm; 13C-NMR (125 MHz, CDCl3) δ 180.6, 169.1, 113.0, 35.4, 20.1, 13.3 ppm; IR (KBr): 3437, 2965, 2875, 1663, 1619, 1411, 1398, 1148, 933, 864 cm⁻¹; HRMS (m/z) (APCI): calcd for C16H13O2: 221.0872 [M + H⁺]; found 221.0866.

2.6-Dicyclopentyl-4H-pyran-4-one (2j) [78]. The general procedure was used with 1,5-dicyclopentylpenta-1,4-diyn-3-one (79.04 mg, 0.5 mmol, 1 equiv.) and water (1 mL). The crude obtained was purified by column chromatography (petroleum ether/ethyl acetate = 5:1 to 2:1) to afford the product as a white solid (50.19 mg, 57%); m.p. 146.7–150.7 °C; 1H-NMR (500 MHz, CDCl3) δ 6.10 (s, 1H), 1.72 (tt, J = 8.3, 5.0 Hz, 2H), 1.00–0.95 (m, 4H), 0.92–0.88 (m, 4H) ppm; 13C-NMR (125 MHz, CDCl3) δ 179.5, 168.6, 163.6, 131.5, 131.3, 129.0, 126.5, 123.1, 111.3, 21.5 ppm; IR (KBr): 3060, 2926, 1653, 1617, 1493, 1450, 1409, 1061, 937, 866, 772, 691 cm⁻¹; HRMS (m/z) (APCI): calcd for C16H13O2: 221.0872 [M + H⁺]; found 221.0866.

2-Phenyl-6-propyl-4H-pyran-4-one (2k) [78]. The general procedure was used with 1-phenylocta-1,4-diyn-3-one (98.04 mg, 0.5 mmol, 1 equiv.) and water (1 mL). The crude obtained was purified by column chromatography (petroleum ether/ethyl acetate = 5:1 to 2:1) to afford the product as a white solid (83.50 mg, 78%); m.p. 73.5–75.5 °C; 1H-NMR (500 MHz, CDCl3) δ 7.76 (d, J = 7.7 Hz, 1H), 7.34 (d, J = 7.7 Hz, 1H), 6.78 (s, 2H), 2.65–2.61 (m, 8H), 1.69–1.61 (m, 4H), 1.36–1.33 (m, 8H), 0.90 (t, J = 6.9 Hz, 6H) ppm; 13C-NMR (125 MHz, CDCl3) δ 180.1, 168.8, 163.6, 131.5, 131.3, 129.0, 125.8, 114.0, 111.1, 35.6, 20.3, 13.9 ppm; IR (KBr): 3060, 2926, 1653, 1617, 1493, 1450, 1409, 1061, 937, 866, 772, 691 cm⁻¹; HRMS (m/z) (APCI): calcd for C16H13O2: 221.0872 [M + H⁺]; found 221.0866.
2-Phenyl-6-(p-tolyl)-4H-pyran-4-one (2l) [83]. The general procedure was used with 1-phenyl-5-(p-tolyl)pent-1-ene-4,4-diyne-3-one (112.04 mg, 0.5 mmol, 1 equiv.) and water (1 mL). The crude obtained was purified by column chromatography (petroleum ether/ethyl acetate = 5:1 to 2:1) to afford the product as a yellow solid (85.18 mg, 65%); m.p. 106.5–107.8 °C (lit: 106 °C); 1H-NMR (500 MHz, CDCl3) δ 7.88–7.83 (m, 2H), 7.75 (d, J = 8.2 Hz, 2H), 7.54–7.51 (m, 3H), 7.32 (dd, J = 8.1 Hz, 2H), 6.83–6.78 (m, 2H), 2.44 (s, 3H) ppm; 13C-NMR (125 MHz, CDCl3) δ 180.4, 163.6, 163.3, 142.0, 131.5, 131.4, 129.8, 129.1, 128.6, 125.91, 125.86, 111.3, 110.7, 21.5 ppm; IR (KBr): 3064, 2922, 2854, 1646, 1606, 1448, 1413, 1387, 816 cm−1; HRMS (m/z): calculated for C18H13O3 279.1017 [M + H]+; found 279.1016.

