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Synthesis of dihydropyrazolo[3′,4′:3,4]pyrrolo[1,2-a]indoles and spiro-[3*H*-indole-3,3′-[Δ²-1,2,4]-triazolin]-2-ones via intra and intermolecular 1,3-dipolar cycloadditions

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Abstract—A new class of dihydropyrazolo[3′,4′:3,4]pyrrolo[1,2-a]indoles and spiro[3*H*-indole-3,3′-[Δ^2-1,2,4]-triazoline]-2-ones were synthesised via intra and intermolecular 1,3-dipolar cycloaddition reactions in good yields.

1. Introduction

The potent antitumour antibiotic mitomycins[1] have attracted a great deal of interest and a variety of molecular manipulations have been reported without loss of any significant biological activities.[2] Indeed mitomycin C is a clinically useful chemotherapeutic agent for the treatment of various tumors. Although numerous C_1-fused furan, thiophene and pyridine annelated mitomycins are reported, they have their limitations due to the fact that these heterocycles are not prone to ring transformations.[3] The indole nucleous annulated to carbocyclic or heterocyclic ring(s) is present in an astonishing variety of natural products endowed with potent and multiform biological activities.[4] Hence, new and efficient syntheses of such compounds is still important. Several syntheses of mitomycin analogues and other mitosenes have been reported.[5] Access to the pyrrolo[1,2-a]indole skeleton which is common for these compounds is generally carried out by radical cyclizations,[6] metal carbene insertions,[7] or intramolecular cyclizations.[8] The dihydropyrazoles have rich chemistry because of their ready reductive cleavage[9] and susceptibility to ring transformations.[10] We envisioned[11] the construction of a functionalised ring annulated to the 1,2-position of the indole nucleus using a cycloaddition strategy. Undoubtedly, intramolecular cycloaddition reactions have emerged as the single most powerful methodology for the construction of bicyclic and polycyclic ring systems.[12] Our approaches to the synthesis of these target molecules involves intramolecular nitrile imine cycloaddition reactions.

Keywords: Intramolecular cycloaddition; Spiroindoles; Dihydropyrazolopyrrolo indoles; Triazolines; Intermolecular cycloaddition.
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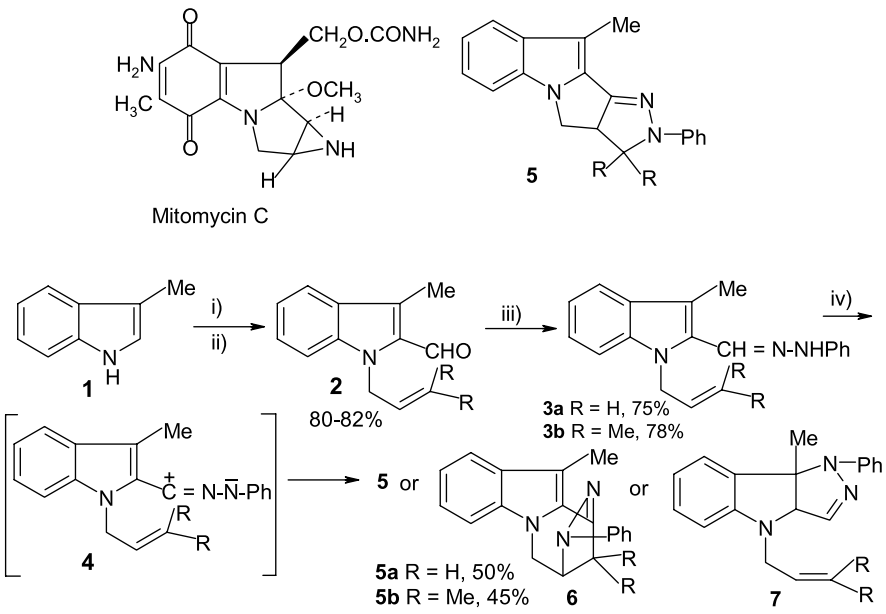
2. Results and discussion

