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Catalyst-free domino-Knoevenagel-hetero-Diels–Alder reaction of terminal alkynes in water: an efficient one-step synthesis of indole-annulated thiopyranobenzopyran derivatives

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ABSTRACT

The domino-Knoevenagel-hetero-Diels–Alder reaction of O-propargylated salicylaldehyde and 1-methylindoline-2-thione in aqueous medium in the absence of Lewis acid has been described for the synthesis of hitherto unreported indole-annulated pentacyclic heterocycles containing oxygen, nitrogen and sulfur. This methodology involves only one step and easy work-up procedure to give the products in 72–80% yields.

Indole subunits are frequently present in many biologically active natural products.[1–11] Some indole derivatives have been found to possess antitumor activity, some cause inflammation and vascication to human skin.[12–15] Thiopyranoindole-annulated heterocyclic compounds are important due to their biological activity.[16,17] Some [6,6]-fused pentacyclic indole alkaloids like aspidospermine, rauniticine, reserpine and yohimbine show extensive bioactivity.[4,7] This wide range of interesting activities of various indole derivatives has prompted studies in the development of an efficient methodology for the synthesis of [6,6]-fused pentacyclic derivatives in which bioactive thiopyrano indole moiety is fused with a benzopyran moiety.

Literature survey reveals several reports on the synthesis of benzopyran and pyranobenzopyran moieties[18–23] but there are a few examples on the synthesis of polycyclic pyranothiopyrans.[24–27] In our laboratory we have synthesized coumarin- and pyrone-annulated [6,6]-fused pyranothiopyrans using sequential Claisen rearrangement[24] and tributyl tin hydride-mediated radical cyclization,[25] respectively. But we were not able to synthesize indole-annulated [6,6]-fused pyranothiopyran ring; rather [6,5]-fused pyranothiofuran[28] and a spiro compound[29] were obtained when the same methodology was applied upon thioindole moiety. More examples on the synthesis of furanothiopyran moieties are available.[30–33] But there are drawbacks in dealing with this protocol due to harsh reaction conditions and use of stoichiometric amount of reagents.[34,35] To avoid these discrepancies there was a need of an efficient and convenient methodology for the synthesis of indole-annulated [6,6]-fused pyranothiopyran system. In that case domino-Knoevenagel-hetero-Diels–Alder reaction is the best one and we have successfully utilized this reaction for the synthesis of indole-annulated [6,6]-fused pyranothiopyran derivatives.[36]

The domino-Knoevenagel-hetero-Diels–Alder addition represents one of the most powerful and efficient reactions for the synthesis of heterocyclic compounds, including natural products.[37–41] Tietze extensively described the domino-Knoevenagel-hetero-Diels–Alder reaction of unsaturated aromatic and aliphatic aldehydes with several 1,3-dicarbonyl compounds for the synthesis of tetracycles with a pyran ring.[42–45] There are several examples of intramolecular domino-Knoevenagel-hetero-Diels–Alder reactions with alkenes[26,27,46–53] but those of alkynes are rare. This may be due to low reactivity of the unactivated alkynes compared to the corresponding alkenes. Very recently Balalaie and co-workers reported[54–58] a few hetero-Diels–Alder reactions of unactivated alkynes using Cu^{I}-catalyst. But to our knowledge there is no example of hetero-Diels–Alder reaction with unactivated alkynes in the absence of Cu^{I}-catalyst. This observation prompted us to undertake a study on hetero-Diels–Alder reaction of unactivated alkynes in the absence of a catalyst. Herein, we report the results of our investigation.

The required precursors **2a–f** were prepared in high yields and purity by the reaction of substituted salicylaldehydes **1a–f** and propargyl bromide in the presence of anhydrous potassium carbonate in dry DMF at room temperature[59] (Scheme 1).

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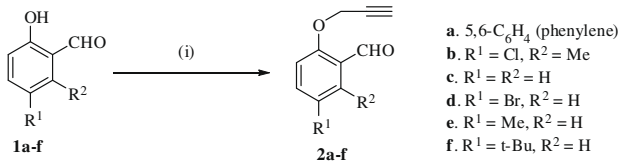


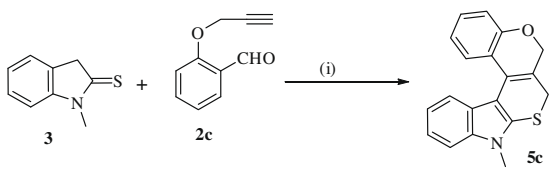
Scheme 1. Reagents and condition: (i) propargyl bromide, anhydrous K_2CO_3, DMF, rt.

