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An efficient synthesis of thiopyrano[5,6-*c*]coumarin/[6,5-*c*]-chromones through intramolecular domino Knoevenagel hetero Diels–Alder reactions

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Abstract—The synthesis of novel polycyclic thiopyrano coumarin/chromone frameworks through intramolecular domino Knoevenagel hetero Diels–Alder reactions of 4-hydroxy coumarin and its benzo-analogous with *S*-prenylated aromatic aldehydes was studied. A high degree of chemoselectivity was achieved by the application of microwave irradiation and a solid support.

Isolation of aza and thio heterocyclic compounds from natural sources is sometimes very difficult and in these cases biochemical studies have to rely on synthetic materials.[1–5] A great deal of interest exists in the chemistry of these substances and in the study of their interaction with bio-molecules. A number of studies on pyrans and benzopyrans have been reported while those of their sulfur-containing analogs are rare.[6,7]

It is only lately that studies of benzothiopyrans have attracted the attention of a number of research groups.[8] To the best of our knowledge, there are relatively few reports on the synthesis of polycyclic pyranobenzothiopyrans.[9] As a result of advances in both synthetic chemistry and biology, there is now an increased demand for an efficient and convenient synthetic method for sulfur-containing polycyclic compounds.

The domino Knoevenagel intramolecular hetero Diels–Alder (IMHDA) reaction is a powerful weapon in organic synthesis, especially in the area of heterocycles and natural products.[10] The most widely used heterodienes are usually those where the olefinic bond is flanked between symmetrical 1,3-dicarbonyl groups.[11] In the present work, it was of interest to study the mode of cycloaddition of a heterodiene, wherein the olefinic segment is flanked by a keto carbonyl and a lactone carbonyl.

In recent years, there has been growing interest in the application of microwave irradiation in organic synthesis due to the short reaction times and operational simplicity coupled with high conversions and high degrees of selectivity.[12]

Coumarin derivatives are widespread in nature and are reported to have various biological activities such as anticoagulant, insecticidal, anthelminthic hypnotic, antifungal, phytoalexin and HIV protease inhibition.[13,14] Many naturally occurring compounds such as isoethuliacoumarin A, isoethuliacoumarin B, isoethuliacoumarin C, ethuliacoumarin A, ethuliacoumarin B and pterophyllin possess the pyrano[3,2-*c*]coumarin skeleton and have been isolated from various sources.[15,16] Their wide ranges of biological applications have simulated considerable interest in evolving newer synthetic methods for the construction of coumarin derivatives.

We have reported a chemoselective synthesis of pyrano[3,2-*c*]coumarin and pyranoquinolinone derivatives[17] in which there exists competition between two intramolecular domino Knoevenagel hetero Diels–Alder reactions. Our continued interest in the area of cycloaddition reactions prompted us to examine the mode of cycloaddition of a heterodiene wherein the olefinic segment is flanked between a keto carbonyl on the one side and a lactone carbonyl on the other side.

In this letter, we describe a novel protocol for the synthesis of thiapyrano[5′,4′:3,4]pyrano[5,6-*c*]coumarin

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and thiapyrano[5′,4′:3,4]pyrano[6,5-*c*]chromones via domino Knoevenagel hetero Diels–Alder reactions between 3-methyl/phenyl-5-(3-methyl-but-2-enylsulfanyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde **2/5**[18] and unsymmetrical 1,3-diones.[19] Thus, treatment of 4-hydroxy coumarin **1** with 3-methyl-5-(3-methyl-but-2-enylsulfanyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde **2** in refluxing ethanol resulted in the formation of cis-fused 8a, 13b-*cis*-8,8,13-trimethyl-11-phenyl-8,8a,9,13b-tetrahydropyrazolo [3″,4″-*b*′]thiapyrano[5′,4′:3,4]pyrano[5,6-*c*]coumarin **3** and 8a,13b-*cis*-8,8,13-trimethyl-11-phenyl-8,8a,9,13b-tetrahydropyrazolo[3″,4″-*b*′]thiapyrano[5′,4′:3,4]pyrano[6,5-*c*]chromone **4** with an overall yield of 64%. The products [coumarin]:[chromone] are formed in the ratio 55:45 without the isolation of the intermediate (Scheme 1).

