Intramolecular domino-Knoevenagel-hetero-Diels-Alder reaction with terminal acetylenes

Malihe Javan Khoshkholgh,a Saeed Balalaie,a,* Hamid R. Bijanzadeh,b and Jürgen H. Grossc

aDepartment of Chemistry, K.N. Toosi University of Technology, P.O. Box 15875-4416 Tehran, Iran
bDepartment of Chemistry, Tarbiat Modares University, P.O. Box 14115-175 Tehran, Iran
cOrganisch Chemisches Institut der Universität Heidelberg, Im Neuenheimer Feld 270, 69120 Heidelberg, Germany
E-mail: balalaie@kntu.ac.ir

Dedicated to Professor Issa Yavari on his 60th birthday

Abstract
New polycyclic pyrans have been synthesized using new and efficient domino-Knoevenagel-hetero-Diels-Alder reaction between O-propargylated salicylaldehydes with 1,3-indanedione in acetonitrile in the presence of CuI. The products are formed in good yields.

Keywords: Domino intramolecular, Knoevenagel-hetero-Diels-Alder, cuprous iodide, inactivated alkynes, O-propargylated salicylaldehydes, 1,3-indanedione

Introduction

The development of a new strategy for the synthesis of complex organic molecules is an important aim in modern organic chemistry. L. F. Tietze introduced the domino-Knoevenagel-hetero-Diels-Alder reaction as a powerful sequential transformation.1 It has been proven that this reaction is a valuable method for the construction of annulated dihydropyrans2 and has already been used for the synthesis of several natural products.3

The reaction can be performed as a two-component transformation using an aldehyde containing an alkene in the side-chain as a dienophile and a 1,3-dicarbonyl compound. Although the advantages of this useful reaction in the construction of polycyclic ring skeletons has been well documented. But its application to the alkynes as the dienophile has been limited,4 which is related to the poor reactivity of unactivated alkynes. Only after the discovery of the remarkable catalytic effect of various transition metal complexes, the synthetic potential of alkyne
transformation could be exploited. Copper(I) iodide has found widespread applications in synthetic organic chemistry. The hetero-Diels-Alder cycloadditions of alkynes containing donor-acceptor substitutes were reported so far, but there is no report for the intramolecular domino Knoevenagel hetero-Diels-Alder reaction with unactivated alkynes. As a continuation of our work on the [4+2] cycloaddition chemistry, herein we report a novel, highly efficient domino Knoevenagel-hetero-Diels-Alder reaction of O-propargylated salicylaldehyde with the 1,3-indanedione as 1,3-dicarbonyl compound in the presence of CuI (Scheme 1).

![Scheme 1. Domino Knoevenagel-hetero-Diels-Alder reaction.](image)

**Results and Discussion**

The O-propargylated salicylaldehydes 2a-c were prepared from the corresponding substituted salicylaldehydes in almost quantitative yields and excellent purity (Scheme 2).

![Scheme 2. Synthesis of O-propargylated salicylaldehydes.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>2-Hydroxy benzaldehyde</td>
<td>2a</td>
<td>90</td>
</tr>
<tr>
<td>b</td>
<td>5-Bromo 2-hydroxy benzaldehyde</td>
<td>2b</td>
<td>94</td>
</tr>
<tr>
<td>c</td>
<td>5-Nitro-2-hydroxy benzaldehyde</td>
<td>2c</td>
<td>92</td>
</tr>
</tbody>
</table>

An extensive screening of the reaction conditions was performed for the reaction of O-propargylated salicylaldehyde (2c) with indanedione. The reaction was carried out in the presence of cuprous iodide or silver acetate as Lewis acid and diammonium hydrogen phosphate as a base for the Knoevenagel condensation. The results are summarized in Table 2. Under
optimized conditions (20 mol. % CuI and 20 mol. % DAHP, refluxing in MeCN) the desired pyran derivative was smoothly formed and isolated in 81% yield (Table 2, entry 2).