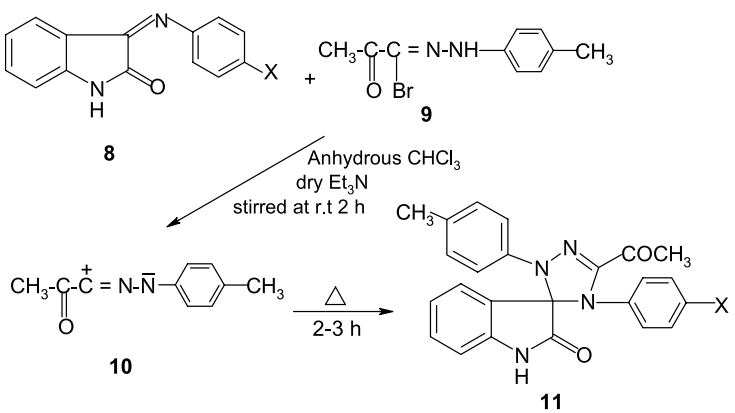
2-Formyl-3-methyl-N-allyl indoles **2** were obtained from 3-methylindole by condensation with allyl bromide under phase transfer conditions followed by in situ Vilsmeier–Haack reactions (80–82%).[13] The aldehydes **2** were further converted into their corresponding phenylhydrazones **3** in 75–78% yields by reaction with phenylhydrazine hydrochloride and sodium acetate in ethanol. Three typical methods for bromination of hydrazones **3**, namely N-bromosuccinimide (NBS) in CCl_4, Lee's method (sodium hypochlorite in sodium hydroxide solution) and NBS in DMF at low temperature (0–10 °C), were not successful (TLC showed a large number of products formed). Therefore, the nitrile imine intermediate was generated in situ by oxidation of the hydrazone **3** with lead tetraacetate in dry acetonitrile at −15 °C, which underwent intramolecular 1,3-dipolar cycloaddition with the alkene to provide 9-methyl-1-phenyl-dihydropyrazolo[3′,4′-3,4]pyrrolo[1,2-a]indole **5a** in 50% yield, without the formation of any strained bridged-ring adduct **6** or cyclized product **7**. Since the NMR spectra of the cycloadduct **5a** showed no signals typical of the allyl group, it is clear that the allylic double bond had taken part in the cycloaddition. The elemental analysis of the cycloadduct **5a** also gave satisfactory results. To further investigate the synthetic scope of this intramolecular cycloaddition strategy 4-bromo-2-methyl-but-2-ene was converted in a similar way to the corresponding cycloadduct **5b** (R=Me), isolated in 45% yield. A similar strategy has been used by Moody et al., who have synthesized various cyclopropapyrrolo[1,2-a]indole and pyrazolino indoles based on intramolecular 1,3-dipolar cycloaddition strategy.[14] In their work, the indole-2-carboxaldehyde was treated with sodium hydride in DMF followed by the appropriate allylbromide to get the corresponding *N*-allyl



Scheme 1. (i) Allylbromide, PTC; (ii) DMF/$POCl_3$; (iii) $PhNHNH_2$·HCl/CH_3COONa; (iv) $Pb(OAc)_4$/MeCN.

derivatives. This was further converted into tosylhydrazones by reaction with toluene-*p*-sulfonylhydrazide in methanol. Finally, thermolysis of the sodium salt of the tosylhydrazone in boiling chlorobenzene afforded cyclopropapyrroloindole in 27% yield. When the sodium salt was decomposed at a lower temperature in boiling benzene, the [3+2] cycloadduct, pyrrolinoindole, was obtained in 29% yield with the loss of the arylsulfonyl group. In contrast, we have performed the intramolecular dipolar cycloaddition of 3-methylindole in a much simpler way and obtained the corresponding pyrazolopyrroloindoles in 50% yield without loss of any diazo or arylsulfonyl group (Scheme 1).

