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Microwave assisted synthesis of indole-annulated dihydropyrano[3,4-*c*] chromene derivatives via hetero-Diels–Alder reaction

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ABSTRACT

An efficient two-step synthesis of indole-annulated dihydropyrano[3,4-*c*]chromene derivatives is achieved via Knoevenagel condensation of *O*-propargylated salicylaldehyde derivatives with indolin-2-ones followed by a microwave-assisted intramolecular-hetero-Diels–Alder reaction of the resulting (*Z*)-3-(2-(prop-2-ynyloxy)benzylidene)indolin-2-ones in the presence of 20 mol % CuI in acetonitrile.

Introduction

Heterocyclic compounds attract special attention in chemical literature because of their abundance in natural products and the diverse biological properties associated with them. There are a large variety of heterocycles known and among them indole and pyran ring systems are of particular importance. Numerous interesting arrays of biological activities have been linked to natural and unnatural compounds possessing a substituted indole nucleus, making it a suitable building block for many therapeutic agents.[1] The pyran ring, on the other hand, is among one of the most widely investigated heterocycles.[2] The benzopyran or chromene core containing chemicals are prevalent in compounds with proven pharmacological properties.[3] Fused chromenes (polycyclic pyrans) are also of interest because of their well-documented antibacterial and novobiocin activities.[4] Thus, the need for the development of efficient and practical syntheses of novel heterocycles with these ring systems is of great significance.

The domino Knoevenagel–hetero-Diels–Alder reaction is a very efficient process in organic synthesis because it allows multiple transformations in a single pot. This reaction provides a valuable method for the construction of polyheterocyclic compounds.[5] Over the past few years, syntheses of several complex annulated dihydropyrans have been achieved using the domino Knoevenagel–hetero-Diels–Alder reaction.[5,6] More recently, the use of Lewis acids, especially CuI, has provided the opportunity for an efficient hetero-Diels–Alder reaction-involving alkynes.[7–9]

To combine the interesting and remarkable biological activities of both indole and polycyclic pyrans we sought a synthesis of indole-annulated dihydropyrano[3,4-*c*]chromene skeleton **4** (Scheme 1). Literature survey disclosed three recent reports describing the synthesis of closely related sulfur-containing analogs of **4**.[10–12] However, to the best of our knowledge the synthesis of chromene **4** has not been reported. Herein, we disclose a Cu-catalyzed microwave-assisted synthesis of indole-annulated dihydropyrano[3,4-*c*]chromene derivatives.

A retrosynthetic analysis of **4** is depicted in Scheme 1. The dihydropyranopyran ring of **4** can be assembled from alkyne **3,** which could be synthetically accessible via a Knoevenagel reaction of *O*-propargylated salicylaldehyde derivatives **2** with indolin-2-ones **1**.

Two types of precursors indolin-2-ones, acetyl (**1a** and **b**) and methyl (**1c**) substituted were chosen to carry out the desired intramolecular Knoevenagel–hetero-Diels–Alder reaction. 1-Acetylindolin-2-one (**1a**) and 1-acetyl-6-chloroindolin-2-one (**1b**) were prepared from commercially available indolin-2-one and 6-chloroindolin-2-one using a published procedure.[13] The methylation of isatin and its subsequent reduction using hydrazine hydrate resulted in 1-methylindolin-2-one (**1c**).[14] The *O*-propargylated salicylaldehyde derivatives **2a–e** were synthesized in high yields (>85%) by reacting substituted salicylaldehydes with propargyl benzenesulfonate analogous as per previously reported procedure using potassium carbonate in DMF.[9]

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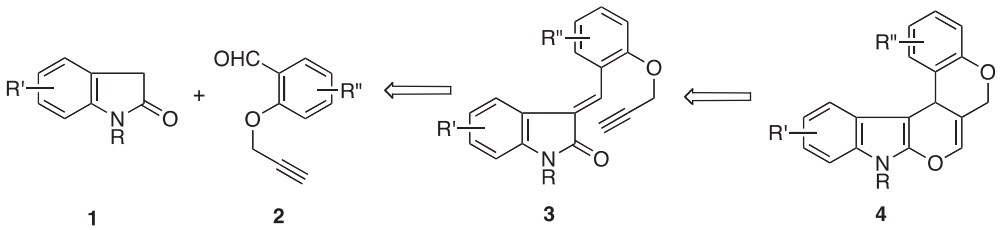
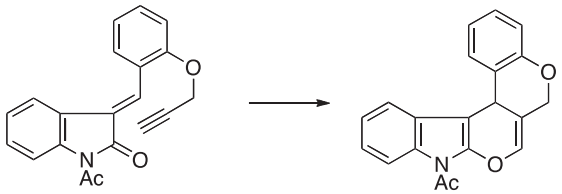


Scheme 1. Retrosynthetic analysis of indole-annulated dihydropyrano[3,4-*c*]chromene.