Table 2. Effect of catalyst and solvent in Knoevenagel-hetero-Diels-Alder reaction of 2c

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>Solvent</th>
<th>Base (20%)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ag(OTf) (20%)</td>
<td>acetonitrile</td>
<td>(NH₄)₂HPO₄</td>
<td>24</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>CuI (20%)</td>
<td>acetonitrile</td>
<td>(NH₄)₂HPO₄</td>
<td>15</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>CuI (20%)</td>
<td>water</td>
<td>(NH₄)₂HPO₄</td>
<td>24</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>CuI (20%)</td>
<td>acetonitrile</td>
<td>-</td>
<td>24</td>
<td>trace</td>
</tr>
<tr>
<td>5</td>
<td>CuI (20%)</td>
<td>ethanol</td>
<td>(NH₄)₂HPO₄</td>
<td>20</td>
<td>56</td>
</tr>
<tr>
<td>6</td>
<td>CuI (20%)</td>
<td>toluene</td>
<td>(NH₄)₂HPO₄</td>
<td>9</td>
<td>40</td>
</tr>
</tbody>
</table>

In the domino Knoevenagel-hetero-Diels-Alder reaction, the desired heterodiene (alkylidene1,3-dicarbonyl compound) is formed \textit{in situ} by Knoevenagel condensation of \textit{O}-propargylated salicylaldehyde with indanedione in the presence of diammonium hydrogen phosphate and undergoes a cycloaddition reaction in refluxing acetonitrile in presence of CuI to give the corresponding pyran ring (Table 3). The structure of the products was assigned on the basis of ¹H-NMR, ¹³C-NMR spectroscopic data and also high-resolution mass spectrometry data.
Table 3. CuI-catalyzed domino Knoevenagel -hetero-Diels-Alder reactions of 2a-c

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%) a</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td><img src="image" alt="Aldehyde a" /></td>
<td><img src="image" alt="Product a" /></td>
<td>48</td>
<td>80</td>
</tr>
<tr>
<td>b</td>
<td><img src="image" alt="Aldehyde b" /></td>
<td><img src="image" alt="Product b" /></td>
<td>54</td>
<td>70</td>
</tr>
<tr>
<td>c</td>
<td><img src="image" alt="Aldehyde c" /></td>
<td><img src="image" alt="Product c" /></td>
<td>15</td>
<td>81</td>
</tr>
</tbody>
</table>

Reactions were performed with aldehydes 2a-c (1 mmol), 1,3-indanedione (1.2 mmol, 146 mg), CuI (0.2 equiv.) and (NH₄)₂HPO₄ (0.2 equiv.) in acetonitrile at reflux; a Isolated yields.

1H-NMR spectra for all products showed an AB quartet for the –OCH₂ group at δ 4.6 and 4.9 ppm with J = 11.5 Hz. The diatropicity of methylene hydrogens is related to oxahelicene structure of the products. The corresponding signals of the O-CH₂ groups in the 13C-NMR spectra appeared at 65-66 ppm.

Although we have not yet established the mechanism, a possible pathway for the domino intramolecular Knoevenagel-hetero-Diels-Alder reaction is shown in Scheme 3. The initial step is Knoevenagel condensation between 1,3-indanedione and the aldehydes 2a-c, could be catalyzed by diammonium hydrogen phosphate. It seems that the triple bond was activated with CuI through formation of a π-complex or copper acetylide which provided the proper condition for hetero-Diels-Alder reaction. The exact reaction mechanism is not clear.
Scheme 3. Plausible mechanism for the formation of tetracyclic pyrans.

In conclusion, we have developed a Cu-catalyzed domino intramolecular Knoevenagel-hetero-Diels-Alder reaction which provided an efficient route to tetracyclic pyran derivatives. Further studies to extend the scope of the synthetic utility for this Cu-catalyzed domino intramolecular Knoevenagel-hetero-Diels-Alder reaction with inactivated alkynes are continuing.

Experimental Section

General Procedures. Melting points were determined with an Electrothermal 9100 apparatus and were uncorrected. IR spectra were obtained on an ABB FT-IR (FTLA 2000) spectrometer. $^1$H NMR and $^{13}$C NMR spectra were run on a Bruker DRX-300 AVANCE at 300 MHz for $^1$H-NMR and 75 MHz for $^{13}$C-NMR. CDCl$_3$ and DMSO-$d_6$ were used as solvents. High-resolution mass spectra were recorded on JEOL JMS-700 (HR-EI) spectrometer.

