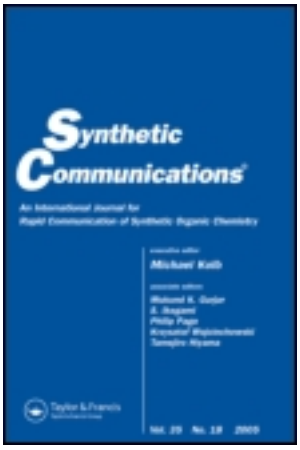

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Microwave-Assisted K-10 Montmorillonite Clay–Mediated Knoevenagel Hetero-Diels–Alder Reactions: A Novel Protocol for the Synthesis of Polycyclic Pyrano[2,3,4-*kl*]xanthene Derivatives

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Abstract: The intramolecular hetero-Diels–Alder reactions of 2-(cyclohex-2-enyloxy)benzaldehyde by Knoevenagel condensation with symmetrical 1,3-diones under three different conditions afforded the pyrano[2,3,4-*kl*]xanthene derivatives in a stereoselective manner in good yield. The structure of one of the products was unambiguously established by x-ray analysis.

Keywords: 1,3-Dione, hetero-Diels–Alder reaction, microwave, pyrano xanthene

INTRODUCTION

The intramolecular Diels–Alder reaction[1] is a powerful method for the synthesis of many polycyclic compounds, including natural products. However, it is a prerequisite that activating groups have to be built into dienophiles to achieve the desired reactivity.[2]

Xanthene derivatives are intermediates in organic synthesis and have many applications in laser technology because of their interesting spectroscopic properties.[3,4] Dibenzoxanthene derivatives find application as candidates as sensitizers in photodynamic therapy (PDT).[5] PDT is a method of treating tumors by combined use of a

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photosensitizer and light.[6] Furthermore, these compounds have recently received great attention because of their wide range of therapeutic and biological properties, such as antibacterial,[7] antiviral,[8] and anti-inflammatory activities.[9]

In continuation of our work in cycloaddition reactions,[10,11] we disclose here our preliminary investigation on the solvent-free, microwave-assisted Knovenagal intramolecular hetero-Diels–Alder reaction, a rapid and expedient way for the synthesis of pyrano[2,3,4-*kl*]xanthene derivatives with a high degree of stereoselectivity.

This methodology is used for the first time for the synthesis of the title compound. The precursors for the hetero-Diels–Alder reaction were readily obtained by the treatment of salicylaldehyde **1–3** with bromocyclohexene **4** in dry acetone in the presence of K_2CO_3 under refluxing condition to give **5–7** in 51–58% yield. See Table 1.

The structure of the products was ascertained from spectral data. The IR spectrum of the compound showed a peak at 1683 cm^{-1}. The ^1H spectrum of **5** exhibited a multiplet in the range δ 1.55–2.02 for cyclohexane ring protons, –OCH protons appeared at δ 4.796 as a multiplet, alkene proton (H_1) appeared as a doublet of doublet in the region δ 5.77 ($J = 9.7$, 1.8), and alkene (H_2) proton appeared as a multiplet in the region δ 5.87–5.92. The aromatic protons resonated in the region δ 6.85–7.43. Finally, an aldehyde proton resonated at δ 10.40 ppm.

The *O*-alkenyl aldehyde thus prepared, **5**, when refluxed with pyrazolone **8** in toluene in the presence of the catalyst ethylenediaminediacetate (EDDA) (Scheme 1), afforded a mixture of intramolecular hetero-Diels–Alder adducts **9** and **10**, which were separated by column chromatography.

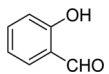
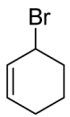
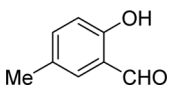
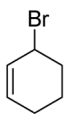
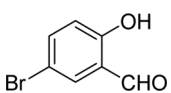
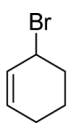
The structure of **9** became evident from the spectral data.

