

Stereoselective intramolecular hetero Diels–Alder reactions of 1-oxa-1,3-butadienes: a novel approach for the synthesis of complex annulated uracils

Ipsita Devi and Pulak J. Bhuyan*

Medicinal Chemistry Division, Regional Research Laboratory, Jorhat 785006, Assam, India

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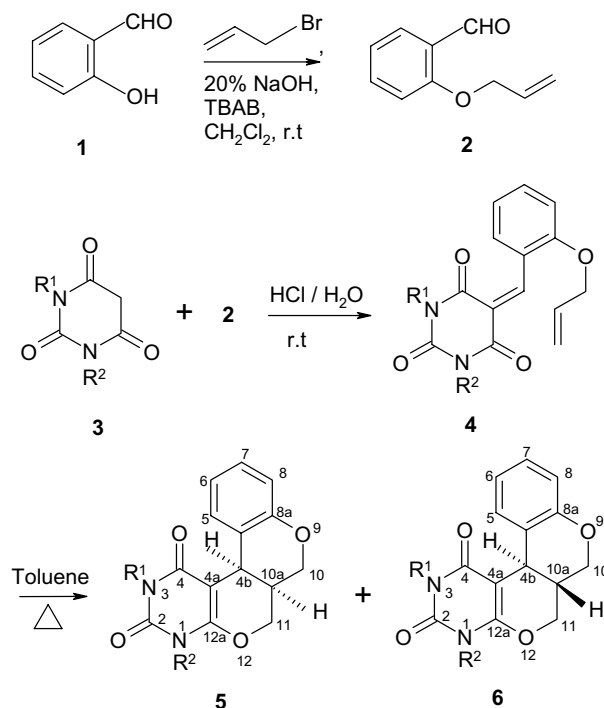
Abstract—The intramolecular hetero Diels–Alder reactions of 1-oxa-1,3-butadienes **4**, obtained from salicylaldehyde **1** via *O*-allylation followed by Knoevenagel condensation with barbituric acids **3** in the presence of hydrochloric acid as catalyst, affords the tetracyclic uracil derivatives **5** and **6** in a stereoselective manner and high overall yields.

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Hetero Diels–Alder reactions¹ are becoming a mainstay of heterocyclic and natural product synthesis. Among these reactions, the oxa-butadiene Diels–Alder reaction² provides a means for construction of functionalised heterocycles in a regio- and stereoselective manner.

Uracil and its annulated derivatives are well recognised by synthetic as well as biological chemists.³ The preparation of naturally occurring complex molecules containing a uracil ring poses significant synthetic challenges.⁴ In this regard the synthetic exploitation of the nucleophilic double bond of uracil is an important strategy for the synthesis of a variety of potential products.⁵ In our continuing interest in the development of highly expedient methods for the synthesis of annulated uracils⁶ of biological importance, we recently reported a novel intermolecular [4+2] cycloaddition reaction⁷ via in situ generation of the heterodiene at the C-5 and C-6 positions of uracils. In the present communication we report a novel intramolecular hetero Diels–Alder approach to the synthesis of complex tetracyclic annulated uracils in a stereoselective manner with excellent yields (Scheme 1).

Our synthetic strategy utilising 1-oxa-1,3-butadienes **4**, which were synthesised from salicylaldehyde **1** via *O*-allylation followed by acid catalysed Knoevenagel



Scheme 1.

condensation with barbituric acids **3**, under thermolytic conditions afforded the tetracyclic *cis* annulated uracils **5** in high yields along with the *trans* fused compounds **6** as minor products.

Keywords: Intramolecular hetero Diels–Alder reaction; Uracil; 1-Oxa-1,3-butadiene; Stereoselective synthesis.

* Corresponding author. Tel.: +91 376 2370121; fax: +91 376 2370011; e-mail: pulak_jyoti@yahoo.com

Table 1. Intramolecular hetero Diels–Alder reactions of 1-oxa-1,3-butadienes **4a–4c**

Entry	Product	R ¹	R ²	Reaction time (h)	Mp (°C)	Yield (%)
1	5a	CH ₃	CH ₃	12	189	75
2	6a	CH ₃	CH ₃	12	146	5
3	5b	H	CH ₃	16	198	70
4	6b	H	CH ₃	16	181	5
5	5c	H	H	18	251	65
6	6c	H	H	18	226	4

Allylation of salicylaldehyde⁸ was accomplished using the phase transfer catalyst TBAB (tetrabutylammonium bromide) in a two-phase system of dichloromethane and 20% aqueous sodium hydroxide. The acid catalysed (HCl) condensation of the aldehyde **2** and barbituric acid **3a** in aqueous medium afforded compound **4a**⁹ in quantitative yield. The structure of **4a** was confirmed from spectroscopic data. Heating¹⁰ **4a** in refluxing toluene for 12h, afforded a mixture of the *cis* hetero Diels–Alder adduct **5a** (75%) and its *trans* fused stereoisomer **6a** (5%) in overall high yields. The structures of the adducts were confirmed from spectroscopic data and elemental analyses. The stereochemistries were determined from the coupling constants of the protons H-4b and H-10a (for the *cis*-isomer $J = 3.0$ Hz and for the *trans*-isomer $J = 9.0$ Hz). Both stereoisomers **5a** and **6a** exhibited strong molecular ion peaks at $(M+H)^+$ 301 (employing the positive ionisation technique).

