



An efficient synthesis of pyrano [4,5-*c*] pyrrole derivatives through microwave–accelerated intramolecular Knoevenagel hetero Diels–Alder reaction

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ARTICLE INFO

Article history:

Received 7 August 2009

Revised 18 September 2009

Accepted 23 September 2009

Available online 27 September 2009

Keywords:

Hetero Diels–Alder reaction

N-Substituted aldehydes

1,3-Diones

Microwave

Pyrano[4,5-*c*]pyrroles

ABSTRACT

Synthesis of novel pyranopyrrole derivatives has been achieved by a one-pot IMHDA reaction of N-substituted aldehydes with various diones in the presence of ethylene diaminediacetate (EDDA) in excellent yields under mild conditions.

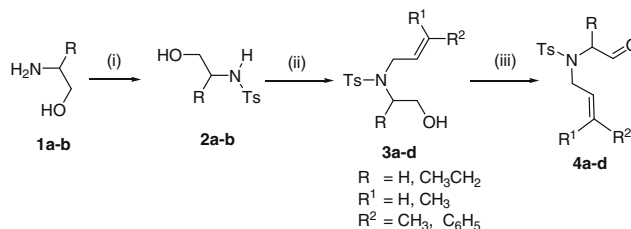
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The intramolecular Diels–Alder reaction is a widely used method for the synthesis of six-membered heterocyclic compounds.^{1a–e} Many heterocycles such as quinolines, pyrroles, and pyrans have received enormous attention from synthetic chemists from the standpoint of both their preparation and their reactivity. The synthesis of pyran and its hydrogenated form has gained importance, since many natural products such as carbohydrates, talaromycines, milbemycines, avermectins, pheromones, and iridoids contain pyran skeleton^{2a–e} and possess interesting biological activities with potential medical applications.^{3a,b} The domino hetero Diels–Alder reaction is one of the most important methods for the construction of heterocyclic compounds.^{4a–h} In the present work, we propose to utilize hetero Diels–Alder reaction as a tool for the construction of pyranopyrroles which are structurally related to natural products. Symmetrical 1,3-diones as heterodienes have been subjected to intramolecular cycloaddition reaction for the synthesis of complex polycyclic heterocycles.⁵ A number of reports are available for the synthesis of pyrans and their benzopyran analogues but there is no literature available on pyranopyrrole derivatives.^{6a–f}

In the course of our investigation directed toward the synthesis of pyrrole derivatives, herein we report a precise and new route for the synthesis of pyranopyrrole derivatives based on tandem Knoevenagel HDA reaction. Domino hetero Diels–Alder reaction has been well exploited by Tietze for the synthesis of polycyclic compounds.^{7a,b} In

our present study, we have used *N*-alkenyl aldehyde for the first time in an intramolecular hetero Diels–Alder reaction for the synthesis of pyranopyrrole derivatives in a stereoselective manner.

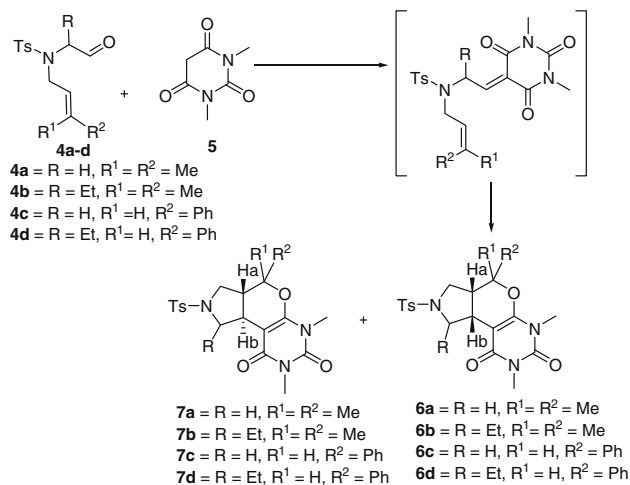
The strategy we have developed begins with the reaction of cyclic 1,3-dicarbonyl compounds and *N*-alkenyl aldehydes in the presence of EDDA in toluene. The required substrates for hetero Diels–Alder reaction were prepared in three steps from commercially available starting materials. In the first step, sulfonylation of ethanolamines **1a–b** with tosyl chloride under standard PTC reaction conditions proceeded well to provide the sulfonamide derivatives **2a–b**. N-Alkylation of sulfonamides **2a–b** with prenyl bromide/cinnamyl bromide in the presence of potassium carbonate yielded *N*-tosyl-*N*-prenyl/cinnamyl-aminoethanols **3a–d** which on oxidation with IBX in DMSO afforded the required *N*-alkenyl aldehydes **4a–d** in good yield (98%) (Scheme 1).