In recent years, a systematic study of spiroindole has been carried out due to the increased spectrum of their biological activities.[15] The indole ring, linked to other heterocyclic system through the spiro carbon atom at C-3, are of interest. In addition, varied pharmacological properties are associated with 1,2,4-triazolines.[16] Thus, it is possible that production of a 1,2,4-triazoline moiety at the C-3 position of the indolinone system could enhance biological activity. We have investigated a facile synthesis of triazolines with a new skeleton **11** in high yields under thermal conditions. Nitrile imines are important intermediates[17] as 1,3-dipoles, investigated by many research groups.[18,19] Diphenyl nitrile imines, are less reactive in comparison to their non-aromatic counterpart, C-acetyl[20] and C-ethoxycarbonyl nitrile imines[21] but they have been more systematically investigated. The reaction of these dipoles with non-conjugated[22] and conjugated imines[23] have been well-studied. The reaction with isatin imines, which is the subject of this study, does not appear to have been previously investigated. Spiro-[3*H*-indole-3,3′-[Δ^2-1-2-4]-triazoline]-2-ones **11** were obtained by the reaction of isatin imines[24] **8** with C-acetyl nitrile imine **10**, generated in situ from the corresponding hydrazinoyl bromide **9**. The reaction time was generally between 4–5 h and the yield was good to excellent. Furthermore, there were no side products formed (Scheme 2). The structure of compounds **11a–e** thus obtained were confirmed on the basis of their IR, ^1H NMR and mass spectral analyses. In the IR spectra $\nu_{C=O}$ of



Scheme 2.

the oxindole appear at 1729–1750 cm^{-1}, $\nu_{C=O}$ of the acetyl at 1660–1679 cm^{-1} and ν_{N-H} at 3253–3337 cm^{-1}. The ^1H NMR spectra of products **11a–e** showed the corresponding resonance peaks as a singlet of methyl, carbomethoxy and N–H groups, at δ_H=2.1–2.2, δ_H=2.5–2.6 and δ_H=8.1–8.2 ppm, respectively.

Entry	X	Product	Yield (%)
1	H	**11a**	80
2	CH_3	**11b**	82
3	OCH_3	**11c**	80
4	Cl	**11d**	70
5	Br	**11e**	65

3. Conclusion

In conclusion, we have demonstrated that a 1,3-dipole (nitrile imine) generated in situ from the corresponding hydrazone oxidatively undergoes intramolecular 1,3-dipolar cycloaddition onto the alkene of an allyl-substituted indole. The dihydropyrazoloindoles and spiroindoles possessing suitable heterocycles have potential as precursors to various mitomycin analogues.

4. Experimental

Materials were obtained from commercial suppliers and were used without further purification. Melting points were determined by using a Buchi melting point apparatus and are uncorrected. IR spectra were recorded for KBr discs on a Perkin–Elmer 240C analyser. ^1H NMR spectra were recorded on 90 MHz spectrometers and chemical shift values are recorded in δ units (ppm) relative to Me_4Si as internal standard. The 270 and 100 MHz NMR spectra were recorded with tetramethylsilane as internal standard (by RSIC, Shillong). Mass spectra were recorded in an AEIMS-30 spectrometer. Elemental analyses were performed on a Hitachi 026 CHN analyser. All solvents were distilled before use. The progress of most reactions was monitored by TLC and chromatographic purification was performed with silica gel 60 (120 mesh, Merck).

4.1. General procedure for the preparation of hydrazones 3

4.1.1. 1-Allyl-3-methylindole-2-carbaldehyde phenylhydrazone 3a. A solution of 2-formyl-3-methyl-*N*-allylindole **2a** (1.99 g, 10 mmol) in ethanol (25 mL) was added dropwise to a well stirred solution of phenylhydrazine hydrochloride (1.44 g, 10 mmol) and sodium acetate (2.05 g, 25 mmol) in water (10 mL). The stirring was continued for 10–15 min after which the reaction mixture was warmed on a water bath for 15 min. The precipitated hydrazone was filtered off, washed with water, dried and recrystallised from ethanol. Concentration of the mother liquor gave additional (10%) hydrazone **3a**. The total yield was 2.45 g (75%). Yellowish solid. Mp 162–165 °C (decomp.). [Found: C, 78.98; H, 6.63; N, 14.44. $C_{19}H_{19}N_3$ requires C, 78.89; H, 6.57; N, 14.53%]. ν_{max} (Nujol) 3210, 1615, 1320, 1160 and 745 cm^{-1}. δ_H (90 MHz, $CDCl_3$) 8.10 (broad, 1H, –NH), 7.18–7.42 (m, 9H, ArH), 6.75 (s, 1H, CH=N), 5.62–6.14 (m, 1H, CH=CH_2), 4.84–5.20 (m, 3H, NCH_2, =CH H), 4.66–4.76 (m, 1H, =CH H) and 2.44 (s, 3H, Me). EI-MS: *m/z* 289 (M^+).