Many reactions including Diels–Alder reaction have been carried out in aqueous medium[60–63] as water is not only available in nature in plenty but is also safe and environment friendly. Therefore, we explored the use of water as a solvent for our proposed work. Accordingly the domino-Knoevenagel-hetero-Diels–Alder reaction of 1-methyl indoline-2-thione **3** with **2a–f** was carried out in an aqueous medium under refluxing condition. We first chose **3** and **2c** as model substrates to optimize the reaction conditions. The results are summarized in Table 1 (Scheme 2).

We have examined the influence of Lewis acid, base and solvents in the reaction. When the reaction of **3** and **2c** was carried out in water under reflux condition in the absence of a catalyst for 5 h the product **5c** was obtained in 78% yield. However, when CuI (20 mol %) was employed as a catalyst, the desired product **5c** was obtained in only 52% yield after refluxing for 5 h (entry 2). When the same reaction was carried out for 8 h the yield slightly improved to 60% (entry 3). Increasing the amount of catalyst loading (30 mol %) decreased the yield (entry 4). The affinity of d^{10} copper ions for soft sulfur atoms[64] may have been detrimental to the Knoevenagel reaction of **2** and **3,** thereby affecting the yield of the product. When the reaction was carried out for 8 h in the presence of triethyl amine, the yield increased to 69% (entry 5). Among the various solvents (water, methanol, acetonitrile and 1,4-dioxane) used, water was found to be superior than the others when CuI (20 mol %) was used as a catalyst and triethyl amine as a base (entries 5–8). Similar results were also obtained when $(NH_4)_2HPO_4$ was used as a base in place of triethyl amine (entries 9–12). Among the various conditions employed, the reaction in aqueous media in the absence of a catalyst was found to give best results (Table 1).

Table 1
Effect of catalyst, solvent and base on the domino-Knoevenagel-hetero-Diels–Alder reaction of **3** and **2c**

Entry	Lewis acid (mol %)	Solvent	Base	Time (h)	Yield (%)
1	—	Water	—	5	78
2	CuI (20)	Water	—	5	52
3	CuI (20)	Water	—	8	60
4	CuI (30)	Water	—	8	57
5	CuI (20)	Water	NEt_3	8	69
6	CuI (20)	MeOH	NEt_3	8	39
7	CuI (20)	CH_3CN	NEt_3	8	35
8	CuI (20)	1,4-dioxane	NEt_3	8	32
9	CuI (20)	water	$(NH_4)_2HPO_4$	8	64
10	CuI (20)	MeOH	$(NH_4)_2HPO_4$	8	35
11	CuI (20)	CH_3CN	$(NH_4)_2HPO_4$	8	34
12	CuI (20)	1,4-dioxane	$(NH_4)_2HPO_4$	8	28



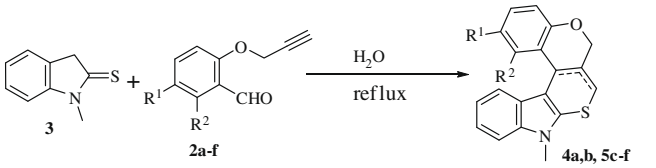
Scheme 2. Reagent and condition: (i) reflux in water.

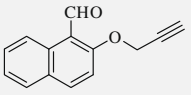
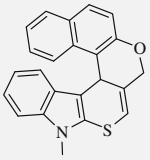
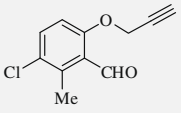
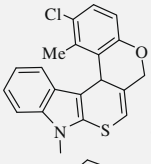
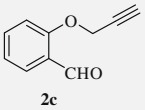
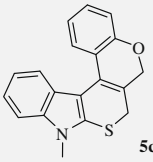
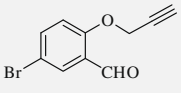
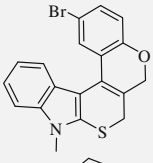
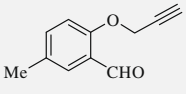
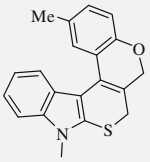
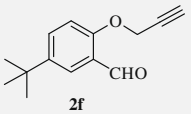
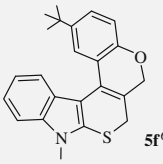
Using the optimized condition, we have examined hetero-Diels–Alder reaction of **3** and several O-propargylated aromatic aldehydes (**2a,b,d–f**). The results are listed in Table 2.