Scheme 1. Synthesis of *N*-alkenyl aldehydes. Reagents and conditions: (i) TBAB, 10% NaOH/benzene, tosyl chloride, 0 °C–rt; 8 h, 90%; (ii) prenyl/cinnamyl bromide, K₂CO₃/acetone, 12 h, 90%; (iii) iodoxybenzoic acid, DMSO, 2–2.5 h, 98%.

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Scheme 2. Synthesis of pyranopyrroles through IMKHDA reaction. Reagents and conditions: Method A: EDDA, toluene, reflux; Method B: toluene, MW.

The alkenyl aldehydes so obtained were reacted with 1,3-diones under suitable reaction conditions to achieve the synthesis of pyranopyrrole ring systems through intramolecular Knoevenagel hetero Diels–Alder reaction. Thus, the reaction of alkenyl aldehyde **4a** with barbituric acid **5** in the presence of EDDA in reflux in toluene proceeded through intramolecular Knoevenagel HDA pathway to afford a mixture of pyranopyrrole **6a** and **7a** (35:65) with an overall yield of 62%. The products were separated by column chromatography and the structures were assigned on the basis of spectroscopic studies. The ¹H NMR spectrum of compound **6a** exhibited two singlets at δ 1.22 and 1.49 for geminal

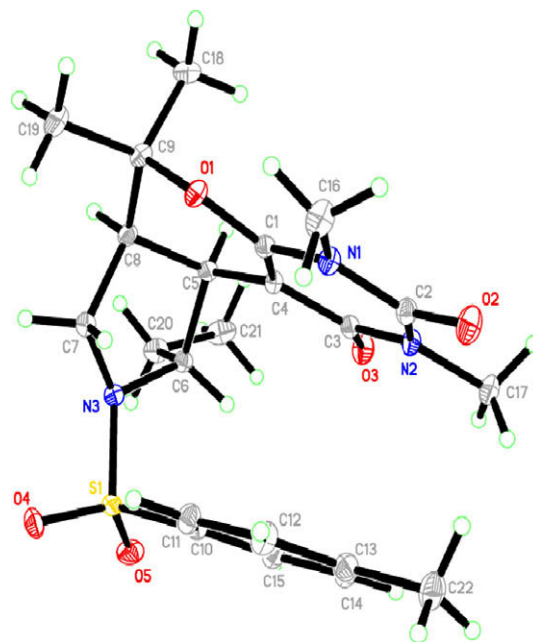


Figure 1. ORTEP diagram of **6b**.

dimethyl protons, a singlet at δ 2.42 for the aromatic methyl, and two singlets at δ 3.27 and 3.28 for *N*-CH₃ protons of the pyrimidine ring. The *N*-CH₂ protons of the pyrrolidine ring were observed as multiplets in 2.96–3.04 (2H) and two doublet of doublets at δ 3.58 (J = 9.0, 9.0, 1H) and δ 4.36 (J = 6.0, 9.0, 1H). Particularly diagnostic were the protons Ha and Hb situated at the ring

Table 1

Reaction times and yields of the domino reactions of **4a–d** with **5** under various conditions

Entry	Aldehydes	1,3-Diones	Conditions	Ratio of the products			
				Time	Cis	Trans	Overall yield (%)
1			Method A	6 h	35	65	62
			Method B	2 min	30	70	74
2			Method A	6 h	20	80	67
			Method B	2 min	15	85	80
3			Method A	6 h	35	65	60
			Method B	2 min	30	70	72
4			Method A	6 h	33	67	63
			Method B	2 min	25	75	75

Reaction conditions: Method A: toluene, reflux; Method B: toluene, MW.