The reaction proceeds via a tandem Knoevenagel and hetero Diels–Alder pathway. This reaction is highly stereoselective affording exclusively cis-fused thiopyrano[3,2-*c*]coumarin derivatives. The cis-stereochemistry of the products was assigned by spectral analysis. Examination of the spectral data revealed that both the keto carbonyl and lactone carbonyl were involved in the cycloaddition leading to the products, **3** and **4**, respectively.

The structure of the products was ascertained from the spectral data. The IR carbonyl absorption of **3** was observed at 1708 cm^{-1} whereas in the case of **4** it was observed at 1639 cm^{-1}.

The coumarin and chromone derivatives were confirmed by the distinguishable carbonyl carbon in the ^{13}C NMR, which appeared at δ 161.26 ppm for the coumarin and at δ 177.61 ppm for the chromone derivative. The ^{1}H NMR spectrum of **3** showed a doublet at δ 4.13 for the H_a proton and a multiplet in the region δ 2.19–2.21 for the H_b proton. The cis-stereochemistry of the products **3** and **4** were confirmed by the coupling constant $J_{Ha,Hb} = 4.0$ Hz. Further, the structure and the cis-stereochemistry of the derivative **3** was confirmed by X-ray single crystal analysis (Fig. 1).[20]

When the same reaction was carried out under microwave irradiation in ethanol for 60 s, the coumarin and chromone derivatives **3** and **4** were obtained in the ratio 76:24 with an overall yield of 82%. Thus, there was an increase in chemical yield with a slight improvement in the chemoselectivity.[21]

We also examined the solvent-free reaction, simply by grinding the two components with K-10 Montmorillonite clay and irradiating the mixture under microwave conditions. This afforded the anticipated cycloadducts in excellent yields with high chemoselectivity and also of sufficient purity. The ratio of the coumarin and chromone was found to be 94:6 with an improved overall yield of 88%. Thus, the pronounced chemoselectivity was achieved in a short duration of time.

With these encouraging results, it was of further interest to study the intramolecular domino Knoevenagel hetero Diels–Alder with other unsymmetrical 1,3-diones **8**, **13** and **18**. In all cases, the intramolecular domino Knoevenagel hetero Diels–Alder reaction yielded the novel thiopyrano[5,6-*c*]coumarin derivative as the major product

