

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

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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.

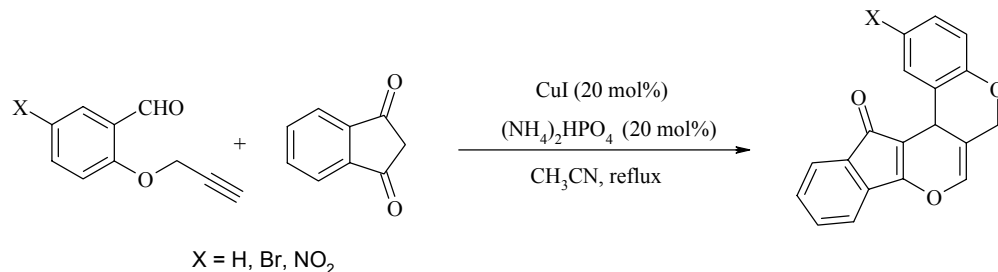
Keywords: Domino intramolecular, Knoevenagel-hetero-Diels-Alder, cuprous iodide, inactivated alkynes, *O*-propargylated salicylaldehydes, 1,3-indanedione

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

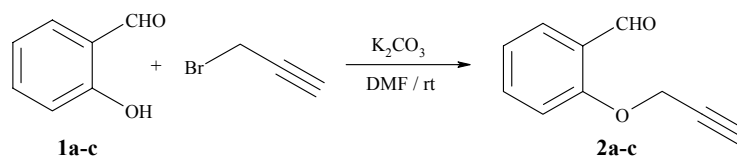
transformation could be exploited.⁵ Copper-(I) iodide has found widespread applications in synthetic organic chemistry.⁶ The hetero-Diels-Alder cycloadditions of alkynes containing donor-acceptor substitutes were reported so far,⁷ but there is no report for the intramolecular domino Knoevenagel hetero-Diels-Alder 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.

Results and Discussion

The *O*-propargylated salicylaldehydes **2a-c** were prepared⁸ from the corresponding substituted salicylaldehydes in almost quantitative yields and excellent purity (Scheme 2).



Scheme 2. Synthesis of *O*-propargylated salicylaldehydes.

Table 1. Synthesis of *O*-propargylated salicylaldehydes

Entry	Aldehyde	Product	Yield (%)
a	2-Hydroxy benzaldehyde	2a	90
b	5-Bromo 2-hydroxy benzaldehyde	2b	94
c	5-Nitro-2-hydroxy benzaldehyde	2c	92

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).

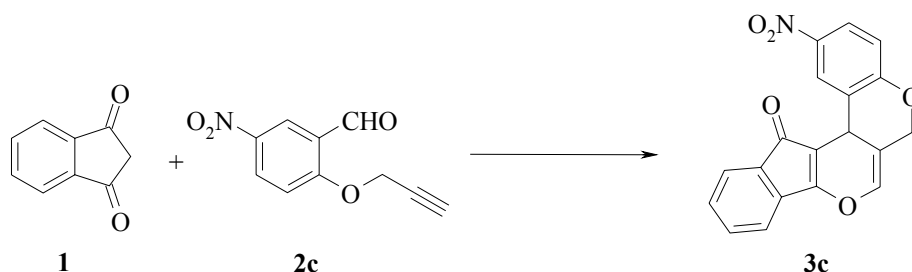


Table 2. Effect of catalyst and solvent in Knoevenagel-hetero-Diels-Alder reaction of **2c**

Entry	Lewis acid	Solvent	Base (20%)	Time (h)	Yield (%)
1	Ag(OTf) (20%)	acetonitrile	(NH ₄) ₂ HPO ₄	24	-
2	CuI (20%)	acetonitrile	(NH ₄) ₂ HPO ₄	15	81
3	CuI (20%)	water	(NH ₄) ₂ HPO ₄	24	-
4	CuI (20%)	acetonitrile	-	24	trace
5	CuI (20%)	ethanol	(NH ₄) ₂ HPO ₄	20	56
6	CuI (20%)	toluene	(NH ₄) ₂ HPO ₄	9	40

In the domino Knoevenagel-hetero-Diels-Alder reaction, the desired heterodiene (alkylidene-1,3-dicarbonyl compound) is formed *in situ* by Knoevenagel condensation of *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.

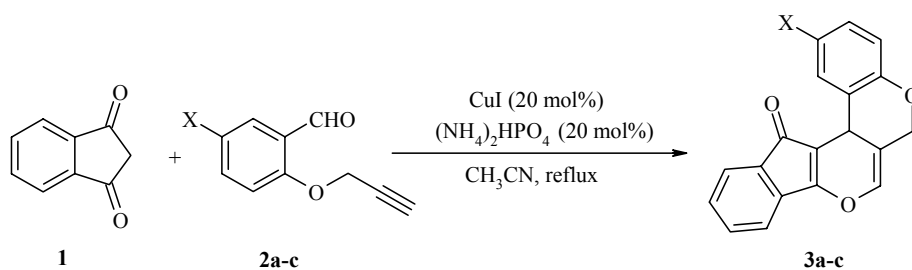
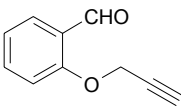
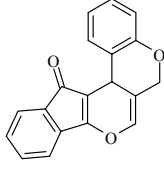
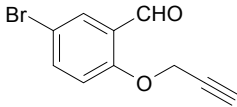
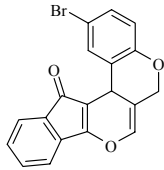
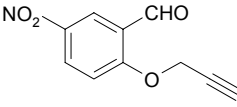
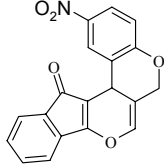