Synthesis of O-propargylated salicylaldehydes (2a-c). To a stirred solution of salicylaldehyde derivatives (5 mmol) and potassium carbonate (5 mmol, 0.069g) in DMF (25 ml), propargyl bromide (6 mmol, 0.071g) was added. After stirring for 4-24 h, water was added and the precipitated solid was filtered and washed with water.

2-(2-Propynyloxy)benzaldehyde (2a). Yield = 90%, m.p. 69-70 °C; IR (KBr, cm$^{-1}$): 3271, 2120,1689; $^1$H NMR (300 MHz, CDCl$_3$): 2.59 (t, 1H, $J$ = 2.4 Hz, acetylenic H), 4.86 (d, 1H, $J$ = 2.4 Hz, -OCH$_2$), 7.11 (t, 1H, $J$ = 7.7 Hz, H-Ar), 7.14 (d, 1H, $J$ = 8.5 Hz, H-Ar), 7.6 (dt, 1H, $J$ = 8.5, 1.5 Hz, H-Ar), 7.9 (dd, $J$ = 7.7, 1.8 Hz, H-Ar), 10.5 (d, 1H, $J$ = 0.5 Hz, H-C=O); $^{13}$C NMR
(75 MHz, DMSO-d$_6$): 56.4, 78.6, 79.0, 114.3, 121.5, 124.8, 127.8, 136.2, 159.5, 188.9; HRMS (70 eV, EI): Calcd for C$_{10}$H$_8$O$_2$ 160.0524. Found 160.0501.

**5-Bromo-2-(2-propynyloxy)benzaldehyde (2b).** Yield 94 %, m.p. 94-96$\degree$C, IR (KBr, cm$^{-1}$): 3281, 2120, 1684; $^1$H NMR (300 MHz, CDCl$_3$): 2.60 (t, 1H, $J = 2.4$ Hz, acetylenic H), 4.84 (d, $J = 2.4$ Hz, OCH$_2$), 7.05 (d, $J = 8.9$ Hz, 1H), 7.66 (dd, 1H, $J = 8.9, 2.6$ Hz, H-Ar), 7.97 (d, 1H, $J = 2.6$ Hz, H-Ar), 10.41 (s, 1H, H-C=O); $^{13}$C NMR (75 MHz, DMSO-d$_6$): 56.8, 78.2, 79.4, 113.4, 117.0, 126.3, 130.0, 138.2, 158.5, 187.8; HRMS (70 eV, EI): Calcd for C$_{10}$H$_7$O$_2$Br $[M]$+ 237.9625. Found: 237.9602. Calcd for C$_{10}$H$_7$O$_2$Br $[M+2]$+ 239.9609. Found: 239.9606.

**5-Nitro-2-(2-propynyloxy)benzaldehyde (2c).** Yield 92 %, m.p. 91.5-93$\degree$C; IR (KBr, cm$^{-1}$): 3245, 2125, 1684.; $^1$H NMR (300 MHz, CDCl$_3$) δ 2.68 (t, 1H, $J = 2.4$Hz, H-acetylenic), 4.99 (d, 2H, $J = 2.4$ Hz, OCH$_2$), 7.30 (d, 1H, $J = 9.2$ Hz, H-Ar), 8.47 (dd, 1H, $J = 9.2, 2.9$ Hz, H-Ar), 8.47 (d, 1H, $J = 2.9$ Hz, H-Ar), 10.48 (s, 1H, H-C=O). 13C NMR (75 MHz, DMSO-d$_6$): 57.4, 77.6, 80.0, 115.2, 123.6, 124.4, 130.6, 141.3, 163.3, 187.6. HRMS (70 eV, EI): Calcd for C$_{10}$H$_7$NO$_4$ 205.0375. Found 205.0356.

**Synthesis of tetracyclic pyran derivatives 3a–c.** A solution of O-propargylated salicylaldehyde 2a-c (1 mmol), 1,3-indanedione (1.2 mmol, 146 mg), CuI (0.2 equiv., 38 mg) and (NH$_4$)$_2$HPO$_4$ (0.2 equiv., 28 mg) in acetonitrile (30 ml) was refluxed for 15-54 h. The progress of the reaction was monitored by TLC (eluent: petroleum–dichloromethane, 2:1). The mixture was filtered and water (5 ml) was added to the filtrate; the resulting (dark yellow solid) was filtered off, and washed with water. The resulting product was obtained in pure form. In all cases, the products did not need further purification.