2-(4-Methoxyphenyl)-6-phenyl-4H-pyran-4-one (2o) [84]. The general procedure was used with 1-cyclopropyl-5-phenylpent-1-ene-4,4-diyne-3-one (140.03 mg, 0.5 mmol, 1 equiv.) and water (1 mL). The crude obtained was purified by column chromatography (petroleum ether/ethyl acetate = 5:1 to 2:1) to afford the product as a yellow solid (93.27 mg, 63%); m.p. 138.7–140.5 °C (lit: 138 °C); 1H-NMR (500 MHz, CDCl3) δ 7.86–7.82 (m, 4H), 7.56–7.51 (m, 3H), 7.32 (d, J = 2.2 Hz, 1H), 6.80 (d, J = 2.2 Hz, 1H), 4.70 (s, 3H) ppm; 13C-NMR (125 MHz, CDCl3) δ 180.4, 163.6, 163.3, 142.0, 131.5, 131.4, 129.8, 128.6, 125.91, 125.86, 111.3, 110.7, 21.5 ppm; IR (KBr): 3059, 2927, 1667, 1650, 1594, 1496, 1448, 1394, 1253, 1193, 1087, 931, 878, 766, 685 cm−1; HRMS (m/z): calculated for C18H15O3 279.1017 [M + H]+; found 279.1016.

2-Cyclopropyl-6-phenyl-4H-pyran-4-one (2p) [85]. The general procedure was used with 1-(2-chlorophenyl)-5-phenylpent-1-ene-4,4-diyne-3-one (132.02 mg, 0.5 mmol, 1 equiv.) and water (1 mL). The crude obtained was purified by column chromatography (petroleum ether/ethyl acetate = 5:1 to 2:1) to afford the product as a yellow solid (93.27 mg, 63%); m.p. 138.7–140.5 °C (lit: 138 °C); 1H-NMR (500 MHz, CDCl3) δ 7.86–7.82 (m, 4H), 7.56–7.51 (m, 3H), 7.32 (d, J = 2.2 Hz, 1H), 6.80 (d, J = 2.2 Hz, 1H), 4.70 (s, 3H) ppm; 13C-NMR (125 MHz, CDCl3) δ 180.4, 163.6, 163.3, 142.0, 131.5, 131.4, 129.8, 128.6, 125.91, 125.86, 111.3, 110.7, 21.5 ppm; IR (KBr): 3059, 2927, 1667, 1650, 1594, 1496, 1448, 1394, 1253, 1193, 1087, 931, 878, 766, 685 cm−1; HRMS (m/z): calculated for C18H15O3 279.1017 [M + H]+; found 279.1016.

2-(4-Fluorophenyl)-6-(4-methoxyphenyl)-4H-pyran-4-one (2q) [85]. The general procedure was used with 1-(4-fluorophenyl)-5-(4-methoxyphenyl)pent-1-ene-4,4-diyne-3-one (139.04 mg, 0.5 mmol, 1 equiv.) and water (1 mL). The crude obtained was purified by column chromatography (petroleum ether/ethyl acetate = 5:1 to 2:1) to afford the product as a yellow solid (93.27 mg, 63%); m.p. 138.7–140.5 °C (lit: 138 °C); 1H-NMR (500 MHz, CDCl3) δ 7.86–7.82 (m, 4H), 7.56–7.51 (m, 3H), 7.32 (d, J = 2.2 Hz, 1H), 6.80 (d, J = 2.2 Hz, 1H), 4.70 (s, 3H) ppm; 13C-NMR (125 MHz, CDCl3) δ 180.4, 163.6, 163.3, 142.0, 131.5, 131.4, 129.8, 128.6, 125.91, 125.86, 111.3, 110.7, 21.5 ppm; IR (KBr): 3059, 2927, 1667, 1650, 1594, 1496, 1448, 1394, 1253, 1193, 1087, 931, 878, 766, 685 cm−1; HRMS (m/z): calculated for C18H15O3 279.1017 [M + H]+; found 279.1016.