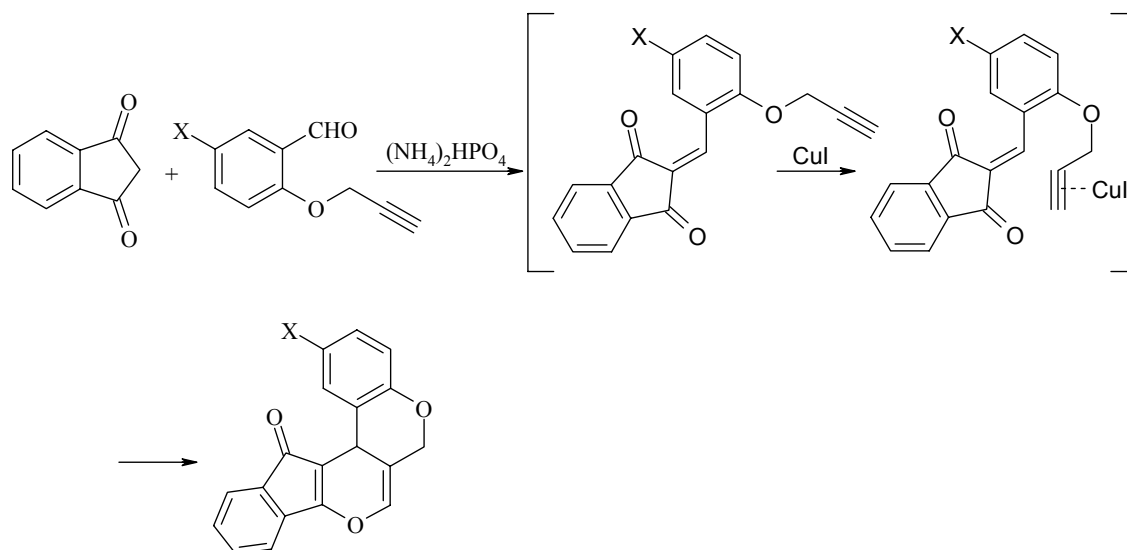
Table 3. CuI-catalyzed domino Knoevenagel -hetero-Diels-Alder reactions of **2a-c**

Entry	Aldehyde	Product	Time (h)	Yield (%) ^a
a			48	80
b			54	70
c			15	81

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 oxa-helicene 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 acetylide⁹ 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. ¹H NMR and ¹³C NMR spectra were run on a Bruker DRX-300 AVANCE at 300 MHz for ¹H-NMR and 75 MHz for ¹³C-NMR. CDCl₃ 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; ¹H NMR (300 MHz, CDCl₃): 2.59 (t, 1H, *J* = 2.4 Hz, acetylenic H), 4.86 (d, 1H, *J* = 2.4 Hz, -OCH₂), 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); ¹³C 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 C₁₀H₈O₂ 160.0524. Found 160.0501.

5-Bromo-2-(2-propynyloxy)benzaldehyde (2b). Yield 94 %, m.p. 94-96 °C, IR (KBr, cm⁻¹): 3281, 2120, 1684; ¹H NMR (300 MHz, CDCl₃): 2.60 (t, 1H, *J* = 2.4 Hz, acetylenic H), 4.84 (d, *J* = 2.4 Hz, OCH₂), 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); ¹³C 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 C₁₀H₇O₂⁷⁹Br [M]⁺ 237.9625. Found: 237.9602. Calcd for C₁₀H₇O₂⁸¹Br [M+2]⁺ 239.9609. Found: 239.9606.

5-Nitro-2-(2-propynyloxy)benzaldehyde (2c). Yield 92 %, m.p. 91.5-93 °C; IR (KBr, cm⁻¹): 3245, 2125, 1684.; ¹H NMR (300 MHz, CDCl₃) δ 2.68 (t, 1H, *J* = 2.4 Hz, H-acetylenic), 4.99 (d, 2H, *J* = 2.4 Hz, OCH₂), 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 C₁₀H₇NO₄ 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 (NH₄)₂HPO₄ (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°C. IR (KBr,): 1703, 1588, 1490, 1458 cm⁻¹. ¹H-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 C₁₉H₁₂O₃: 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°C. IR (KBr, cm⁻¹): 1698, 1636, 1589, 1480; ¹H-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), 7.75 (brs, 1H, H-Ar); ¹³C-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, 130.7, 132.8, 135.2, 137.1, 152.6, 169.5. HRMS (EI): Calcd C₁₉H₁₁O₃⁷⁹Br 365.9892. Found: 365.9920. Calcd C₁₉H₁₁O₃⁸¹Br 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°C; IR (KBr, cm⁻¹): 1702, 1625, 1592, 1508, 1482, 1400, and 1343; ¹H-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 $\text{C}_{19}\text{H}_{11}\text{O}_5\text{N}$ 333.0637. Found: 333.0616.

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