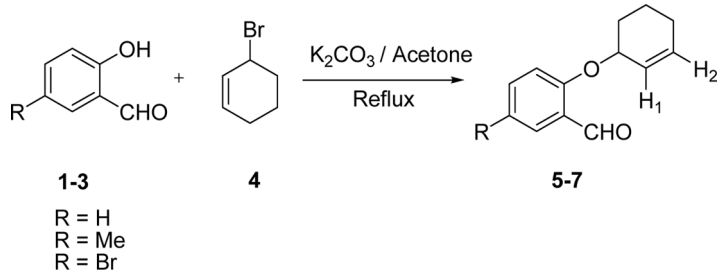
In the ^1H NMR spectrum of the compound **9**, multiplets appeared in the region δ 1.76–2.32 as a result of cyclohexane ring protons, a single at δ 2.15 as a result of $–CH_3$ protons of the pyrazole ring, and two multiplets in the regions δ 4.11–4.19 and δ 4.72–4.73 for H_1 and H_3 protons. Ring junction proton H_2 appeared as a doublet at δ 4.12 ($J = 5.1$). The aromatic protons showed multiplets in the region δ 6.82–7.73. Further the *cis*-annulation of the ring structure for **9** was discerned by small coupling constant $J = 5.1$ Hz, which was further confirmed by the single-crystal X-ray analysis (Figure 1).[12]

The molecular ion peak in the mass spectrum of the compound **9** appeared at m/z 358.3 (M^+).

For the *trans*-product **10**, the ^1H NMR spectrum showed multiplets in the region δ 1.75–2.35 due to cyclohexane ring protons and a singlet at δ 2.32 due to $–CH_3$ protons of the pyrazole ring. Two multiplets appeared

Table 1. Synthesis of 2-cyclohex-2-enyloxy benzaldehyde

Entry	Salicylidehyde	Conditions	Time (h)	Yield (%)
1		 K_2CO_3 / Acetone reflux	5	58
2		 K_2CO_3 / Acetone, reflux	5.5	54
3		 K_2CO_3 / DMF, rt	6	51



Scheme 1. Reaction of bromocyclohexene with salicylaldehyde.

in the regions δ 4.13–4.21 and δ 4.70–4.72 for H_1 and H_3 protons. A ring junction proton appeared as a doublet at δ 4.23 ($J = 7.8$). The aromatic protons showed multiplets in the region δ 6.83–7.71. Further, the *trans*-annulation of the compound **10** was discerned by the coupling constant $J = 7.8$ Hz. This was further supported by nuclear Overhauser effect (NOE) studies, which showed weak interaction between H_1 and H_2.

By applying microwave conditions on solid support, the overall yield increased to 76% (Table 2). In a short duration of time, microwave irradiation proved to be highly beneficial for obtaining good yield of the products with high stereoselectivity.

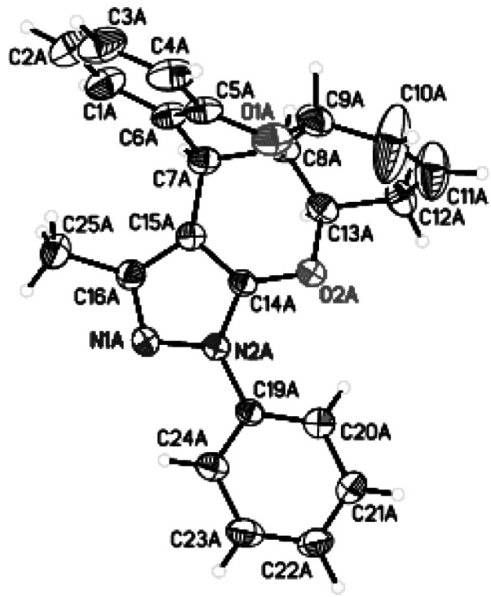
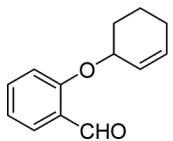
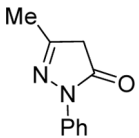
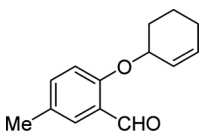
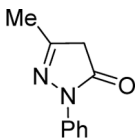
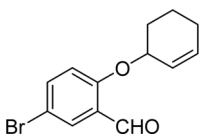
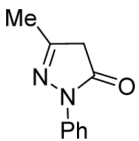