2-(4-Fluorophenyl)-6-(4-methoxyphenyl)-4H-pyran-4-one (2r) [85]. The general procedure was used with 1-(4-fluorophenyl)-5-(4-methoxyphenyl)pent-1-ene-4,4-diyne-3-one (139.04 mg, 0.5 mmol, 1 equiv.) and water (1 mL). The crude obtained was purified by column chromatography (petroleum ether/ethyl acetate = 5:1 to 2:1) to afford the product as a yellow solid (93.27 mg, 63%); m.p. 138.7–140.5 °C (lit: 144–148 °C); 1H-NMR (500 MHz, CDCl3) δ 7.86–7.82 (m, 2H), 7.80–7.77 (m, 2H), 7.27–7.18 (m, 2H), 7.05–7.00 (m, 2H), 6.72 (dd, J = 3.7, 1.9 Hz, 2H), 3.89 (s, 3H) ppm; 13C-NMR (100 MHz, CDCl3) δ 180.2, 165.6, 163.4, 163.2, 162.6, 132.8, 131.9, 131.5, 131.4, 131.2, 130.7, 129.1, 127.2, 126.0, 116.8, 111.2 ppm; IR (KBr): 3059, 2931, 1667, 1650, 1600, 1580, 1403, 1250, 1000, 910, 665 cm−1; HRMS (m/z): calculated for C18H15O3 279.1017 [M + H]+; found 279.1016.
165.8, 163.4, 163.3, 162.2 (d, $J = 8.9$ Hz), 128.1 (d, $J = 8.8$ Hz), 127.8 (d, $J = 3.3$ Hz), 127.6, 123.6, 116.4 (d, $J = 22.1$ Hz), 114.6, 111.0, 109.9, 55.5 ppm; IR (KBr): 3673, 3067, 2969, 1657, 1610, 1509, 1422, 1385, 1270, 1227, 1169, 1074, 1021, 841 cm$^{-1}$; HRMS (m/z) (ESI): calcd for C$_{15}$H$_{13}$FO$_3$ 297.0929 [M + H$^+$]; found 297.0913.

2-Phenyl-4H-pyran-4-one (2r) [86]. The general procedure was used with 1-phenylpenta-1,4-diyn-3-one (77.02 mg, 0.5 mmol, 1 equiv.) and water (1 mL). The crude obtained was purified by column chromatography (petroleum ether/ethyl acetate = 5:1 to 2:1) to afford the product as a yellow solid (43.02 mg, 50%); yellow solid; m.p. 102.2–103.5 °C (lit: 100–102 °C); 1H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.84 (d, $J = 5.8$ Hz, 1H), 7.74 (dd, $J = 7.9$, 1.7 Hz, 2H), 7.51–7.44 (m, 3H), 6.78 (d, $J = 2.3$ Hz, 1H), 6.38 (dd, $J = 5.8$, 2.3 Hz, 1H) ppm; 13C-NMR (100 MHz, CDCl$_3$) $\delta$ 179.0, 163.9, 154.8, 131.4, 131.0, 129.0, 125.7, 117.0, 112.3 ppm; IR (KBr): 3090, 1675, 1650, 1590, 1549, 1490, 1402, 1350, 1050, 931, 875, 795, 730, 650 cm$^{-1}$; HRMS (m/z) (ESI): calcd for C$_{11}$H$_9$O$_2$ 173.0604 [M + H$^+$]; found 173.0603.

