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Domino-Knoevenagel-hetero-Diels–Alder reactions: an efficient one-step synthesis of indole-annulated thiopyranobenzopyran derivatives

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ABSTRACT

Rapid one-step synthesis of hitherto unreported indole-annulated pentacyclic heterocycles containing oxygen, nitrogen, and sulfur has been described by domino-Knoevenagel-hetero-Diels–Alder reaction. The reaction sequence provides a route to the synthesis of a novel type of polyheterocycles in excellent yields with high stereoselectivity.

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Indole nucleus is an important subunit present in many biologically active natural products.¹ Compounds possessing indole moiety show antitumor activity,² cause inflammation, and vessication to human skin.³ Compounds containing thiopyranoindole moiety are important because of their biological activity.⁴ Some [6,6]fused pentacyclic indole alkaloids such as reserpine, rauniticine, yohimbine, and aspidospermine show extensive bioactivity.^{1b,f} These extensive bioactivities of various indole derivatives prompted us to undertake a study on the synthesis of [6,6]-fused pentacyclic indole derivatives in which bioactive thiopyrano indole moiety is fused with a benzopyran moiety.

There are several examples for the synthesis of benzopyrans and pyranobenzopyrans moieties while those of their sulfur containing analogs are rare.⁵ Literature survey reveals that there are few reports for the synthesis of polycyclic pyranothiopyrans.⁶ We have reported coumarin- and pyrone-annulated [6,6]-fused pyranothiopyran ring systems using sequential Claisen rearrangement^{6d} and tributyltinhydride-mediated radical cyclization,^{6c} respectively. However, applying the same methodology upon indoline-2-thione derivatives we could not obtain the expected [6,6]fused pyranothiopyran ring rather, [6,5]-fused pyranothiofurans⁷ and a spiro compound⁸ were obtained. More reports on the synthesis of furanothiopyran moieties are available.⁹ However, the scope of these protocols is limited by number of steps, by harsh reaction conditions, and by stoichiometric amounts of reagents.¹⁰ [6,6]-fused pentacyclic pyranothiopyran system. We, therefore, attempted to find an efficient and convenient synthetic methodology for the synthesis of such sulfur containing polycyclic compounds.

The hetero Diels–Alder reaction is one of the most efficient and powerful synthetic tool for the synthesis of heterocycles, including natural products.¹¹ Tietze et al. extensively described the domino-Knoevenagel-hetero-Diels–Alder reaction (DKHDA) of unsaturated aromatic and aliphatic aldehydes with several 1,3-dicarbonyl compounds for the synthesis of tetracycles with a pyran ring.¹² Desimoni et al. have reported a comparative study between hetero-Diels–Alder and intramolecular ene reaction upon (*E*)-1-acetyl-3-arylideneindolin-2-one.¹³ During the last few years there are several reports by the application of this methodology.^{6a,b,14} Here-in, we report the results of our present investigation applying DKHDA strategy.

The required precursors **2a–g** were prepared in very good yields by refluxing aromatic hydroxyl-aldehydes **1a–g** with allyl or crotyl bromide in dry acetone in the presence of anhydrous K_2CO_3 and a catalytic amount of Nal¹⁵ (Scheme 1).

To examine the Knoevenagel-hetero-Diels–Alder reaction of 1methylindoline-2-thione (**3**) with *O*-allyl aromatic aldehydes (**2**) we first used *O*-allyl salicylaldehyde as a precursor of the heterodiene. When the reaction was carried out at room temperature using **3** (0.613 mmol, 1 equiv), **2a** (0.613 mmol, 1 equiv), and NEt₃ (1 equiv) in acetic acid, the reaction rate was slow and the product was obtained in only 15% yield after 24 h. But when the reaction was carried out at refluxing condition using **3** (0.613 mmol, 1 equiv), **2a** (0.613 mmol, 1 equiv), and NEt₃



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Figure 1. Single-crystal X-ray structure of compound 4a.



Scheme 1. Reagents and conditions: (i) allyl bromide, anhydrous K_2CO_3 , acetone, Nal, reflux.

(1 equiv) in acetic acid the reaction time was drastically reduced to 2 h affording **4a** in 96% yield (Scheme 2).

The reaction is highly stereoselective affording exclusively the *cis*-[6,6]-fused thiopyranobenzopyran derivatives. The structure and stereochemistry of the product **4a** have been determined by spectral analysis¹⁶ and single-crystal XRD data¹⁷ (Fig. 1).