**6H-Indeno[2’,1’:5,6]pyrano[3,4-c]chromen-13(13bH)-one (3a).** m.p. 183-184$\degree$C. IR (KBr,): 1703, 1588, 1490, 1458 cm$^{-1}$. $^1$H-NMR (300 MHz, DMSO-d$_6$): 4.61 (d, 1H, $J = 11.6$ Hz, -OCH), 4.66 (d, 1H, $J = 11.6$ Hz, -OCH), 4.7 (s, 1H, CH), 6.78 (d, 1H, $J = 8.1$ Hz, H-Ar), 6.86 (brs, 1H, =CH), 6.89 (t, 1H, $J = 7.5$ Hz, H-Ar), 7.13 (t, 1H, $J = 7.7$ Hz, H-Ar), 7.19 (d, 1H, $J = 6.6$ Hz, H-Ar), 7.34-7.39 (m, 2H, H-Ar), 7.53 (d, 1H, $J = 7.2$ Hz, H-Ar), 7.7 (d,1H, $J = 7.8$ Hz, H-Ar). 13C-NMR (75 MHz, DMSO-d$_6$): 29.1, 65.4, 107.6, 112.9, 116.7, 118.7, 120.6, 121.5, 125.5, 128.0, 128.2, 130.8, 131.0, 133.1, 135.6, 136.9, 153.4, 169.5. HRMS (EI): Calcd for C$_{19}$H$_{12}$O$_3$: 288.0786. Found: 288.0789.

**2-Bromo-6H-Indeno[2’,1’:5,6]pyrano[3,4-c]chromen-13(13bH)-one (3b).** m.p. 195-196$\degree$C. IR (KBr, cm$^{-1}$): 1698, 1658, 1589, 1480; $^1$H-NMR (300 MHz, DMSO-d$_6$): 4.64 (d, 1H, $J = 11.5$ Hz, -OCH), 4.73 (d, 1H, $J = 11.5$ Hz, -OCH), 4.74 (s, 1H, CH), 6.72 (d, 1H, $J = 8.7$ Hz, H-Ar), 7.26-7.30 (m, 2H, H-Ar), 7.32 (brs, 1H, =CH), 7.44-7.53 (m, 3H, H-Ar), 7.47 (brs, 1H, H-Ar); $^{13}$C-NMR (75 MHz, DMSO-d$_6$): 28.8, 65.3, 106.7, 111.4, 111.6, 118.5, 118.8, 121.4, 127.3, 130.4, 130.5, 130.6, 132.8, 135.2, 137.1, 152.6, 169.5. HRMS (EI): Calcd C$_{19}$H$_{11}$O$_3$Br 365.9892. Found: 365.9920. Calcd C$_{19}$H$_{11}$O$_3$Br $[^{81}$Br] 367.9871. Found: 367.9863.

**2-Nitro-6H-Indeno[2’,1’:5,6]pyrano[3,4-c]chromen-13(13bH)-one (3c).** m.p 219-220$\degree$C; IR (KBr, cm$^{-1}$): 1702, 1625, 1592, 1508, 1482, 1400, and 1343; $^1$H-NMR (300 MHz, DMSO-d$_6$): 4.82 (d, 1H, $J = 11.6$ Hz, -OCH), 4.85(brs, 1H, CH), 4.89 (d, 1H, $J = 11.6$ Hz, -OCH), 6.97 (d, 1H, $J = 9.1$ Hz, H-Ar), 7.32 (d, 1H, $J = 6.8$ Hz, H-Ar), 7.40 (brs, 1H, =CH), 7.45-7.58 (m, 3H,
H-Ar), 8.02 (dd, 1H, $J = 6.5, 2.7$ Hz, H-Ar), 8.59 (d, 1H, $J = 1.7$ Hz, H-Ar); $^{13}$C-NMR (75 MHz, DMSO-d$_6$): 28.9, 66.3, 110.6, 117.6, 118.7, 121.6, 123.9, 124.7, 125.8, 130.5, 130.9, 133.0, 137.8, 140.5, 159.1. HRMS (EI): Calcd C$_{19}$H$_{11}$O$_5$N 333.0637. Found: 333.0616.

Acknowledgement

Saeed Balalaie is grateful to National Research Institute for Science Policy (NRISP) (Grant No. 3234) for the financial support.

References and Notes