Table 1
Optimization of intramolecular-hetero-Diels–Alder reaction conditions



Entry	Catalyst (mol %)	Solvent	Temperature (°C)	Time (min)	Yield (%)
1	10	CH_3CN	200	25	30
2	20	CH_3CN	200	25	38
3	20	CH_3CN	200	5	65
4	10	CH_3CN	200	5	35
5	30	CH_3CN	200	5	60
6	40	CH_3CN	200	5	55
7	20	CH_3CN	150	5	40
8	20	Dioxane	130[a]	10	20
9	20	DMF	200	10	0
10	20	Water	190[a]	10	0

[a] Highest temperature achieved in microwave.

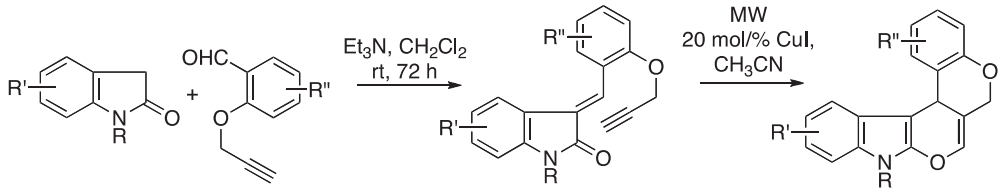
Similar to previous reports of hetero-Diels–Alder reactions involving unreactive terminal alkynes,[9] we pursued a one-step synthesis of dihydropyrano[3,4-*c*]chromene derivatives under domino Knoevenagel–hetero-Diels–Alder reaction conditions. Using indolin-2-one **1a** and salicylaldehyde derivative **2a** as model reactants, the single-pot condensation–cyclization reaction was attempted in the presence of 20 mol % CuI and $(NH_4)_2HPO_4$ in refluxing acetonitrile.[9] Unfortunately, the desired product **4a** was not obtained even after refluxing for up to 72 h. Instead, the condensation product **3a** was isolated in low yield (<20%) along with the recovery of unreacted starting materials. Subsequently, the same reaction was carried out under microwave irradiation (200 °C), and a similar observation was recorded. Efforts to synthesize **4a** analogous to other known domino Knoevenagel–hetero-Diels–Alder reaction conditions of substituted alkynes[8,15] were also unsuccessful. These repeated failures prompted us to first synthesize and isolate the Knoevenagel condensation intermediates **3a–i** and subsequently try the intermolecular hetero-Diels–Alder cyclization on them to obtain the desired indole-annulated dihydropyranopyrans. The Knoevenagel condensation to synthesize compounds **3a–i** was tried in dichloromethane analogous to previously reported similar condensations using two different bases, Et_3N[16] and ethylenediamine-*N*,*N*′-diacetic acid (EDDA).[17] Although the time required for the reaction to undergo completion was longer in the case of Et_3N (72 h) compared to EDDA (8 h), the product yields were significantly higher with Et_3N. In contrast, the condensation catalyzed with EDDA, despite being rapid, resulted in the hydrolysis of the N-acetyl group giving a mixture of **3a** and its deacetylated analog in almost 1:1 ratio. To eliminate the chromatographic purification step and increase the efficiency we decided to use Et_3N in dichloromethane and 72 h stirring at room temperature to carry out the synthesis of 3-(2-(prop-2-ynyloxy)benzylidene)indolin-2-one derivatives **3a–j**.[18] The pure products **3a–j** were obtained in excellent yields (>85%) upon crystallization using acetonitrile. Synthesis of methyl substituted 3-(2-(prop-2-ynyloxy)benzylidene)indolin-2-one analog **3j** was achieved under similar conditions starting with 1-methyl indolin-2-one (**1c**).