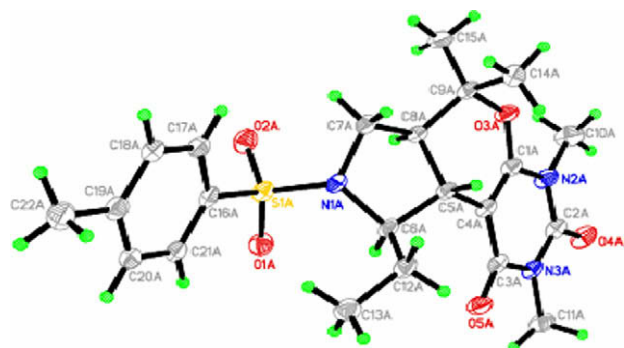


Figure 2. ORTEP diagram of 7b.

junctions showing doublets of triplets at δ 1.89 ($J = 6.0, 12.0$) and δ 2.48 ($J = 6.0, 12.0$), respectively. On the other hand, the ^1H NMR spectrum of **7a** exhibited one doublet of triplet at δ 2.59 ($J = 9.0, 9.0$) and one multiplet at δ 2.96–3.04 for Ha and Hb protons, respectively. The low value of the coupling constant (6 Hz) between Ha and Hb in **6a** indicated the cis fusion at the ring junctions. Similar type of δ values were observed for trans product **7a**, but the trans fusion at the ring junction was discerned by the high coupling constant value (9 Hz).

To improve the reaction yields and chemoselectivity, we carried out the reaction under microwave conditions.^{8a–f} We were pleased to find that the reaction in toluene under microwave irradiation without base worked well to provide adducts **6a** and **7a** (30:70) with an overall yield of 74%. Thus, there was an increase in the

Table 2

Reaction times and yields of the domino reactions of **4a–d** with various symmetrical 1,3-diones under various conditions

Entry	Aldehydes	1,3-Diones	Conditions	Ratio of the products			
				Time	Cis	Trans	Overall yield (%)
1	 4a	 8	Method A	6 h	31	69	63
			Method B	2 min	30	70	75
2	 4b	 8	Method A	6 h	25	75	66
			Method B	2 min	20	80	80
3	 4c	 8	Method A	6 h	23	77	60
			Method B	2 min	15	80	77
4	 4d	 8	Method A	6 h	19	81	64
			Method B	2 min	15	85	81
5	 4a	 11	Method A	8 h	18	80	57
			Method B	2.5 min	15	85	68
6	 4b	 11	Method A	8 h	17	83	60
			Method B	2 min	15	85	75

Table 2 (continued)

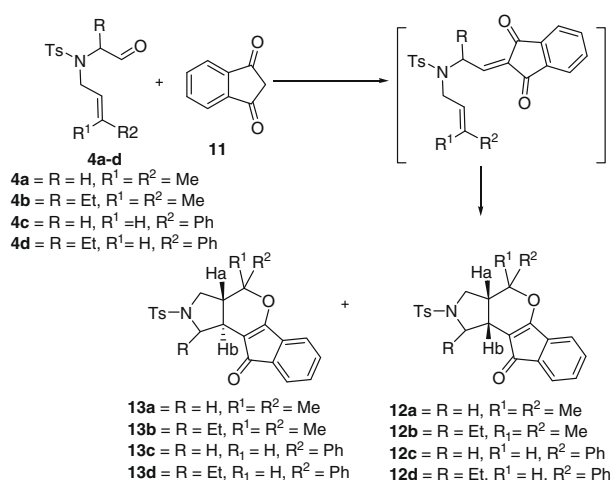
Entry	Aldehydes	1,3-Diones	Conditions	Ratio of the products			
				Time	Cis	Trans	Overall yield (%)
7			Method A	8 h	12	88	58
			Method B	2.5 min	10	90	68
8			Method A	8 h	15	85	63
			Method B	2.5 min	11	89	72