In order to extend the utility of this methodology, we have further carried out the reaction by using several different O-allylated aromatic aldehydes (**2b**–**g**). The results are listed in Table 1. Reaction of **3** with 1 equiv of **2b** and 1 equiv of NEt₃ in refluxing acetic acid gave product **4b** in 92% yield (entry 2). When the same reaction was carried out with **2c** and **2d**, the desired products **4c** and **4d** were obtained in 89 and 86% yields, respectively (entries 3 and 4), 85% yield of the product was obtained when the reaction was carried out with **2e** (entry 5). Similarly treatment of **2f** with **3** under the same reaction condition afforded product **4f** in 90% yield (entry 6), whereas that of **2g** gave product **4g** in 92% yield (entry 7). In all the cases the reactions were carried out for 2 h and the structures of the products were determined by comparison of their spectral data with those of the product **4a**. In all the cases the stereochemistry of the ring juncture protons was found to be cis.

The stereochemistry of the final product of Diels–Alder reaction depends on the *endo-* and *exo-*orientation of the dienophile in the transition state. We were unable to isolate the intermediate heterodiene **5**. However, a probable explanation for the cis-stereo-



Scheme 2. Reagents and conditions: (i) 1 equiv 3, 1 equiv 2a, 1 equiv NEt₃, AcOH, reflux.

Table 1 Results of domino-Knoevenagel-hetero-Diels-Alder reactions of substrate $\mathbf{3}^a$



^a All reactions are carried out in refluxing AcOH for 2 h.

^b Isolated yields.



Scheme 3. Probable explanation for the stereochemistry of the compounds **4**.

chemistry of the product (4) is given in Scheme 3. The intermediate 5 may undergo rotation around single bond to assume the structure 5a which may then undergo cyclization via endo selectivity of the hetero-Diels-Alder reaction (path b). The reaction does not occur via exo selectivity to afford the product 6 perhaps due to the sp²- geminal effect of 1,3-allylic strain.¹⁸

In conclusion, we have demonstrated an efficient and simple strategy for the synthesis of indole annulated-[6,6]-thiopyranobenzopyrans in excellent yields by domino-Knoevanagal-hetero-Diels-Alder reactions. The reaction is a general one and highly stereoselective leading to cis-annulated polyheterocycles in a single step.

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- mixture of 1-methylindoline-2-thione (**3**)(1 equiv) and 0-allvl Α salicylaldehyde (2a)(1 equiv) was refluxed in acetic acid in the presence of triethylamine (1 equiv) for 2 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 ethylacetate $(3 \times 25 \text{ mL})$. The combined organic extract was washed with saturated solution of sodium bicarbonate followed by brine solution and dried over anhydrous Na2SO4. The solvent was distilled off. The resulting product was purified by column chromatography over silica gel (60-120 mesh) using petroleum ether-ethyl acetate (97:3) mixture as eluent to give compounds (**4a**). Yield: 96%, colorless solid; mp 162–164 °C; IR (neat): $\nu_{max} = 1274, 1466, 1485, 2876 \text{ cm}^{-1}; ^{1}\text{H} \text{ NMR} (\text{CDCl}_3, 300 \text{ MHz}): \delta_{\text{H}} = 2.45 \text{ (dq}, 1485$ $V_{\text{max}} = 1274$, 1460, 1463, 2676 cm⁻¹, 11 NMR (CDC3, 500 M12), $c_{H} = 2.49$ (dq, J = 2.1, 9.3 Hz, 1H), 2.97 (d, J = 12.9 Hz, 1H), 3.35 (t, J = 12.3 Hz, 1H), 3.62 (s, 3H), 4.41 (dd, J = 2.1, 11.4 Hz, 1H), 4.52 (dd, J = 2.1, 11.4 Hz, 2H), 6.72–6.80 (m, 2H), 7.06 (t, J = 7.2 Hz, 1H), 7.16–7.20 (m, 1H), 7.28–7.32 (m, 3H), 7.60–7.63 (m, 1H) ppm. ¹³C NMR (100 MHz): 26.1, 30.1, 32.1, 32.7, 70.3, 108.0, 108.4, 116.5, 117.0, 119.8, 120.5, 121.1, 125.1, 127.9, 129.2, 129.5, 130.2, 137.3, 151.9 ppm. HRMS: *m*/*z* calcd for C₁₉H₁₇NOS [M+H]⁺: 308.1104; found; 308.1094.
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