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A facile and efficient synthesis of highly functionalised 3,3′-dispiropyrrolidine- and 3,3′-dispiropyrrolizidine bisoxindoles via [3+2] cycloaddition

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Abstract

The [3+2] cycloaddition reaction of azomethine ylides with isomerised Morita–Baylis–Hillman adducts, both dipoles and dipolarophiles are derived from isatin, afforded highly functionalised 3,3′-dispiro pyrrolidine- and 3,3′-dispiropyrrolizidine bisoxindoles in high yields.

Keywords: Isatin; Azomethine ylides; Morita–Baylis–Hillman adduct; Dispiropyrrolidine oxindoles; Bispiropyrrolizidine oxindoles; Cycloaddition

1. Introduction

3′-Spiro oxindoles and their derivatives have become important synthetic targets as these structural frameworks form the core units of many naturally occurring molecules that possess significant biological activities (Fig. 1).[1,2] These derivatives have served as potential synthetic intermediates for the total synthesis of alkaloids, drug intermediates and clinical pharmaceuticals.[1] Hence, a number of synthetic routes have been developed for the preparation of these structural frameworks.[3–10] 1,3-Dipolar cycloaddition reactions constitute one of the most fundamental reactions for the stereoselective construction of five-membered heterocyclic compounds.[11,12] Azomethine ylides are a class of powerful reagents used in [1,3]-dipolar cycloaddition reactions which in general afford a range of pharmacologically important heterocyclic compounds.[13–20]

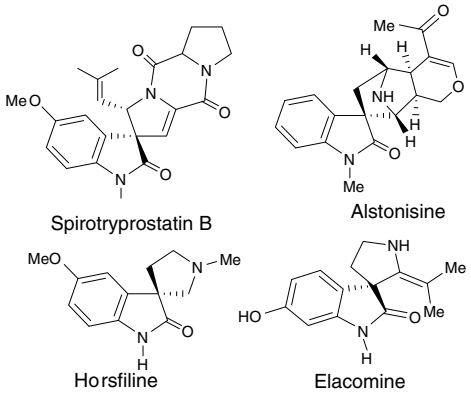

Fig. 1. Spirooxindole alkaloid natural products.

Dispiro derivatives of heterocyclic systems are important synthetic targets and only a few reports are known.[21,22] The Morita–Baylis–Hillman (MBH) adducts and their derivatives play an important role in synthetic organic chemistry as they serve as synthons for the construction of many complex molecular architectures.[23] The

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synthetic versatility of isatin and its derivatives has led to the extensive use of this compound in synthetic organic and natural product chemistry.[24]

We have been exploring the novel synthetic applications of MBH adducts. [25–28] Recently, we focussed our attention to MBH adducts derived from isatin for the synthesis of novel heterocycles.[29–31] Our recent report reveals the synthesis of 3-spiropyrrolizidine and 3-spiropyrrolidine oxindoles from MBH-adducts of isatin and heteroaldehydes via [3+2] cycloaddition of azomethine ylides. [31] However, there is no report on the [3+2] cycloaddition reaction of bromo- and methoxy isomerised MBH adducts of isatin which in general would afford structurally different dispiro bisoxindoles derivatives in a stereoselective manner. In this context, we were interested in exploring the reactivity pattern of isomerised MBH adducts of isatin with azomethine ylides (**C** or **E**) generated in situ from isatin and sarcosine/proline by a thermal decarboxylative route as per the retrosynthetic analysis shown in Figure 2. The reaction furnished a library of highly functionalised dispiropyrrolidine oxindole derivatives in excellent yield in a single step. The results of the study are the content of this Letter.

As shown in Scheme 1, the preliminary experiment was carried out between the bromo-isomerised MBH adduct **1** of *N*-methylisatin and azomethine ylide **C** (generated in situ from sarcosine and isatin) in refluxing toluene using montmorillonite K10 clay as catalyst. The reaction afforded highly substituted 3,3′-dispiropyrrolidine bisoxindole **7** in 40% yield.