Reaction conditions: Method A: toluene, reflux; Method B: toluene, MW.

chemical yield with a slight improvement in the chemoselectivity. Encouraged by these findings, we expanded the scope of the hetero Diels–Alder reaction by changing the alkenyl substituent of the internal dipolarophile. Thus, the reaction of **4b** with barbituric acid **5** (Scheme 2) was tested under optimized reaction conditions and the results are summarized in Table 1. The substrate **4b** also reacted in the same way as **4a**, but gave better yield of the product in shorter duration of time. These results show the efficiency of the prenyl-substituted dienophile.

Having optimized the reaction conditions for the stereoselective synthesis of pyrano[4,5-*c*]pyrrole derivatives, we conducted the intramolecular Knoevenagel hetero Diels–Alder reaction by employing various symmetrical diones, namely dimedone and indane-1,3-dione with aldehydes **4a–d** (Schemes 3 and 4). The results are summarized in Table 2. The intramolecular Knoevenagel hetero Diels–Alder reaction of **4a–d** with indane-1,3-dione in refluxing toluene completed in 6 h (Scheme 4). As observed in the former case, we readily isolated the expected *cis* and *trans* pyrano[4,5-*c*]pyrrole derivatives simply by changing from toluene/reflux conditions to microwave irradiation.⁹

The structures of the *cis* and *trans* products were determined on the basis of detailed 2D NMR studies. The structures of the cycloadducts were further unambiguously supported by the single crystal



Scheme 4. Synthesis of pyranopyrroles through IMKHA reaction. Reagents and conditions: Method A: toluene, reflux; Method B: toluene, MW.

X-ray diffraction analysis of some of the products (see Figs. 1 and 2).^{10a,b} Similarly, the protocol was extended further to other 1,3-diones and alkenyl aldehydes **4a–d** to form a series of pyranopyrroles in moderate to good yields.

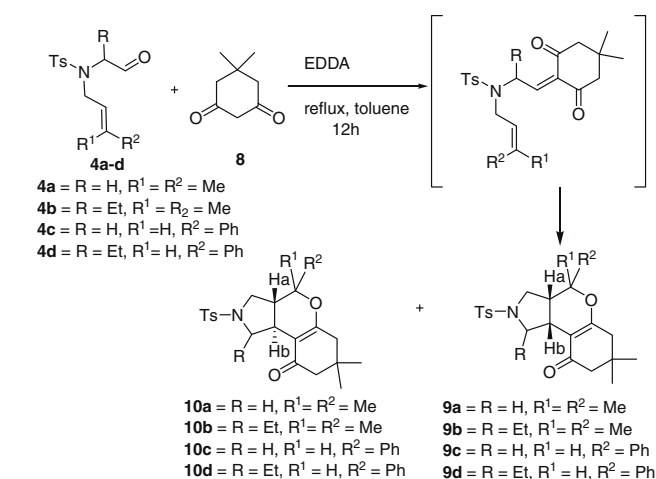
In conclusion, we have synthesized *cis* and *trans* isomers of the pyranopyrrole derivatives through intramolecular domino Knoevenagel hetero Diels–Alder reaction. The preceding studies demonstrate the scope of the intramolecular Knoevenagel hetero Diels–Alder reaction for the synthesis of *cis* and *trans* pyrrolo pyrrole products. We have shown that use of microwave irradiation improves the overall yield of the products as well as stereoselectivity.

Acknowledgment

M.J. and R.R. thank UGC New Delhi for financial support. We are grateful to Dr. K.K. Balasubramanian, Shasun Chemicals Ltd. for Microwave Synthesiser facility.

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Scheme 3. Synthesis of pyranopyrroles through IMKHA reaction. Reagents and conditions: Method A: toluene, reflux; Method B: toluene, MW.