Next, the intramolecular Cu-catalyzed hetero-Diels–Alder reaction on **3a** was attempted to obtain the desired indole-annulated dihydropyrano[3,4-*c*]chromene derivatives under microwave irradiation as well as conversational refluxing conditions. A 25 min microwave irradiation at 200 °C in dry acetonitrile in the presence of 10 mol % CuI resulted in the formation of desired **4a** in low yield (30%). However, the conventional refluxing condition failed to yield the desired product even after 72 h of heating. Thus, we settled with the microwave conditions and attempted to further optimize the reaction parameters to maximize the yield of desired dihydropyrano[3,4-*c*]chromene derivatives. The reaction was carried out in the presence of four different concentrations of CuI (10, 20, 30, and 40 mol %). As indicated in Table 1, the best conversion of **3a** to the cyclized product **4a** was obtained in the presence of 20 mol % of CuI with 5 min of irradiation at 200 °C.[18] Lowering the reaction temperature resulted in lower yield (Table 1, entry 7). Furthermore, running the reactions in solvents other than acetonitrile led to either lower yields (dioxane, entry 8) or no product at all (DMF and water, entries 9 and 10).

Subsequently, using the optimized reaction conditions, the indole-annulated dihydropyrano[3,4-*c*]chromene derivatives **4a–i** were synthesized in 60–71% yields (Table 2). The structures of the products were confirmed using spectroscopic and HRMS data. The characteristic ^1H NMR signals of AB quartet for O–CH_2 and singlet for OCH groups for the dihydropyrano[3,4-*c*]chromene ring system were observed in between 4.8–5.1 ppm and 6.6–7.0 ppm, respectively. Interestingly, a mixture of orange-colored non-polar compounds appeared in all of the hetero-Diels–Alder reactions as side-products, which could be attributed to the loss in the yields of the desired compounds. The side-products appeared as a single spot on TLC, but the NMR data indicated it to be mixture of compounds. Repeated attempts to isolate and characterize these side-products were unsuccessful in our hands, mainly due to their non-polar nature. Their separation using silica based column chromatography proved to be quite challenging as they were eluting together even with hexanes. We are currently investigating this further.

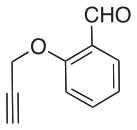
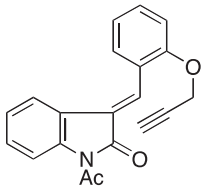
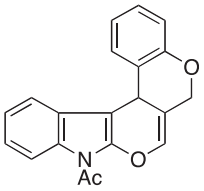
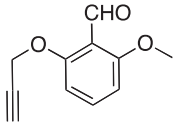
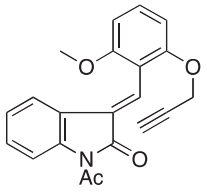
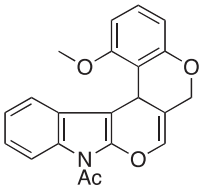
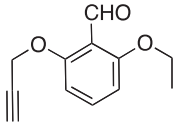
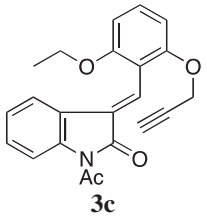
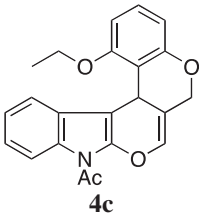
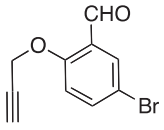
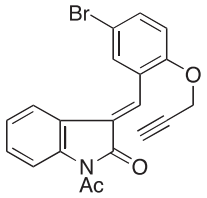
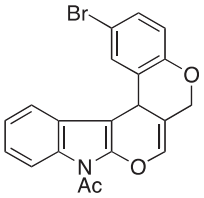
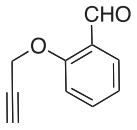
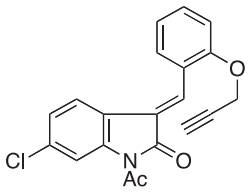
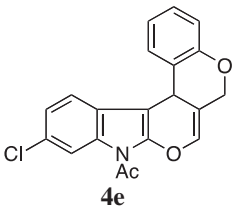
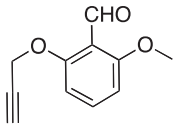
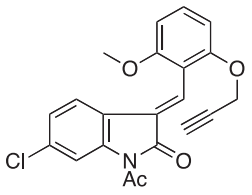
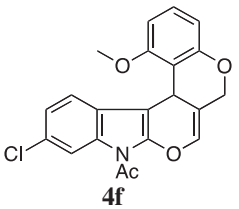
As shown in Table 2, no significant aromatic substitution effect on the intramolecular-hetero-Diels–Alder reaction was observed in the formation of the cyclized products **4a–i**. It was interesting to note that relatively bulky naphthalene based indole-annulated dihydropyrano[3,4-*c*]chromene **4i** was successfully obtained using this methodology. In contrast to acetyl-substituted compounds **3a–i**, the intramolecular-hetero-Diels–Alder cyclization of 1-methyl substituted **3j** under the optimized reaction condition was unsuccessful (Table 2).