The bromo isomerised MBH adducts **1** and **1a** were prepared from the MBH adduct of *N*-methylisatin by treatment with aqueous HBr in the presence of silica gel (100–200 mesh) and under solvent free microwave irradiation. The *E*-isomer **1a** was converted to the *Z*-isomer **1** by increasing microwave irradiation time (ca. 10 min). The geometries of isomers **1a** (*E*) and **1** (*Z*) were established based on ^{1}H NMR chemical shift studies. Thus, the methylene proton of the *E*-isomer was observed at δ 5.23

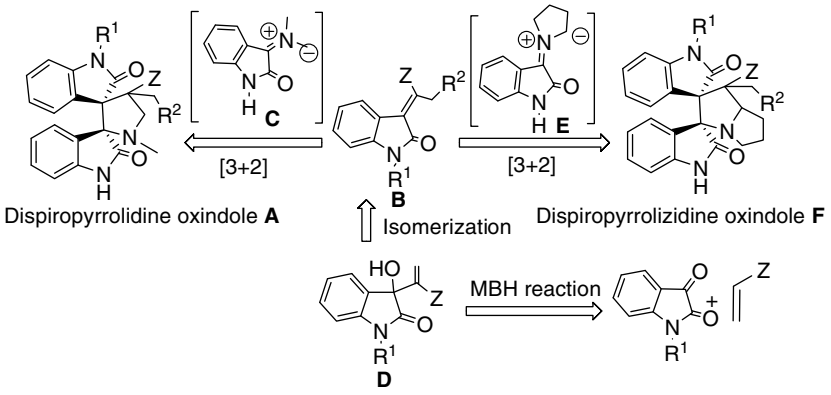
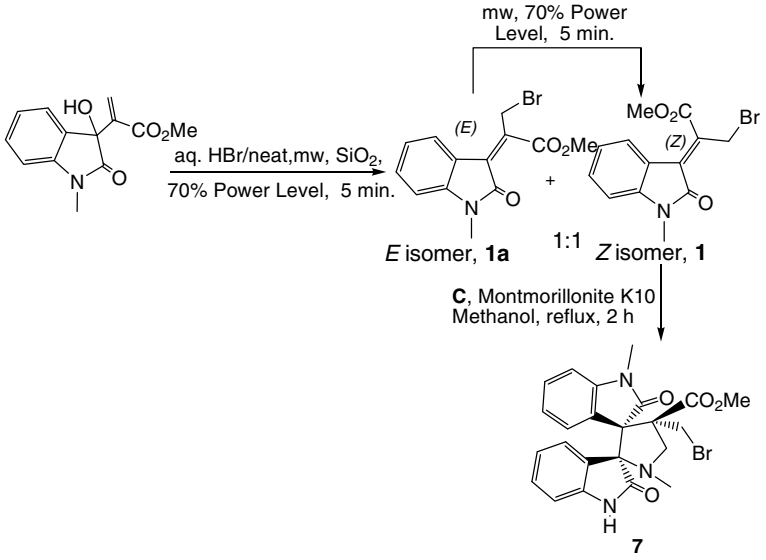


Fig. 2. Retrosynthetic analysis of dispiro bisoxindoles **A** and **F**.



Scheme 1. Optimization of the reaction conditions.

while the *Z*-isomer was observed at δ 4.49. The major isomer **1** was purified using column chromatography on silica gel and used for the cycloaddition study.

Optimization of the reaction was carried out in different solvents (methanol, toluene, acetonitrile and dioxane), with and without montmorillonite K10 clay. When toluene was used as the solvent, we isolated a 40% yield of the desired product **7**. A remarkable increase in the yield (75%) of compound **7** was observed with methanol as the solvent and freshly activated 100% w/w montmorillonite K10 clay catalyst under reflux for 2 h. The reactions in acetonitrile and dioxane provided none of the desired product.

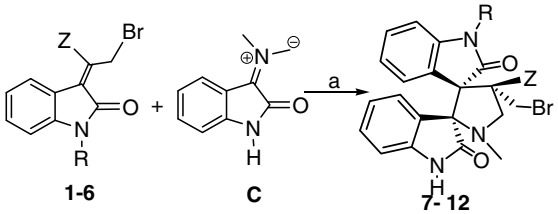
The structure of compound **7** was determined based on the spectroscopic studies. Thus, the proton NMR spectrum of compound **7** showed two doublets centred at δ 3.54 and δ 3.72 with coupling constants $J = 9$ Hz indicating the presence of two pyrrolidine ring protons. Two doublets centred at δ 4.44 and δ 4.88 indicated two mutually coupled protons ($J = 9$ Hz) at the carbon attached to bromine. A singlet at δ 7.64 was due to the free hydrogen attached to the nitrogen of the oxindole moiety. In the ^{13}C NMR spectrum, two signals at δ 65.6 and δ 79.3 indicated the presence of two spiro carbons and signals at δ 175.2, 177.3 and 180.1 correspond to the carbonyl groups of the oxindole moiety and the ester group. The *endo*/*exo* selectivity of product **7** was assigned based on the literature analogy.[31,32]