4.1.2. 1-(2-Methylbut-2-enyl)-3-methylindole-2-carbaldehyde phenylhydrazone 3b. Following the above procedure, 1-(2-methylbut-2-enyl)-3-methylindole-2-carbaldehyde **2b** (2.25 g, 10 mmol), with phenylhydrazine hydrochloride (1.44 g, 10 mmol) and sodium acetate (2.05 g, 25 mmol) in ethanol-water gave the title compound **3b** in 78% (2.75 g) yield as a yellowish solid. Mp 170–172 °C (decomp.). [Found: C, 79.61; H, 7.32; N, 13.36. $C_{21}H_{23}N_3$ requires C, 79.49; H, 7.25; N, 13.25%]. ν_{max} (KBr) 3200, 1610, 1350, 1165, 1050 and 670 cm^{-1}. δ_H (90 MHz, $CDCl_3$) 7.62 (br, 1H, NH), 7.10–7.26 (m, 9H, ArH), 6.72 (s, 1H, CH=N), 5.12 (s, 3H, NCH_2CH), 2.36 (s, 3H, Me), 1.86 (s, 3H, Me), 1.64 (s, 3H, Me). EI-MS: *m/z* 317 (M^+).

4.1.3. 9-Methyl-1-phenyl-dihydropyrazolo [3′,4′:3,4]-pyrrolo[1,2-a]indole 5a. A solution of lead tetraacetate (2.30 g, 5.2 mmol) in dry acetonitrile (30 mL) was added dropwise to a stirred and cooled solution of 1-allyl-3-methylindole-2-carbaldehyde phenylhydrazone **3a** (1.01 g, 3.48 mmol) in dry acetonitrile (100 mL) at −15 °C during 1 h, after which the reaction mixture was set aside at the same temperature. The resultant precipitate was filtered off and filtrate was evaporated to dryness. The residue thus obtained was poured into water and extracted with dichloromethane (50 mL×3). The combined organic extracts were washed with water several times, dried and distilled in a rotary evaporator to afford a residue, which on crystallization from ethanol gave 9-methyl-1-phenyl-dihydropyrazolo[3′,4′:33,4] pyrrolo[1,2-a]indole **5a** in 50% yield (0.5 g) as pale yellow needles. Mp 182–184 °C. [Found: C, 79.29; H, 5.88; N, 14.58. $C_{19}H_{17}N_3$ requires C, 79.40; H, 5.96; N, 14.62%]. δ_H (270 MHz, $CDCl_3$) 1.98 (s, 3H), 3.90 (dd, *J*=3.9, 10.3 Hz 1H), 4.01–4.10 (m, 1H), 4.13 (dd, *J*=10.3, 3.2 Hz, 1H), 4.31 (dd, *J*=10.3, 8.1 Hz, 1H), 4.78 (br, s, 1H), 7.12 (t, *J*=7.2 Hz, 1H), 7.25 (t, *J*=7.0 Hz, 1H), 7.32–7.50 (overlapping, 7H). ^{13}C NMR (100 MHz, $CDCl_3$) 21.1, 48.7, 50.8, 62.6, 94.9, 109.7, 119.6, 121.2, 125.8, 127.5, 128.5, 129.1, 130.5, 133.5, 137.1, 142.0, 147.1. EI-MS: *m/z* 287 (M^+).