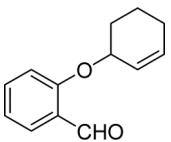
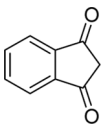
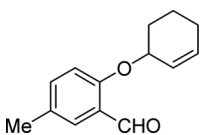
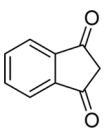
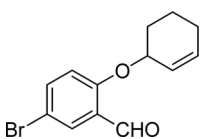
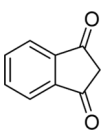
Figure 1. ORTEP diagram of **9a**.

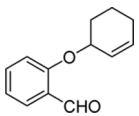
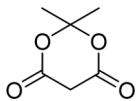
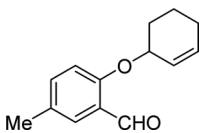
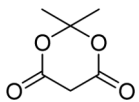
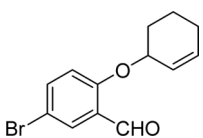
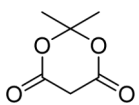
Table 2. Reaction times and yields of the domino reactions of various diones with aldehydes 1–3 under various conditions[a]

Entry	Aldehydes	Activated ketones	Conditions	Time	Ratio of the products		Overall yield (%)
					cis	*trans*	
1			Method A	3.0 h	55	45	52
			Method B	10 min	63	27	63
			Method C	1.2 min	74	26	76
2			Method B	16 min	70	30	59
			Method A	3.5 h	57	43	42
			Method C	2.6 min	76	24	70
3			Method A	4.0 h	52	48	40
			Method B	17 min	71	29	52
			Method C	2.5 min	78	22	65

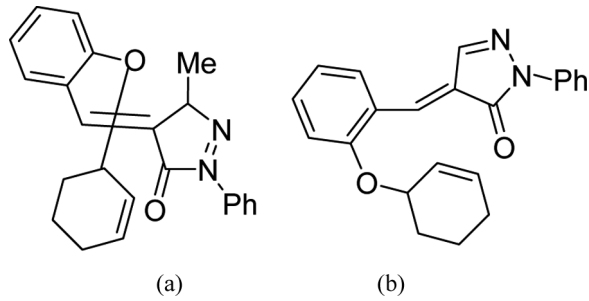
(*Continued*)

Table 1. Continued

Entry	Aldehydes	Activated ketones	Conditions	Time	Ratio of the products		Overall yield (%)
					cis	*trans*	
4			Method A	2.0 h	53	47	64
			Method B	11 min	73	27	73
			Method C	1.5 min	80	20	86
5			Method A	2.5 h	56	44	61
			Method B	16 min	76	24	69
			Method C	1.8 min	81	19	76
6			Method A	3.0 h	51	49	60
			Method B	11 min	72	28	65
			Method C	2.0 min	83	17	71

7			Method A	4.5 h	50	50	44
			Method B	18 min	77	33	52
			Method C	2 min	81	19	63
8			Method A	5.5 h	53	47	41
			Method B	25 min	76	24	47
			Method C	3 min	83	27	54
9			Method A	5.5 h	52	48	39
			Method B	30 min	74	26	46
			Method C	3.5 min	84	26	54

[a]Reaction conditions: method A: toluene reflux; method B: toluene, MW; method C: K-10 montmorrilonite clay, MW.