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 - General procedure for the intramolecular domino Knoevenagel hetero Diels–Alder reaction:** Method A: To a solution of 4-hydroxyquinolinone (1 mmol) in toluene the corresponding 2(*N*-prenyl-*N*-tosylamino)acetaldehyde (1 mmol) and the base EDDA (1 mmol) were added and the reaction mixture was refluxed, till the completion of the reaction. The solvent was then evaporated under reduced pressure and the residue was subjected to column chromatography using hexane–ethyl acetate (7.5:2.5) mixture.
Method B: A solution of 1,3-diones (1 mmol) and the corresponding aldehyde (1 mmol) in toluene (2 ml) without base was irradiated with microwave (MODEL = Chem Discover benchmate microwave 300 W, *P* = 100, *T* = 110 °C, 20 MHz) until the TLC showed the disappearance of the starting material. After removal of the solvent, the crude reaction mixture was subjected to column chromatography using hexane–ethyl acetate (7.5:2.5) mixture.
Representative spectral data of the products; Compound **6a**: white solid; mp: 180–182 °C; IR (KBr): 1695.3, 1637.4, 1340.4, 1159.1 cm^{−1}; ¹H NMR (300 MHz, CDCl₃) δ 1.22 (s, 3H), 1.49 (s, 3H), 1.89 (dt, *H*_a, *J* = 6.0, 12.0 Hz), 2.42 (s, 3H), 2.48 (dt, *H*_a, *J* = 6.0, 12.0 Hz), 2.96–3.04 (m, 2H), 3.27 (s, 3H), 3.28 (s, 3H), 3.58 (dd, 1H, *J* = 9.0, 9.0 Hz), 4.36 (dd, 1H, *J* = 6.0, 9.0 Hz), 7.33 (d, 2H, *J* = 9.0 Hz), 7.40 (d, 2H, *J* = 6.0 Hz); ¹³C NMR: 20.67, 21.49, 27.70, 28.16, 28.96, 33.81, 47.63, 49.65, 52.20, 83.87, 86.54, 127.26, 129.82, 134.54, 143.57, 150.97, 155.79, 161.92. MS *m/z*: 419.79 (M⁺); Anal. Calcd for C₂₀H₂₅N₃O₅S: C, 57.19; H, 5.97; N, 9.98. Found: C, 57.31; H, 6.12; N, 10.10.
Compound **7a**: white solid; mp: 160–162 °C; IR (KBr): 1695.3, 1647.1, 1342.4, 1159.1 cm^{−1}; ¹H NMR (300 MHz, CDCl₃) δ 1.24 (s, 3H), 1.41 (s, 3H), 2.40 (s, 3H), 2.59 (dt, *H*_a, *J* = 9.0, 9.0 Hz), 2.96–3.04 (m, 2H), 3.14 (s, 3H), 3.20 (s, 3H), 3.58–3.65 (m, 2H), 3.98 (d, 1H, *J* = 12.0 Hz), 7.17 (d, 2H, *J* = 9.0 Hz), 7.57 (d, 2H, *J* = 9.0 Hz); ¹³C NMR: 21.57, 25.02, 26.25, 27.61, 28.13, 30.87, 32.68, 45.21, 47.34, 51.74, 80.45, 85.07, 127.26, 128.91, 133.57, 143.73, 150.42, 154.18, 162.21. MS *m/z*: 419.86 (M⁺); Anal. Calcd for C₂₀H₂₅N₃O₅S: C, 57.28; H, 6.00; N, 10.02. Found: C, 57.12; H, 6.11; N, 10.18.
