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Stereoselective intramolecular hetero Diels–Alder reactions of 1-oxa-1,3-butadienes: synthesis of novel annelated pyrrolo[1,2-*a*]indoles

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Abstract—Novel classes of pyrano-1,3-dioxane-, pyranopyrimidine- and pyranopyrazole-fused pyrrolo[1,2-*a*]indoles are synthesised via stereoselective intramolecular 1-oxa-1,3-butadiene hetero Diels–Alder reactions.

The mitomycins are an important class of naturally occurring heterocyclic antitumour antibiotics that possess a 2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indole unit as the basic skeleton.[1] Subsequent to the discovery and total synthesis of mitomycin C, a number of compounds have been synthesised by molecular modifications at the pyrrolo[1,2-*a*]indole without significant loss of biological activity.[2] Therefore, large efforts have been directed towards the synthesis of functionalised pyrrolo[1,2-*a*]indole derivatives as mitomycin analogues and as a result, numerous heterocycle-annelated pyrrolo[1,2-*a*]indole derivatives have been reported.[3] Substituted indoles and hydroxybenzenes are typically used as the starting materials for the synthesis of these molecules.[4] In an earlier publication[5] we reported the synthesis of novel dihydro- and tetrahydroisoxazole fused pyrrolo[1,2-*a*]indoles as mitomycin analogues via intramolecular 1,3-dipolar cycloaddition reactions, which could be subsequently transformed into azirdines.

Hetero Diels–Alder reactions are becoming a mainstay of heterocyclic and natural product synthesis.[6] Among these reactions the oxa-butadiene Diels–Alder reaction provides a means for the construction of functionalised heterocycles in a regio- and stereoselective manner.[7] As part of our interest in this area,[8] we report here the synthesis of novel classes of pyrano-1,3-dioxane-, pyranopyrimidine- and pyranopyrazole-fused pyrrolo[1,2-*a*]indoles as mitomycin analogues via intramolecular oxabutadiene hetero Diels–Alder reactions (Scheme 1).

2-Formyl-3-methyl-*N*-allylindole **2** was synthesised from 3-methylindole **1** by *N*-allylation with allyl bromide under phase transfer catalytic conditions followed by Vilsmeier formylation.[5] Treatment of **2** with Meldrum's acid **3a** in the presence of a catalytic amount of piperidine in ethanol afforded the 1-oxa-1,3-butadiene **4a** in high yield.[9] The structure of **4a** was confirmed from spectroscopic data. Heating **4a** in refluxing toluene for 6 h. afforded the *cis* hetero Diels–Alder cycloadduct **5a** as the sole adduct in excellent yield.[10] The structure of the compound was ascertained from spectroscopic data and elemental analysis. The stereochemistry was determined as *cis* from the coupling constant of proton H-5b ($J = 3$) with H-11a. The mass spectrum of compound **5a** exhibited a strong ion at 326 $(M+H)^+$.

The reaction was then extended by generating the oxabutadienes **4b–d** from the condensation of **2** with barbituric acids **3b–d** in the presence of HCl. On refluxing in toluene, **4b–d** afforded the *cis* hetero Diels–Alder adducts **5b–d** in high yields (Table 1). The structures of the cycloadducts were confirmed from spectroscopic data and elemental analysis. The reaction was further extended by reacting 1-phenyl-3-methylpyrazol-5-one **6** with **2** in the presence of piperidine as catalyst. The isolated oxabutadiene **7** (80% yield), on refluxing in toluene, gave the cycloadduct **8**, but only in a poor yield (48%). However, when the reaction was performed in xylene, a better yield of the cycloadduct was obtained

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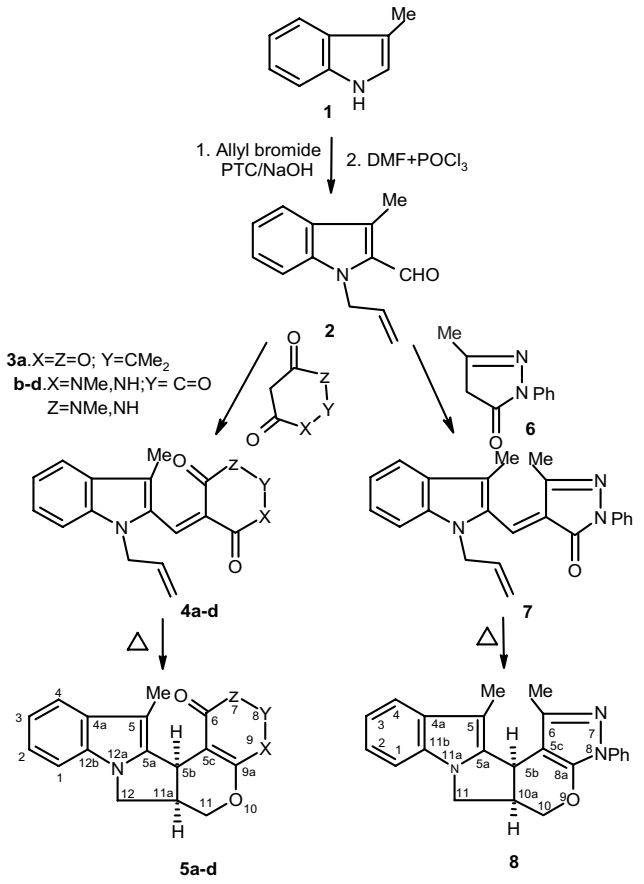