3.3. Control Experiments

3.3.1. Deuterium Labeling Experiments (Scheme 5).

![Scheme 5](image)

The reaction mixture of 1 (0.5 mmol), TfOH (1 equiv.), and D$_2$O (1 mL) in a 15 mL test tube was stirred at 100 °C for 36 h, and monitored periodically by TLC. Upon completion, the reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with water and brine, dried over MgSO$_4$ and filtered. The solvent was removed under vacuum. The residue was purified by flash column chromatography (petroleum ether and ethyl acetate, $v/v = 5:1$ to 2:1) to afford 4-pyrone $2a$-d (100.04 mg, 80%) as a yellow solid; m.p. 116.1–119.5 °C; 1H-NMR (500 MHz, CDCl$_3$) $\delta$ 7.90–7.83 (m, 4H), 7.55–7.51 (m, 6H), 6.84 (s, 0.12H).

3.3.2. O$^{18}$-Labelling Experiment (Scheme 6)

![Scheme 6](image)

The reaction mixture of 1a (0.5 mmol), TfOH (1 equiv.), and H$_2$O$^{18}$ (1 mL) in a 15 mL test tube was stirred at 100 °C for 36 h, and monitored periodically by TLC. Upon completion, the reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with water and brine, dried over MgSO$_4$ and filtered. The solvent was removed under vacuum. The residue was purified by flash column chromatography (petroleum ether and ethyl acetate, $v/v = 5:1$ to 2:1) to afford 4-pyrone O$^{18}$-2a (78%).
3.3.3. Gram-Scale Synthesis (Scheme 7).

\[
\text{1a} \xrightarrow{\text{TfOH (1 equiv.) \& H}_2\text{O, 100 °C}} \text{2a} \quad 53\% \text{(0.6572 g, 5 mmol scale)}
\]

Scheme 7.

The reaction mixture of 1a (5 mmol), TfOH (1 equiv.) and H2O (10 mL) in a 50 mL round-bottom flask was stirred at 100 °C for 36 h, and monitored periodically by TLC. Upon completion, the reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with water and brine, dried over MgSO4 and filtered. The solvent was removed under vacuum. The residue was purified by flash column chromatography (petroleum ether and ethyl acetate, v/v = 5:1 to 2:1) to afford 4-pyrone 2a (53%).

4. Conclusions

We have developed a simple and efficient transition-metal-free method for the synthesis of substituted 4-pyrones from diynones and H2O. Water is a cheap, green and readily available starting material, which converted to the desired 4-pyrone products via a nucleophilic addition/cyclization/dehydrogenation process. The operational simplicity, good yields, and environmentally benign nature of this method make it an attractive route to 4-pyrones. Further studies on the applications of 4-pyrones in drug design are currently ongoing in our laboratory.

Supplementary Materials: The following are available online at www.mdpi.com/link: copies of NMR spectra and HRMS spectra of products.

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Author Contributions: Yan-Li Xu and Qing-Hu Teng conceived and designed the experiments. The experimental work was conducted by Qing-Hu Teng under the supervision of Ying-Ming Pan and Xian-Li Ma who are the lead author; Qing-Hu Teng and Wei Tong analyzed the data; Heng-Shan Wang contributed reagents/materials/analysis tools; Yan-Li Xu and Qing-Hu Teng wrote the paper.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>TfOH</td>
<td>trifluoromethanesulfonic acid</td>
</tr>
<tr>
<td>PTSA</td>
<td>4-methylbenzenesulfonic acid</td>
</tr>
<tr>
<td>HCl</td>
<td>hydrochloric acid</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
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<td>HOAc</td>
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<td>Ph</td>
<td>phenyl</td>
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<td>methyl</td>
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</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
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<td>tBu</td>
<td>tertiary butyl</td>
</tr>
<tr>
<td>n-Pr</td>
<td>n-propyl</td>
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NMR  
HRMS  
nuclear magnetic resonance  
high-resolution mass

References


Sample Availability: Samples of the compounds 2a-2r, 2a-d and 2a-o are available from the authors.

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