To show the general nature of the reaction, bromo isomerised MBH adducts of isatins **2**–**6** bearing different substituents (ester, sulfone, nitrile) and various saturated, unsaturated, aromatic substituents on the isatin nitrogen (methyl, benzyl, propargyl and allyl) were reacted with azomethine ylide **C**, under optimised conditions (Table 1, entries 1–6). The reaction afforded highly functionalised dispiro bisoxindole compounds **7**–**12** in excellent yields (75–85%). The functional groups on the dispiro bisoxindoles can be modified further. However, the [3+2] cycloaddition of adducts **1**–**6** with azomethine ylide **E**, failed to provide the expected products probably due to the steric effect of the bulky bromine atom at the allylic position. All the new compounds were thoroughly characterised by the spectroscopic methods (IR, ^{1}H, ^{13}C NMR and FAB-mass spectra). The results are summarised in Table 1.

The excellent results obtained from the bromo isomerised MBH adducts **1**–**6**, prompted us to explore the [3+2] cycloaddition reactivity pattern of the methoxy isomerised MBH adducts **13**–**16** of isatin with azomethine ylides **C** and **E**. The MBH adducts **13**–**16** were prepared from the corresponding MBH adducts of isatin in refluxing acetonitrile with a small excess of trimethyl orthoformate and montmorillonite K10 clay as the catalyst for 30 min. The reactions furnished only *Z* isomers **13**–**16** in 75–80% yields. The geometry of the isomers was assigned based on our recent report.[33] All the cycloaddition reactions of compounds **13**–**16** with dipole **C** under optimised conditions afforded the corresponding dispiropyrrolidine bisoxindole derivatives **17**–**20** in excellent yields (Table 2, entries 1–4). However, adducts **13** and **14** on reaction with ylide **E** afforded only moderate yields of the dispiropyrrolizidine derivatives **21** and **22**, respectively (Table 2, entries 5 and 6).

It should be noted that, in contrast to our previous report,[31] the reactions of methoxy isomerised MBH-adducts of isatin with dipole **E** derived from proline and isatin showed less reactivity towards the isomerised MBH adducts, possibly due to the steric effects of the two bulky functional groups present on the isomerised adducts which hinders the approach of the dipole. It should be noted that the cycloaddition reaction reported herein proceeds to the products with the formation of two quaternary carbons (two spiro centres) in a one-pot reaction. The compounds reported herein may serve as synthons for alkaloid natural product synthesis.

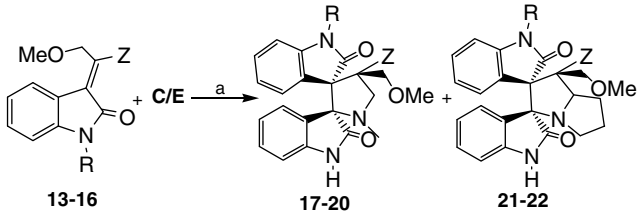
Table 1
Synthesis of dispiropyrrolidine bisoxindoles 7–12 from *E*-bromo isomerised MBH adducts 1–6 and dipole **C**



Entry	Z	R	Product	Yield (%)
1	CO_2Me	Methyl	**7**	75
2	CO_2Me	Benzyl	**8**	85
3	CO_2Me	Allyl	**9**	82
4	CO_2Me	Propargyl	**10**	80
5	SO_2Ph	Methyl	**11**	75
6	CN	Methyl	**12**	78

Reagents and condition: (a) Montmorillonite K10 clay, methanol, reflux, 2 h.