Similarly, compounds **4b** and **4c** were synthesised by utilising **2** and barbituric acids **3b** and **3c** under acidic conditions. On refluxing in toluene, **4b** and **4c** afforded the two isomeric series of the compounds **5b** and **5c** and **6b** and **6c** as reported in Table 1. The structures of the cycloadducts were confirmed from spectroscopic data and elemental analyses.

In conclusion, the results delineated here demonstrate a novel intramolecular hetero Diels–Alder reaction of 1-oxa-1,3-butadienes and the synthesis of complex annulated uracils in a stereoselective manner and in overall high yields.

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- To a stirred solution of *N,N*-dimethyl barbituric acid **3a** (280mg, 0.18mmol) in aqueous HCl (23mL, 13%), was added allylated aldehyde **2** (300mg) dropwise at room temperature. After stirring for 1.5h the precipitated light yellow solid was filtered and washed with hot water and ethanol. The resulting material was obtained in 90% yield (488mg) after drying and was confirmed as **4a** from spectroscopic data. Mp 145–146°C. ¹H NMR 90MHz (CDCl₃): δ 3.15 (s, 3H), 3.25 (s, 3H), 4.45 (d, $J = 9.0$, 2H), 5.25 (m, 2H), 5.75–6.20 (m, 2H), 6.50–7.20 (m, 4H). ν_{\max} (KBr): 1675, 1700, 1745 cm⁻¹. $(M+H)^+$ 301. Similarly compounds **4b** and **4c** were synthesised by reaction of **3b** and **3c** with **2**. Compound **4b** mp 135°C (yield 87%); **4c** mp 189°C (85%).
- Compound **4a** (200mg) was allowed to reflux in toluene (8mL) at 110°C for 12h. After completion of the reaction (monitored by TLC) the solvent was removed under reduced pressure. The residue was purified by preparative TLC using: hexane ethyl acetate (3:2) as eluent, to give **5a** (150mg, 75% yield) and **6a** (10mg, 5% yield). Compound **5a**: Mp 189°C. ¹H NMR 300MHz (CDCl₃): δ 2.35 (m, 1H), 3.32 (s, 3H), 3.44 (s, 3H), 4.33 (m, 4H), 4.65 (d, 1H, $J = 3.0$ Hz), 6.75–7.46 (m, 4H). ¹³C NMR 75MHz (CDCl₃): δ 164.1 (C-12a), 156.1 (C-2), 151.8 (C-4), 150.8, 130.5, 128.0, 123.0, 121.7, 116.7 (Ph), 90.3 (C-4a), 67.8 (C-10), 65.5 (C-11), 30.5 (N–CH₃), 29.5 (C-10a), 28.8 (N–CH₃), 28.3 (C-4b). ν_{\max} (KBr): 1575, 1705 cm⁻¹. $(M+H)^+$ 301. CHN analysis (calcd %) C, 64.00; H, 5.37; N, 9.33; (C₁₆H₁₆N₂O₄) (found %) C, 64.23; H, 5.30; N, 9.39. Compound **6a**: Mp 146°C. ¹H NMR 300MHz (CDCl₃): δ 2.35 (m, 1H), 3.30 (s, 3H), 3.42 (s, 3H), 4.31 (m, 4H), 4.65 (d, 1H, $J = 9.0$ Hz), 6.74–7.45 (m, 4H). ¹³C NMR 75MHz (CDCl₃): δ 163.1 (C-12a), 156.1 (C-2), 152.8 (C-4), 147.8, 130.5, 129.0, 123.0, 120.7, 116.7 (Ph), 90.3 (C-4a), 66.8 (C-10), 65.5 (C-11), 31.5 (N–CH₃), 29.5 (C-10a), 28.7 (N–CH₃), 28.3 (C-4b). ν_{\max} (KBr): 1575, 1705 cm⁻¹. $(M+H)^+$ 301. CHN analysis (calcd %) C, 64.00; H, 5.37; N, 9.33; (C₁₆H₁₆N₂O₄) (found %) C, 64.12; H, 5.32; N, 9.37.