Table 2
Synthesis of indole-annulated dihydropyrano[3,4-*c*]chromene derivatives **4a–i**



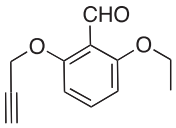
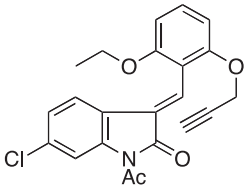
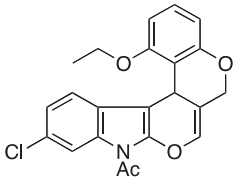
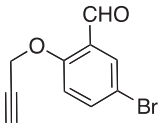
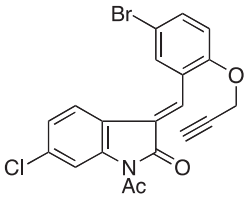
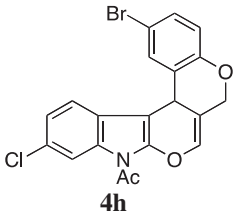
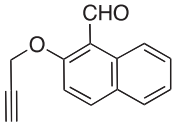
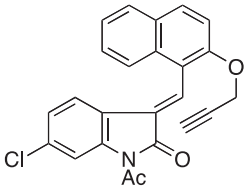
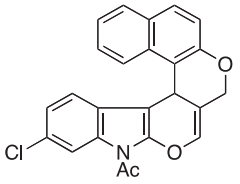
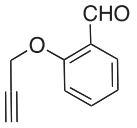
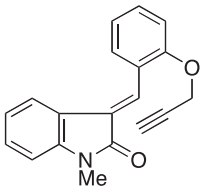
1a R = Ac, R' = H
1b R = Ac, R' = Cl
1c R = Me, R' = H

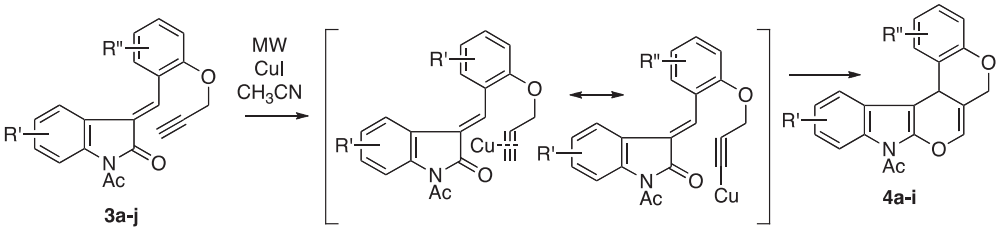
2a-e **3a-j** **4a-i**

Indolin-2-one **1a–c**	Aldehyde **2a–e**	Product **3a–j**	Product **4a–i**	Isolated yield (%) **4a–i**
1a	 **2a**	 **3a**	 **4a**	65
1a	 **2b**	 **3b**	 **4b**	66
1a	 **2c**	 **3c**	 **4c**	71
1a	 **2d**	 **3d**	 **4d**	63
1b	 **2a**	 **3e**	 **4e**	64
1b	 **2b**	 **3f**	 **4f**	64

(*continued on next page*)

Table 2 (*continued*)

Indolin-2-one **1a–c**	Aldehyde **2a–e**	Product **3a–j**	Product **4a–i**	Isolated yield (%) **4a–i**
1b	 **2c**	 **3g**	 **4g**	67
1b	 **2d**	 **3h**	 **4h**	61
1b	 **2e**	 **3i**	 **4i**	60
1c	 **2a**	 **3j**	–	0



Scheme 2. A plausible mechanism for the formation of indole-annulated dihydropyrano[3,4-*c*]chromenes.