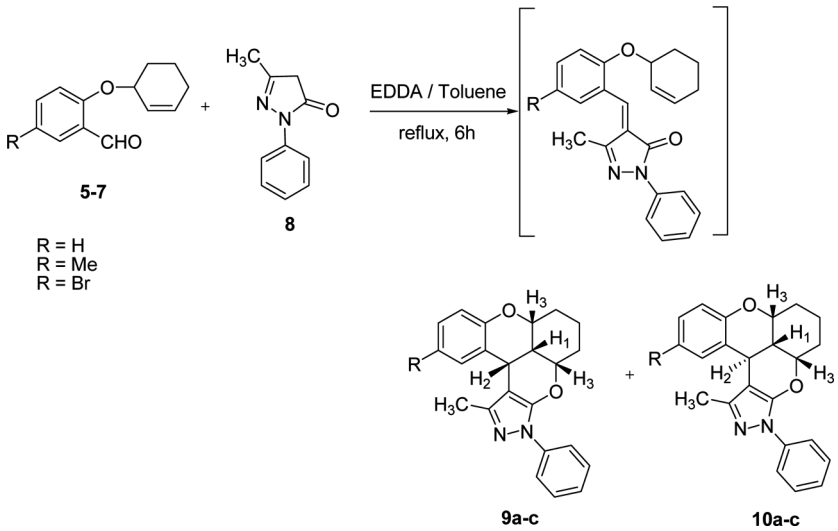


(a) (b)

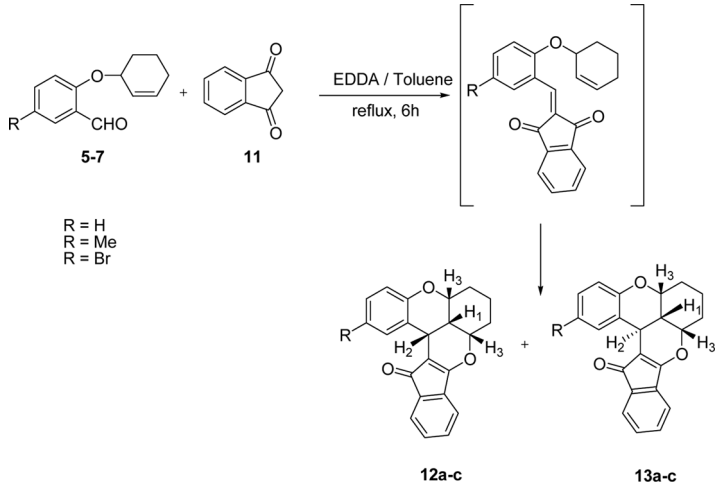
Figure 2.

By applying microwave conditions on solid support, the yield of the product **9** increased to 74% (Table 2). In a short duration of time, microwave irradiation proved to be highly beneficial for obtaining good yield of the product with high steroselectivity.

Encouraged by these findings, we contemplated expanding the substrate scope of the hetero-Diels–Alder reaction by taking other salicylaldehyde derivatives. Thus, the reaction of **1** with pyrazolone **4** (Scheme 2) was carried out under optimized reaction conditions, and the results are summarized in Table 2.

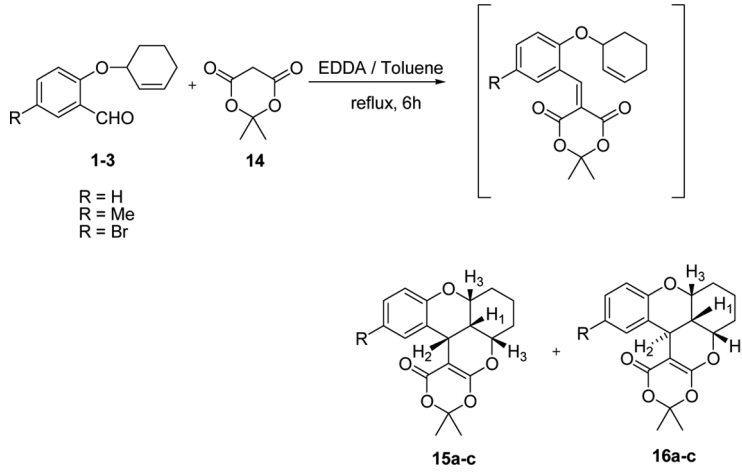


Scheme 2.



Scheme 3.