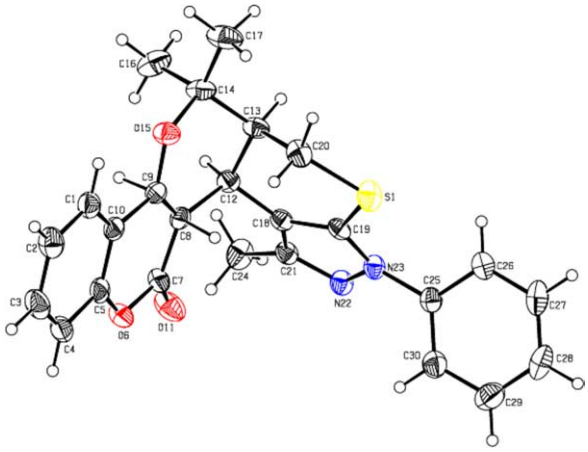
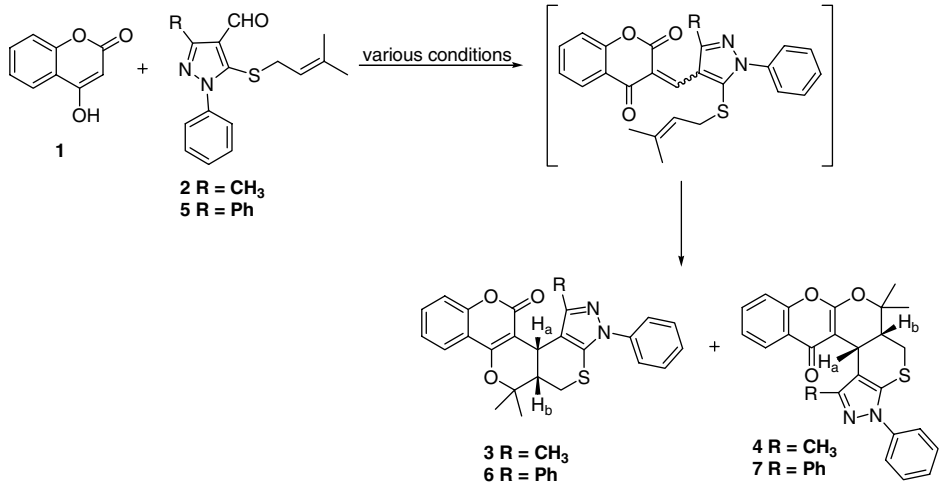
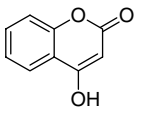
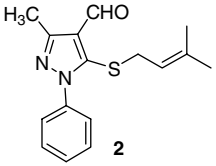
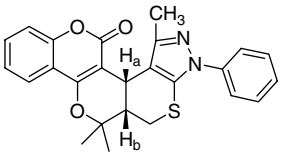
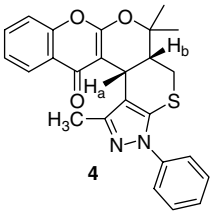
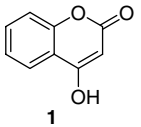
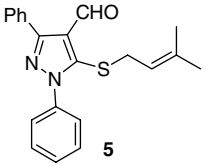
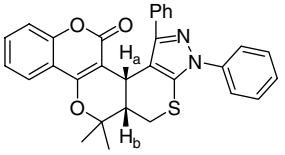
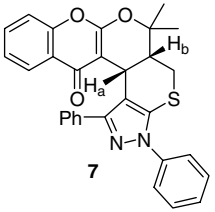
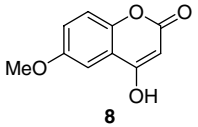
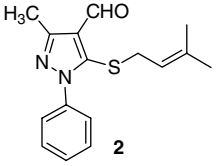
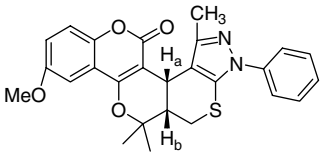
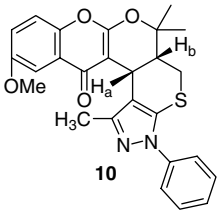
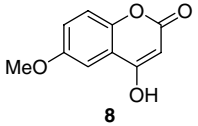
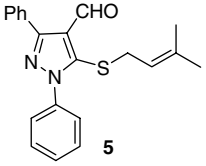
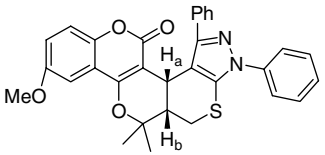
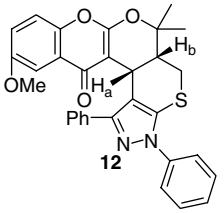
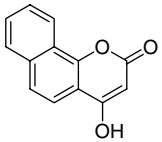
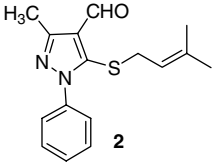
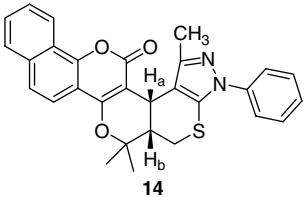
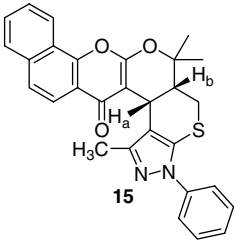


Figure 1. ORTEP diagram of **3**.