The mechanism of the cyclization appears to be in agreement with the previously proposed mechanism of similar hetero-Diels–Alder reactions on compounds possessing unreactive terminal alkynes.[8,9] The alkyne functionality is activated with CuI upon formation of a π-complex, which may be assisting in the subsequent intramolecular-hetero-Diels–Alder reaction as depicted in Scheme 2. It has been recently reported in the synthesis of analogous indole-annulated thiopyranobenaopyrans that the double bond of fused thiopyran ring underwent migration when *p*-substituted aldehydes were reacted with indoline-2-thione to afford products with extended conjugation.[11] However, we did not observe such migration in our reactions.

In conclusion, we have described a microwave assisted hetero-Diels–Alder reaction for the synthesis of indole-annulated dihydropyrano[3,4-*c*]chromene derivatives using CuI as the catalyst. The use of microwave conditions not only made the reaction feasible but also added additional beneficial features to the reaction such as shortened reaction time and low catalyst loading.

Acknowledgments

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18. *Procedure for the synthesis of (E)-1-acetyl-3-(2-(prop-2-ynyloxy)benzylidene) indolin-2-one (**3a**)*: a mixture of 1-acetyl indolin-2-one (**1a**, 5.71 mmol, 1 g), propagylated salicylaldehyde (**2a**, 5.71 mmol, 0.92 g) and triethylamine (3.4 mmol, 0.35 g) was stirred in dichloromethane for 72 h. The excess of dichloromethane was evaporated and solid residue was crystallized using acetonitrile to give **3a** in 92% yield. Melting point: 103–106 °C.^{1}HNMR (300 MHz, $CDCl_3$): δ 8.33 (d, J = 8 Hz, 1H), 8.03, (s, 1H), 7.72 (d, J = 8 Hz, 1H), 7.64 (d, J = 8 Hz, 1H), 7.46 (dd, J = 7.5, 7 Hz, 1H), 7.33 (t, J = 8 Hz, 1H), 7.18–7.02 (m, 3H), 6.09–6.82 (m, 2H), 4.79 (s, 2H), 2.79 (s, 3H), 2.55 (s, 1H).^{13}CNMR (75 MHz, $CDCl_3$): δ 170.9, 168.5, 156.1, 140.1, 134.9, 131.7, 130.0, 129.9, 126.0, 124.4, 124.0, 122.3, 122.1, 121.2, 116.6, 112.7, 78.0, 76.1, 56.2, 26.9.ESI-HRMS (amu): calcd $C_{20}H_{15}NNaO_3$ $[M+Na]^+$: 340.0944; found $[M+Na]^+$: 340.0947. Procedure for the synthesis of indole-annulated dihydropyrano[3,4-*c*]chromene **4a**: A microwave glass vial with a magnetic stirrer bar was charged with **3a** (0.16 mmol, 50 mg) and CuI (20 mol %, 6 mg) in dry acetonitrile. The vial was sealed and subjected to microwave irradiation for 5 min at 200 °C (Discover™ single mode cavity microwave synthesizer (CEM Corp.). The reaction mixture was cooled and subjected to flash column chromatography (ethylacetate/hexanes, 10:80) to give **4a** in 65% yield. Melting point: 167–169 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.49 (d, J = 8 Hz, 1H), 7.63 (d, J = 7.5 Hz, 1H), 7.38–7.36 (m, 2H), 7.30 (s, 1H), 7.17 (dd, J = 8, 7.5 Hz, 1H), 6.89–6.80 (m, 3H), 5.01 (s, 1H), 4.91 (d, J = 12 Hz, 1H), 4.76 (d, 1H), 2.67 (s, 3H).^{13}CNMR (75 MHz, $CDCl_3$): δ 168.8, 153.4, 143.2, 135.3, 132.0, 128.3, 127.9, 126.5, 124.2, 124.1, 120.8, 118.2, 117.2, 116.5, 111.1, 93.0, 67.4, 31.6, 29.7, 26.5. ESI-HRMS (amu): calcd $C_{20}H_{15}NNaO_3$ $[M+Na]^+$: 340.0944; found $[M+Na]^+$: 340.0933.