To the best of our knowledge there is no report on the hetero-Diels–Alder reaction of unactivated alkynes in the absence of a catalyst. In the present instance the reactivity may perhaps be explained by considering the presence of soft sulfur atom in the diene moiety of the substrates. The sulfur atom may offer itself a reacting centre and polarizability compared to other hetero atoms. Moreover, there are empty d-orbitals in the sulfur atom having a symmetry matching that of the π-orbitals of the acetylene moiety for interaction.

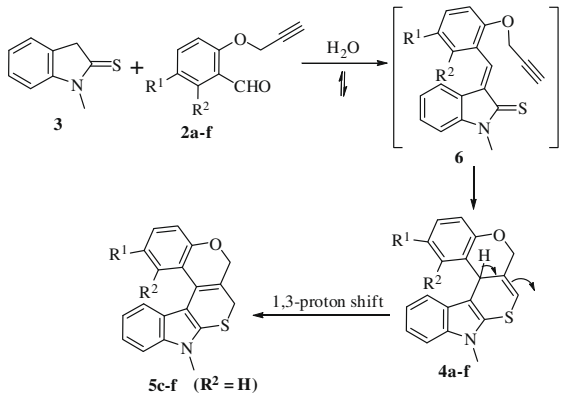
A probable mechanism for the domino-Knoevenagel-hetero-Diels–Alder reaction is shown in Scheme 3. Although we could not isolate the intermediates **6** we can reasonably assume that a combination of a Knoevenagel condensation between the thioindole **3** and the O-propargylated aldehydes **2a–f** and a hetero-

Table 2
Domino-Knoeveagel-hetero-Diels–Alder reaction of **3** and **2a–f**[a] in aqueous medium



Entry	Aromatic aldehyde (**2**)	Product[c]	Yield[b] (%)
1	 **2a**	 **4a**[65]	78
2	 **2b**	 **4b**[65]	72
3	 **2c**	 **5c**[65]	78
4	 **2d**	 **5d**[65]	75
5	 **2e**	 **5e**[65]	80
6	 **2f**	 **5f**[65]	73

[a] All the reactions were carried out in refluxing aqueous medium for 5 h.
[b] Isolated yields.
[c] The products were characterized from elemental analyses and spectroscopic data.



Scheme 3. Probable mechanism of domino-Knoeveagel-hetero-Diels–Alder reaction.

Diels–Alder reaction may produce the indole-annulated polyheterocycles **4**. However, we could isolate only products **4a** and **4b** and no other corresponding products **4c–f** were isolated. Instead products **5c–f** were obtained. The fact that substituents in *ortho*-position of the aldehyde group led to unconjugated products (**4a,b**) clearly indicates peri-hindrance, which is substantially diminished in case of an sp^3-hybridized angular carbon. Substrates without a substituent in the *ortho*-position with respect to the aldehyde group afforded conjugated products **5c–f** involving a 1,3-prototropic shift of the intermediates **4c–f**.

In conclusion, we have demonstrated a simple and efficient strategy for the synthesis of indole-annulated [6,6]-fused thiopyranobenzopyrans in 72–80% yields by domino-Knoevenagel-hetero-Diels–Alder reaction of unactivated terminal acetylene in the absence of any Lewis acid. The condition applied is mild, and water is used as a reaction medium which is environment friendly. A remarkable feature of this one-pot reaction is that C–C and C–S bond formation occurs in the absence of any catalyst and base.

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65. A mixture of 1-methylindoline-2-thione (**3**) (1 equiv) and 2-propargyloxynaphthaldehyde (**2a**) (1 equiv) was refluxed in water for 5 h. After completion of the reaction as monitored by TLC the reaction mixture was cooled and diluted with water (50 mL). This was extracted with ethyl acetate (3 × 25 mL). The combined organic extract was washed with brine and dried over anhydrous Na_2SO_4. The solvent was distilled off. The crude product was purified by column chromatography over silica gel (60–120 mesh) using petroleum ether–ethyl acetate mixture (98:2) as eluent to give compound **4a.** Yield: 78%, colourless solid; mp 186–188 °C; IR(neat): ν_{max} = 749, 1456, 1613, 2920 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ_H = 3.74 (s, 3H), 4.65 (d, *J* = 12.6 Hz, 1H), 4.85 (d, *J* = 12.9 Hz, 1H), 5.12 (s, 1H), 5.34 (d, *J* = 8.1 Hz, 1H), 6.36 (t, *J* = 7.2 Hz, 1H), 6.64 (s, 1H), 6.87 (t, *J* = 7.5 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 1H), 7.25–7.40 (m, 3H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.90 (d, *J* = 7.5 Hz, 1H) ppm. MS: *m*/*z* = 355 (M^+). Anal. Calcd for $C_{23}H_{17}NOS$: C, 77.72; H, 4.82; N, 3.94. Found: C, 77.89; H,