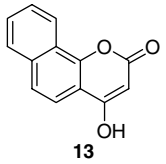
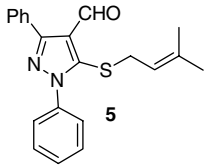
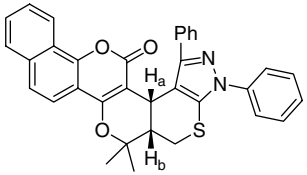
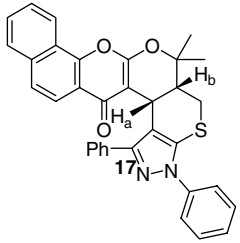
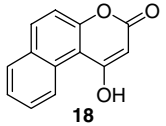
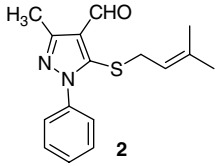
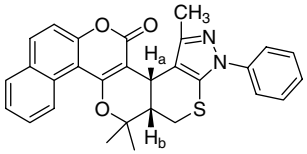
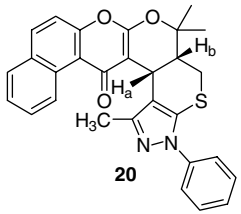
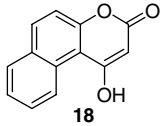
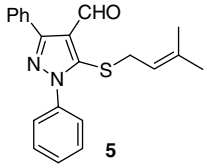
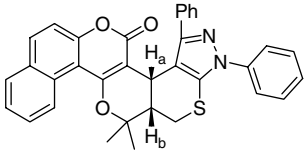
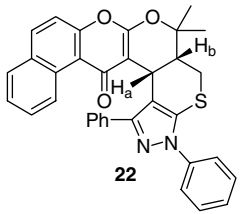
Scheme 1.

Table 1. Study on chemoselectivity of coumarin and chromone derivatives synthesized through intramolecular domino Knovenegal hetero Diels–Alder reaction

Entry	1,3-Dione	Aromatic aldehyde	Products		Conditions	Time	Overall yield (%)	Coumarin/ chromone
1	 **1**	 **2**	 **3**	 **4**	A B C	9 h 60 s 25 s	64 82 88	55:45 76:24 94:6
2	 **1**	 **5**	 **6**	 **7**	A B C	10 h 1.25 min 45 s	67 85 90	59:41 74:26 91:9
3	 **8**	 **2**	 **9**	 **10**	A B C	7 h 60 s 40 s	58 80 91	56:44 71:29 92:8
4	 **8**	 **5**	 **11**	 **12**	A B C	8 h 1.5 min 50 s	68 76 84	54:46 70:30 95:5
5	 **13**	 **2**	 **14**	 **15**	A B C	5 h 2.5 min 55 s	54 72 87	52:48 72:28 90:10

(*continued on next page*)

Table 1 (*continued*)

Entry	1,3-Dione	Aromatic aldehyde	Products		Conditions	Time	Overall yield (%)	Coumarin/ chromone
6	 **13**	 **5**	 **16**	 **17**	A B C	6 h 1.5 min 23 s	64 76 90	58:42 70:30 93:7
7	 **18**	 **2**	 **19**	 **20**	A B C	4.5 h 3.5 min 55 s	58 79 82	51:49 70:30 89:11
8	 **18**	 **5**	 **21**	 **22**	A B C	5.5 h 4.5 min 65 s	62 80 85	54:46 72:28 95:5

Method A: ethonal reflux, method B: ethanol microwave, method C: K-10 Montmorillonite clay, microwave irradiation.

in good yield. The results obtained under various reaction conditions are shown in Table 1.

From Table 1 it is obvious that the thiopyrano[5,6-*c*]coumarin adducts were predominant over the chromone derivative under microwave irradiation using K-10 Montmorillonite clay. The structure of all the products was confirmed through spectral analysis. The cis-annulation of the thiopyrano-pyrano rings of all the products was apparent from the coupling constant as previously described.

In conclusion, we have described an efficient synthesis of novel thiopyrano-pyrano-coumarin/chromone polycycles in one-pot via a domino Knoevenagel hetero Diels–Alder reactions under different reaction conditions with good overall yields and chemoselectivity. Of the various conditions employed that the solvent-free approach on a solid support accelerated by microwave irradiation was found to be synthetically useful in achieving a high degree of chemoselectivity with substantial reduction in time as well as being environmentally friendly.