Compound **9a**: white solid; mp: 146–148 °C; IR (KBr): 1619.4, 1334.7, 1155.1 cm^{−1}; ¹H NMR (300 MHz, CDCl₃) δ 1.01 (s, 6H), 1.09 (s, 3H), 1.36 (s, 3H), 1.78 (dt, *H*_a, *J* = 6.0, 12.0 Hz), 2.18 (m, 5H), 2.42 (s, 3H), 2.89 (m, H, *H*_b), 3.51 (dd, 1H, *J* = 6.0, 9.0 Hz), 4.33 (dd, 1H, *J* = 6.0, 12.0 Hz), 7.31 (m, 2H), 7.73 (d, 2H, *J* = 6.0 Hz); ¹³C NMR: 20.54, 21.51, 27.90, 28.28, 28.59, 32.04, 33.67, 42.44, 47.56, 49.75, 50.45, 52.09, 80.07, 109.75, 127.26, 129.74, 134.82, 143.34, 169.66, 196.66. MS *m/z*: 403.32 (M⁺); Anal. Calcd for C₂₂H₂₉NO₄S: C, 65.32; H, 7.21; N, 3.42. Found: C, 65.45; H, 7.10; N, 3.50.
Compound **10a**: white solid; mp: 199–201 °C; IR (KBr): 1612.2, 1334.6, 1159.1 cm^{−1}; ¹H NMR (300 MHz, CDCl₃) δ 0.736 (s, 3H), 0.94 (s, 3H), 1.17 (s, 3H), 1.29 (s, 3H), 1.87–2.11 (m, 4H), 2.39–2.45 (m, 1H), 2.40 (s, 3H), 2.87 (t, 1H, *J* = 9.0 Hz), 2.98 (t, 1H, *J* = 6.0), 3.37–3.41 (distorted dt, 1H, *J* = 3.0, 12.0 Hz), 3.50–3.64 (m, 2H), 7.28 (d, 2H, *J* = 6.0 Hz), 7.65 (d, 2H, *J* = 6.0 Hz); ¹³C NMR: 21.47, 25.17, 26.36, 27.56, 28.30, 31.80, 31.86, 42.67, 45.30, 47.46, 50.70, 52.30, 80.05, 109.27, 127.65, 129.61, 134.65, 143.15, 168.53, 197.48. MS *m/z*: 403.92 (M⁺); Anal. Calcd for C₂₂H₂₉NO₄S: C, 65.41; H, 7.16; N, 3.37. Found: C, 65.52; H, 7.26; N, 3.52.
Compound **12a**: white solid; mp: 149–151 °C; IR (KBr): 1721.1, 1335.7, 1158.1 cm^{−1}; ¹H NMR (300 MHz, CDCl₃) δ 1.24 (s, 3H), 1.52 (s, 3H), 1.80 (dt, *H*_a, *J* = 9.0, 12.0 Hz), 2.28–2.38 (m, 1H), 2.95–3.05 (m, 2H), 3.57 (dd, *H*_a, *J* = 6.0, 12.0 Hz), 4.17 (dd, 1H, *J* = 6.0, 12.0 Hz), 7.07–7.76 (m, 8ArH); ¹³C NMR: 20.64, 21.50, 27.98, 33.05, 47.64, 50.63, 50.70, 83.57, 106.47, 118.13, 121.14, 127.30, 129.84, 130.31, 131.88, 133.10, 134.66, 137.44, 143.61, 174.06. MS *m/z*: 409.43 (M⁺); Anal. Calcd for C₂₃H₂₃NO₄S: C, 67.31; H, 5.68; N, 3.28. Found: C, 67.43; H, 5.51; N, 3.39.
Compound **13a**: white solid; mp: 171–173 °C; IR (KBr): 169.3, 1334.7, 1159.1 cm^{−1}; ¹H NMR (300 MHz, CDCl₃) δ 1.30 (s, 3H), 1.46 (s, 3H), 2.00 (s, 3H), 2.52 (dt, *H*_a, *J* = 6.0, 12.0 Hz), 2.90 (t, 1H, *J* = 12.0), 2.97 (t, 2H, *J* = 6.0 Hz), 3.55–3.64 (m, 2H), 3.57 (d, 1H, *J* = 12.0 Hz), 6.91–7.53 (m, 8ArH); ¹³C NMR: 21.42, 25.83, 26.44, 31.13, 45.95, 46.79, 50.74, 80.63, 106.54, 117.72, 120.74, 127.16, 129.32, 129.99, 131.78, 133.28, 137.41, 143.46, 172.61. MS *m/z*: 409.36 (M⁺); Anal. Calcd for C₂₃H₂₃NO₄S: C, 67.49; H, 5.51; N, 3.45. Found: C, 67.60; H, 5.62; N, 3.59.
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