Scheme 1.

Table 1.

Compound	X	Y	Z	Reaction time (h)	Mp °C	Yield
5a	O	CMe_2	O	6	225	85
5b	NMe	C=O	NMe	8	328	85
5c	NH	C=O	NH	8	>330	80
5d	NMe	C=O	NH	8	>330	78
8	—	—	—	10	315	48

(63%). The structure of the compound was confirmed from spectroscopic data and elemental analysis.

In conclusion, the results delinesated here demonstrates the synthesis of novel classes of annulated pyrrolo[1,2-*a*]indoles in excellent yields via stereoselective intramolecular hetero Diels–Alder reactions of oxa-butadienes. The presence of the C-5 methyl group in the annelated pyrrolo[1,2-*a*]indoles enhances their importance due to the possibility of side chain manipulations. Further study of the reaction is in progress.

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9. An equimolar amount of 1-allyl-2-formyl-3-methylindole **2** (0.796 g, 4 mmol) and Meldrum's acid **3a** (0.576 g, 4 mmol) in the presence of one drop of piperidine in ethanol (15 mL) was stirred at room temperature for 4 h. The solid product appeared in the clear solution while stirring. The reaction mixture was cooled in ice water, filtered, the precipitate washed with a small amount of cold ethanol and dried to give **4a** (1.15 g, 90%). Mp. 135 °C. ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.50 (s, 6H), 2.30 (s, 3H), 4.20 (d, J = 9.0, 2H), 5.30 (m, 2H), 5.80–6.20 (m, 2H), 6.75–7.20 (m, 4H). ν_{max} (KBr): 1780 cm^{-1}. *m/z* 326 $(M+H)^+$.
10. Compound **4a** (500 mg) was heated at reflux in toluene (15 mL) for 6 h. After completion of the reaction (monitored by TLC), the solvent was removed under reduced pressure. The solid compound obtained was purified by column chromatography (silica gel 60–120 mesh) using chloroform as eluent, giving **5a** (0.425 g, 85%) Mp 225 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40 (s, 3H), 1.50 (s, 3H), 2.36 (s, 3H), 3.25 (m, 1H), 4.02 (d, J = 4.0, 2H), 4.20 (d, J = 3.8, 2H), 4.65 (d, J = 3.0, 1H), 6.75–7.46 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.0 (C-12b), 157.1 (C-9a), 152.4 (C-6), 132.8 (C-5a), 126.6, 124.4, 122.0, 120.4 (Ph), 120.2 (C-4a), 112 (C-5), 90.3 (C-5c), 63.5 (C-11), 52.0 (C-8), 37.4 (C-12), 29.6 (C-11a), 28.5 (C-5b), 27.2, 26.5, 23.0 (CH_3). ν_{max} (KBr): 1775 cm^{-1}. *m/z* 326 $(M+H)^+$. Analysis (calcd %) C, 70.15; H, 5.84; N, 4.30; ($C_{19}H_{19}NO_4$) (found %) C, 70.23; H, 5.70; N, 4.50%. Compound **8**, mp 315 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.36 (s, 3H), 2.95 (s, 3H), 3.18 (m, 1H), 4.05 (d, J = 4.2, 2H), 4.23 (d, J = 3.9, 2H), 4.68 (d, J = 3.0, 1H), 6.70–7.46 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.8 (C-11b), 153.2 (C-8a), 135.1

(C-6), 132.8 (C-5a), 126.6, 126.3, 125.2, 124.8, 124.3, 123.8, 123.4, 122.6, 122.0, 120.4 (Arom), 120.5 (C-4a), 112 (C-5), 89.5 (C-5c) 64.0 (C-10), 38.4 (C-11), 31.5 (CH_3), 30.1 (C-10a), 29.0 (C-5b), 23.2 (CH_3). *m/z* 356 $(M+H)^+$. Analysis (calcd %) C, 77.74; H, 5.90; N, 11.83; ($C_{23}H_{21}N_3O$) (found %) C, 77.70; H, 5.87; N, 11.85.