These reactions follow the same pattern as observed for substrates **2,3** but with even better yield and shorter reaction time. Under the optimum reaction conditions, we have also carried out the intramolecular Knoevenagel hetero-Diels–Alder reaction by employing various symmetrical 1,3-diones, namely indane 1,3 dione (**11**) and dimedone (**13**) with aldehyde **1–3** (Schemes 3 and 4). The results are summarized in Table 2. The reaction of indane-1,3-dione (**11**) and 2-(cyclohex-2-enyloxy)



Scheme 4.

benzaldehydes (**1–3**) in refluxing toluene proceeded via the domino Knoevenagel hetero-Diehls–Alder (DKHDA) reaction to furnish a mixture of cycloadducts **12** and **13** in an overall yield of 51–53% (Scheme 3).

Interestingly, when subjected to the intramolecular Knoevenagal hetero-Diels–Alder reaction, all symmetrical 1,3-diones showed similar results under optimized reaction conditions with the aldehydes **1–3**.

In all cases studied, the *cis*-annulated products were predominately obtained in all the reactions taken for investigation. As already described by Tietze et al.,[16] under kinetic control, the *endo*-transititon state **A** forms the *cis*-adduct, which is energetically more favorable than the *exo*-transititon state **B** (Figure 2).

In conclusion, the preceding studies demonstrate the scope of the intramolecular Knoevenagal hetero-Diels–Alder reaction for the synthesis of pyrano[2,3,4-*kl*]xanthene derivatives. The observations reported here show that the reaction medium plays an important role in the outcome of domino Knoevenagal hetero-Diels–Alder reaction and that this method can be used for the synthesis of a variety of pyrano[2,3,4-*kl*] xanthene derivatives with a high degree of stereoselectivity.

GENERAL PROCEDURE FOR THE INTRAMOLECULAR DOMINO KNOEVENAGEL HETERO-DIELS–ALDER REACTION

Method A

To a refluxing solution of active methylene compound (1 mmol) in 10 mL of dry toluene, the aldehyde **1–3** (1 mmol) was added, and the reaction mixture was refluxed until the disappearance of the starting material as evidenced by thin-layer chromatography (TLC). After the completion of the reaction, the solvent was evaporated in a rotavapor, and the residue was subjected to flash-column chromatography using hexane–ethylacetate (8:2).

Method B

A solution of active methylene compound (1 mmol) and the corresponding aldehyde 1–3 (1 mmol) in dry toluene were irradiated in a microwave (600 W power) until TLC showed the disappearance of the starting material. After the removal of the solvent, the crude reaction mixture was subjected to flash-column chromatography using silica gel to yield the product.

Method C

A mixture of active methylene compound (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 in a microwave until the disappearance of the starting material as evidenced by TLC. After the completion of the reaction, clay was separated by filtration after extracting the product with dichloromethane (2×15 mL). Removal of the solvent and purification of the crude reaction mixture by flash-column chromatography gave the pure product.

Data

Synthesis of 2-(Cyclohex-enyloxy)benzaldehyde **5**

A solution of salicylaldehyde (10 mmol) in acetone (20 mL) was treated with solid K_2CO_3 (16 mmol) and 3-bromo cyclohexene (12 mmol). The mixture was refluxed for 3 h, and the resulting mixture was filtered. The filtrate was evaporated in a vacuum, and the crude viscous liquid was subjected to column chromatography to give the pure product. ^{1}H NMR ($CDCl_3$): 1.54–2.019 (m, 6H, ring proton), 4.79 (m, 1H, –OCH), 5.77 (dd, H_1, $J = 9.7$, 1.8), 5.87–5.92 (m, H_2), 6.85–7.43 (m, 4H, Ar H), 10.39 (s, H, –CHO). ^{1}C NMR ($CDCl_3$): 18.84, 20.22, 28.39, 72.02, 114.48, 125.49, 125.61, 128.13, 129.98, 132.77, 136.45, 158.70, 190.14 ppm.