Acknowledgements

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19. Representative procedure for the preparation of thiopyrano-pyrano ring systems:
Method A: To a refluxing solution of unsymmetrical 1,3-dione (1 mmol) in 10 mL of dry ethanol, aldehyde **2** or **5** (1 mmol) was added and the reaction mixture was refluxed until the disappearance of the starting material as evidenced by thin layer chromatography. After completion of the reaction, the solvent was evaporated and the residue was subjected to flash column chromatography using hexane/ethyl acetate mixture (9:1).
Method B: A solution of unsymmetrical 1,3-dione (1 mmol) and the corresponding aldehyde (1 mmol) in dry ethanol/toluene were irradiated using a domestic microwave oven (Kenstar, 800 W power) until the thin layer chromatography indicated complete disappearance of the starting material. After the removal of the solvent, the crude reaction mixture was subjected to flash column chromatography as above.
Method C: A mixture of 1,3-dione (1 mmol), the corresponding aldehyde (1 mmol) and K-10 Montmorillonite clay (1.0 g) was thoroughly ground in a mortar. The reaction mixture was irradiated using a domestic microwave oven (Kenstar, 800 W power) until the complete disappearance of the starting material as evidenced by thin layer chromatography. After completion of the reaction, the clay was separated by filtration and extracted with dichloromethane (2×15 mL). Removal of the solvent and purification of the crude reaction mixture by flash column chromatography gave the pure product.
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21. 8a,13b-*cis*-8,8,13-Trimethyl-11-phenyl-8,8a,9,13b-tetrahydropyrazolo[3″,4″-*b*′]thiapyrano[5′,4′:3,4]pyrano[5,6-*c*]coumarin **3**: IR (KBr): 1708 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 1.53 (s, 3H), 1.57 (s, 3H), 2.19–2.21 (m, $1H_b$), 2.47 (s, 3H), 2.92 (dd, $J = 13.0$, 7.0 Hz, 1H), 3.07 (dd, $J = 3.4$, 13.0 Hz, 1H), 4.13 (d, $J = 4.0$ Hz, $1H_a$), 7.24–7.78 (m, 9H); ^{13}C

NMR (125 MHz, $CDCl_3$): δ 13.3, 24.6, 25.8, 27.1, 28.2, 40.5, 80.1, 101.0, 113.3, 115.5, 116.4, 122.7, 123.1, 123.7, 126.9, 129.2, 131.1, 132.0, 139.4, 151.2, 152.8, 158.2, 161.3 ppm; Mass m/z: 430 (M^+); Anal. Calcd for $C_{25}H_{22}N_2O_3S$: C, 69.76; H, 5.12; N, 6.51. Found: C, 69.98; H, 5.00; N, 6.32.

8a,13b-*cis*-8,8,13-Trimethyl-11-phenyl-8,8a,9,13b-tetrahydropyrazolo[3″,4″-*b*′]thiapyrano[5′,4′:3,4]pyrano[6,5-*c*]chromone **4**: IR (KBr): 1639 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 1.56 (s, 3H), 1.58 (s, 3H), 2.17–2.18 (m, $1H_b$), 2.52 (s, 3H), 3.02 (dd, $J = 12.8$, 7.0 Hz, 1H), 3.12 (dd, $J = 3.4$, 12.8 Hz, 1H), 4.22 (d, $J = 4.0$ Hz, $1H_a$), 7.34–7.78 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.4, 24.6, 25.6, 27.2, 27.5, 40.9, 82.8, 96.5, 113.7, 116.3, 116.9, 122.7, 123.1, 123.7, 125.1, 126.1, 129.2, 132.0, 139.4, 150.9, 152.8, 161.9, 177.6 ppm; Mass m/z: 430 (M^+).

10a,15b-*cis*-10,10,15-Trimethyl-13-phenyl-10,10a,11,15b-tetrahydropyrazolo[3″,4″-*b*′]thiapyrano[5′,4′:3,4]pyrano[5,6-*c*]-α-naphthocoumarin **14**: IR (KBr): 1710 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 1.56 (s, 3H), 1.62 (s, 3H), 2.21–2.24 (m, $1H_b$), 2.42 (s, 3H), 3.13 (dd, $J = 13.2$, 7.4 Hz, 1H), 3.62 (dd, $J = 4.0$, 13.2 Hz, 1H), 4.24 (d, $J = 4.0$ Hz, $1H_a$), 6.77–7.81 (m, 11H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.6, 25.1, 25.9, 26.9, 28.0, 40.2, 81.0, 103.3, 114.5, 114.9, 115.9, 117.8, 121.5, 123.0, 123.6, 125.8, 127.6, 127.9, 133.0, 134.0, 137.1, 139.2, 150.3, 151.2, 159.1, 162.5 ppm; Mass m/z: 480 (M^+); Anal. Calcd for $C_{29}H_{24}N_2O_3S$: C, 72.50; H, 5.00; N, 5.83. Found: C, 72.33; H, 4.81; N, 6.08.