4.1.4. 9-Methyl-1-phenyl-2,2′-dimethyl-dihydropyrazolo [3′,4′:3,4]pyrrolo[1,2-a]indole 5b. Following the above procedure, 1-(2-methylbut-2-enyl)-3-methylindole-2-carbaldehyde phenyl hydrazone **3b** (1.10 g, 3.5 mmol) with lead tetraacetate (2.3 g, 5.2 mmol) in dry acetonitrile at −15 °C gave the title compound **5b** in 45% yield (0.46 g) as a pale yellow solid. Mp 124–126 °C. [Found: C, 79.89; H, 6.63; N, 13.46. $C_{21}H_{21}N_3$ requires C, 79.96; H, 6.71; N, 13.32%]. δ_H (270 MHz, $CDCl_3$) 1.16 (s, 3H), 1.33 (s, 3H), 2.21 (s, 3H), 4.20 (dd, *J*=10.3, 2.9 Hz, 1H), 4.36 (dd, *J*=10.3, 8.1 Hz, 1H), 4.11 (m, 1H), 7.22 (t, *J*=7.3 Hz, 1H), 7.34 (t, *J*=7.1 Hz, 1H), 7.37–7.52 (overlapping, 7H). ^{13}C NMR (100 MHz, $CDCl_3$) 12.5, 19.7, 21.6, 49.7, 50.9, 63.1, 95.0, 109.5, 119.6, 121.3, 125.1, 127.6, 128.7, 129.2, 132.9, 133.4, 137.1, 141.2, 148.1. EI-MS: *m/z* 315 (M^+).

4.2. Reaction of hydrazinoyl bromide 9 with isatin imines 8 and synthesis of spiroindoles 11

To a solution of isatinimine **8a** (10 mmol) in anhydrous chloroform (15 mL) was added hydrazinoyl bromide **9** (10 mmol) and stirred well. To this solution, dry triethylamine (15 mmol) dissolved in 10 mL of anhydrous $CHCl_3$ was added dropwise in 40 min. After stirring for 10 min the solution was refluxed with stirring for 3 h and cooled to room temperature (monitored by TLC). The chloroform was then removed under reduced pressure and the residue was treated with dry benzene (20 mL). The precipitated triethylamine hydrobromide was filtered off and the solvent was removed under reduced pressure. The product thus obtained was then purified by column chromatography on silica gel using $CHCl_3$ as eluent and isolated the corresponding cycloadduct **11a** in 80% yield without the formation of any side products. The physical and spectral data of the cycloadduct is recorded below.

4.2.1. Compound 11a. Yellow needles, yield 80% (3.15 g), mp 148–51 °C. [Found: C, 72.62; H, 5.14; N, 14.18. $C_{24}H_{20}N_4O_2$ requires C, 72.72; H, 5.05; N, 14.14%]. ν_{max} (cm^{-1}) 3339 (N–H), 1750 (C═O), 1660 ($COCH_3$): δ_H (90 MHz, $CDCl_3$) 8.25 (bs, 1H, NH), 6.4–7.5 (m, 13H, ArH), 2.5–2.55 (s, 3H, $COCH_3$), 2.18–2.2 (s, 3H, CH_3); δ_c (100 MHz, $CDCl_3$) 36.2 (CH_3), 41.1 ($COCH_3$), 96.8 (spiro carbon), 111.3, 113.6, 119.5, 122.6, 125.8, 127.7, 128.4, 128.6, 129.7, 130.5, 131.8, 133.0, 141.7, 145.8, 170.03 (C═O), 175.11 (C═O). EI-MS: *m/z* 396 (M^+). Similarly other isatin imines were reacted with hydrazinoyl bromides and the corresponding cycloadducts **11b–e** were isolated in high yields. The physical and spectral data of the spiroindoles are recorded below.