5,11a,15b-*cis*-3-Methyl-1-phenylpyrazolo[3,2-c]-5,11a,12,13,14,15b-octahydro-1*H*-pyrano[2,3,4-*kl*]xanthene

Yellow solid; mp: 182 °C. ^{1}H NMR ($CDCl_3$): 1.76–2.32 (m, 6H, ring proton), 2.15 (s, 3H, $–CH_3$), 4.11–4.19 (m, H_1), 4.72–4.73 (m, H_3), 4.12 (d, H_1, $J = 5.1$), 6.82–7.73 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 13.99, 17.06, 28.78, 30.18, 30.63, 36.47, 67.91, 76.07, 95.88, 115.08, 117.41, 118.72, 119.41, 123.69, 126.81, 127.20, 130.72, 152.16. MS: $m/z = 358.3$ (M^+). Anal. calcd. for $C_{23}H_{22}N_2O_2$: C, 77.07; H, 6.19; N, 7.82%. Found: C, 76.93; H, 6.08; N, 8.01%.

5,11a,15b-*trans*-Indan-1-one[3,2-c]-5,11a,12,13,14,15b-octahydro-1*H*-pyrano[2,3,4-*kl*]xanthene

Yellow solid; mp: 210 °C. ^{1}H NMR ($CDCl_3$): δ 1.75–2.35 (m, 6H, ring proton), 2.32 (s, 3H, $–CH_3$), 4.13–4.21 (m, H_1), 4.70–4.72 (m, H_3), 4.23

(d, H_2, $J = 7.8$), 6.83–7.71 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 13.93, 17.11, 28.81, 30.23, 30.59, 36.43, 67.89, 76.11, 95.85, 115.18, 117.23, 118.74, 119.41, 123.58, 126.79, 127.22, 130.75, 152.13. MS: $m/z = 358.39$ (M^+). Anal. calcd. for $C_{23}H_{22}N_2O_2$: C, 77.07; H, 6.19; N, 7.82%. Found: C, 76.93; H, 6.08; N, 8.03%.

5,11a,15b-*cis*-Indan-1-one[3,2-c]-5,11a,12,13,14,15b-octahydro-1*H*-pyrano[2,3,4-*kl*]xanthene

Yellow crystalline solid; mp: 170 °C. ^1H NMR ($CDCl_3$): δ 1.57–2.27 (m, 6H, ring proton), 4.14–4.15 (m, H_1), 4.71–4.72 (m, H_3), 4.11 (d, H_2, $J = 5.0$), 4.23 (d, H_2, $J = 7.8$), 6.81–7.73 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 15.70, 18.76, 30.47, 31.88, 32.31, 38.14, 69.61, 76.61, 77.77, 97.59, 116.78, 119.12, 120.42, 121.12, 125.40, 128.51, 128.91, 132.43, 138.66, 147.17, 148.25, 153.86. MS: $m/z = 229.21$ (M^+). Anal. calcd. for $C_{22}H_{18}O_3$: C, 79.98; H, 5.49. Found: C, 79.79; H, 5.61%.

5,11a,15b-*trans*-Indan-1-one[3,2-c]-5,11a,12,13,14,15b-octahydro-1*H*-pyrano[2,3,4-*kl*]xanthene

Yellow crystalline solid, mp: 225 °C. ^1H NMR ($CDCl_3$): δ 1.57–2.27 (m, 6H, ring proton), 4.14–4.15 (m, H_1), 4.71–4.72 (m, H_3), 4.11 (d, H_2, $J = 5.0$), 4.23 (d, H_2, $J = 7.8$), 6.81–7.73 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 15.70, 18.76, 30.47, 31.88, 32.31, 38.14, 69.61, 76.61, 77.77, 97.59, 116.78, 119.12, 120.42, 121.12, 125.40, 128.51, 128.91, 132.43, 138.66, 147.17, 148.25, 153.86. MS: $m/z = 229.18$ (M^+). Anal. calcd. for $C_{22}H_{18}O_3$: C, 79.98; H, 5.49. Found: C, 79.76; H, 5.62%.

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