4.77; N, 3.85.*Compound* **4b:** Yield: 72%, colourless solid; mp 166–168 °C; IR(neat): ν_{max} = 751, 1461, 1659, 2924 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ_H = 2.34 (s, 3H), 3.72 (s, 3H), 4.49 (d, *J* = 12.3 Hz, 1H), 4.59 (s,1H), 4.73 (d, *J* = 12.6 Hz, 1H), 6.20 (d, *J* = 8.1 Hz, 1H), 6.80 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 9.0 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 7.18 (d, *J* = 8.1 Hz, 1H), 7.34 (d, *J* = 8.7 Hz, 2H) ppm. MS: *m*/*z* = 353 (M^+). Anal. Calcd for $C_{20}H_{16}ClNOS$: C, 67.88; H, 4.56; N, 3.96. Found: C, 67.73; H, 4.62; N, 3.89.*Compound* **5c:** Yield: 78%, colourless solid; mp 180–182 °C; IR(neat): ν_{max} = 751, 1457, 1601, 2917 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ_H = 3.47 (s, 2H), 3.78 (s, 3H), 4.80 (s, 2H), 6.96- 6.98 (m, 2H), 7.07 (t, *J* = 7.5 Hz, 1H), 7.17–7.21 (m, 2H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.45 (dd, *J* = 1.5, 7.6 Hz, 1H) ppm. ^{13}C NMR (100 MHz): 30.2, 36.1, 72.8, 102.7, 108.3, 109.9, 116.7, 118.0, 119.9, 120.7, 121.4, 125.7, 126.5, 127.3, 127.8, 128.0 129.0, 137.8, 153.7 ppm. MS: 327.93 $(M+Na)^+$. Anal. Calcd for $C_{19}H_{15}NOS$: C, 74.72; H, 4.95; N, 4.59. Found: C, 74.98; H, 4.93; N, 4.66.*Compound* **5d:** Yield: 75%, colourless solid; mp 140–142 °C; IR(neat): ν_{max} = 743, 1474, 1619, 2918 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ_H = 3.47 (s, 2H), 3.79 (s, 3H), 4.81 (s, 2H), 6.85 (d, *J* = 8.6 Hz, 1H), 7.14 (t, *J* = 7.2 Hz, 1H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.29–7.39 (m, 3H), 7.58 (s, 1H) ppm. MS: *m*/*z* = 383, 385 (M^+). Anal. Calcd for $C_{19}H_{14}BrNOS$: C, 59.38; H, 3.67; N, 3.64. Found: C, 59.61; H, 3.63; N, 3.59.*Compound* **5e:** Yield: 80%, colourless solid; mp 108–110 °C; IR(neat): ν_{max} = 747, 1464, 1611, 2918 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ_H = 2.23 (s, 3H), 3.47 (s, 2H), 3.78 (s, 3H), 4.76 (s, 2H), 6.87 (d, *J* = 8.1 Hz, 1H), 6.98 (dd, *J* = 1.4, 8.1 Hz, 1H), 7.06 (t, *J* = 7.9 Hz, 1H), 7.17 (t, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 1.4 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H) ppm. MS: *m*/*z* = 319 (M^+). Anal. Calcd for $C_{20}H_{17}NOS$: C, 75.20; H, 5.36; N, 4.39. Found: C, 75.01; H, 5.43; N, 4.31.*Compound* **5f:** Yield: 73%, colourless solid; mp 178–180 °C; IR(neat): ν_{max} = 743, 1474, 1619, 2918 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ_H = 1.25 (s, 9H), 3.48 (s, 2H), 3.79 (s, 3H), 4.78 (s, 2H), 6.90 (d, *J* = 8.3 Hz, 1H), 7.03 (t, *J* = 7.2 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 7.20 (dd, *J* = 2.2, 8.4 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 2.1 Hz, 1H) ppm. MS: *m*/*z* = 361 (M^+). Anal. Calcd for $C_{23}H_{23}NOS$: C, 76.42; H, 6.41; N, 3.87. Found: C, 76.54; H, 6.44; N, 3.76.