4.2.2. Compound 11b. Yellow needles, yield 82% (3.30 g), mp 188–90 °C. [Found: C, 73.09; H, 5.27; N, 13.63. $C_{25}H_{22}N_4O_2$ requires C, 73.17; H, 5.36; N, 13.65%]. ν_{max} (cm^{-1}) 3363 (N–H), 1739 (C═O), 1660 ($COCH_3$): δ_H (90 MHz, $CDCl_3$) 8.10 (bs, 1H, NH), 6.3–7.3 (m, 12H, ArH), 2.45–2.4 (s, 3H, $COCH_3$), 2.1–2.2 (s, 6H, CH_3); δ_c (100 MHz, $CDCl_3$), 35.9 (CH_3), 36.1 (CH_3), 40.9 ($COCH_3$), 97.02 (spiro carbon), 111.9, 113.1, 118.8, 122.6, 124.8, 127.1, 128.2, 128.9, 129.1, 130.8, 132.1, 133.5, 141.8, 146.1, 147.2, 171.11 (C═O), 175.19 (C═O). EI-MS: *m/z* 410 (M^+).

4.2.3. Compound 11c. Yellow needles, yield 80% (3.45 g), mp 75–77 °C. [Found: C, 70.29; H, 5.25; N, 13.03 $C_{25}H_{22}N_4O_3$ requires C, 70.42; H, 5.16; N, 13.14%]. ν_{max} (cm^{-1}) 3253 (N–H), 1729 (C═O), 1679 ($COCH_3$): δ_H (90 MHz, $CDCl_3$) 8.05–8.15 (bs, 1H, NH), 6.4–7.5 (m, 12H, ArH), 4.6–4.7 (s, 3H, OCH_3), 2.5–2.6 (s, 3H, $COCH_3$), 1.15–1.2 (s, 3H, CH_3); δ_c (100 MHz, $CDCl_3$), 37.6 (CH_3), 41.2 ($COCH_3$), 60.1 (OCH_3), 96.2 (spiro carbon), 111.5, 113.6, 120.1, 121.8, 124.8, 127.1, 128.1, 128.8, 129.2, 130.5, 131.2, 133.0, 140.8, 146.1, 168.8 (C═O), 172.81 (C═O). EI-MS: *m/z* 426 (M^+).

4.2.4. Compound 11d. Yellow needles, yield 70% (3.0 g), mp 197–99 °C. [Found: C, 66.98; H, 4.33; N, 12.88. $C_{24}H_{19}ClN_4O_2$ requires C, 66.89; H, 4.41; N, 13.00%]. ν_{max} (cm^{-1}) 3337 (N–H), 1742 (C═O), 1660 ($COCH_3$): δ_H (90 MHz, $CDCl_3$) 7.8–7.9 (bs, 1H, NH), 6.3–7.3 (m, 12H, ArH), 2.4–2.5 (s, 3H, $COCH_3$), 2.1–2.2 (s, 3H, CH_3); δ_c (100 MHz, $CDCl_3$), 37.6 (CH_3), 41.2 ($COCH_3$), 97.0 (spiro carbon), 111.1, 112.8, 119.1, 122.6, 124.1, 126.8, 128.0, 128.8, 129.6, 130.8, 132.0, 133.8, 141.1, 146.6, 147.6, 170.0 (C═O), 174.7 (C═O). EO-MS: m/z 430 (M^+).

4.2.5. Compound 11e. Yellow semi solid, yield 65% (3.10 g). [Found: C, 60.53; H, 3.85; N, 11.90 $C_{24}H_{19}BrN_4O_2$ requires C, 60.63; H, 4.00; N, 11.79%]. ν_{max} (cm^{-1}) 3342 (N–H), 1745 (C═O), 1663 ($COCH_3$): δ_H (90 MHz, $CDCl_3$) 8.3 (bs, 1H, NH), 7.75–7.83 (m, 12H, ArH), 2.35–2.5 (s, 3H, $COCH_3$), 2.1–2.15 (s, 3H, CH_3); δ_c (100 MHz, $CDCl_3$), 35.9 (CH_3), 42.5 ($COCH_3$), 96.3 (spiro carbon), 111.8, 113.8, 120.1, 122.8, 125.0, 127.8, 128.1, 128.8, 129.6, 130.6, 131.8, 133.6, 140.8, 145.6, 169.9 (C═O), 174.9 (C═O). EI-MS: *m/z* 474 (M^+).

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