Table 2
Synthesis of dispiropyrrolidine and dispiropyrrolizidine bisoxindoles from MBH adducts **13**–**16**



Entry	Z	R	Dipole **C**/**E**	Product	Yield (%)
1	CO_2Me	Methyl	**C**	**17**	75
2	CO_2Me	Allyl	**C**	**18**	85
3	CO_2Me	Benzyl	**C**	**19**	80
4	CN	Methyl	**C**	**20**	82
5	CO_2Me	Methyl	**E**	**21**	45
6	CO_2Me	Allyl	**E**	**22**	40[b]

Reagents and condition: [a] Montmorillonite K 10, methanol, reflux, 2 h. [b] 12 h.

2. Conclusion

In conclusion, we have synthesised a library of pharmacologically important highly functionalised dispiropyrrolidine and dispiropyrrolizidine oxindoles starting from *E*-bromo and *Z*-methoxy isomerised MBH adducts of isatin with azomethine ylides using eco-friendly montmorillonite K10 clay as a catalyst. Further studies using this reagent are underway in this laboratory.

3. General experimental procedure for cycloaddition

A mixture of isomerised Morita–Baylis–Hillman adduct of isatin (100 mg, 0.404 mmol), L-(−) proline or sarcosine (1.2 equiv), isatin (1.2 equiv) and montmorillonite K-10 clay (100% w/w) in methanol (1 mL) was refluxed for 2–12 h. After completion of the reaction (TLC), the crude mixture was filtered through a pad of Celite and then purified by silica gel column chromatography to afford the desired products (40–85%).

3.1. Spectral data for selected compounds

3.1.1. Compound **7**

FTIR (CH_2Cl_2): ν_{max}: 1225, 1355, 1480, 1470, 1614, 1731, 1735, 2124, 2928, 3210 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.2 (s, 3H), 2.97 (s, 3H), 3.54 (d, 1H, $J = 9$ Hz), 3.60 (s, 3H), 3.73 (d, 1H, $J = 9$ Hz), 4.45 (d, 1H, $J = 9$ Hz), 4.89 (d, 1H, $J = 9$ Hz), 6.53–6.60 (m, 2H), 6.92–6.95 (m, 2H), 7.10–7.12 (m, 1H), 7.22–7.38 (m, 1H), 7.38–7.47 (m, 2H), 7.64 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 26.7, 35.3, 51.9, 53.7, 59.5, 65.6, 79.3, 107.8, 108.3, 110.2, 122.4, 122.8, 124.1, 126.6, 128.5, 131.2, 133.3, 141.4, 144.8, 175.2, 177.3, 180.1; FAB mass: calcd for $C_{23}H_{22}BrN_3O_4$ is 484.34; found: $M^+ = 484.29$ and M+2 = 486.21.

3.1.2. Compound **10**

FTIR (CH_2Cl_2): ν_{max}: 750, 1470, 1488, 1614, 1731, 1730, 2924, 3287; ^1H NMR ($CDCl_3$/DMSO-d_6/TMS, 300.1 MHz): δ 1.25–1.28 (m, 1H), 2.18 (s, 3H), 3.52 (d, 1H, $J = 8.5$ Hz), 3.60 (s, 3H), 3.74 (d, 1H, $J = 9.8$ Hz), 4.39 (d, 2H, $J = 9.8$ Hz), 4.97 (d, 1H, $J = 8.6$ Hz), 6.51–6.53 (m, 2H), 6.80–6.86 (m, 2H), 7.02–7.06 (m, 2H), 7.25 (t, 1H, $J = 6$ Hz), 7.43 (d, 1H, $J = 6$ Hz), 7.47 (d, 1H, $J = 6$ Hz), 9.67 (s, 1H); ^{13}C NMR($CDCl_3$/TMS, 75.3 MHz): δ 36.2, 48.7, 57.1, 59.4, 61.2, 63.3, 64.4, 78.5, 79.5, 79.9, 108.2, 109.2, 116.1, 120.7, 125.3, 128.1, 128.5, 131.7, 140.2, 141.9, 142.4, 172.5, 172.7, 178.1; FAB mass: calcd for $C_{25}H_{22}BrN_3O_4$ is 508.36; found: $M^+ = 508.69$ and M+2 = 510.71.

3.1.3. Compound **17**

FTIR (CH_2Cl_2): ν_{max}: 753, 1223, 1355, 1470, 1488, 1614, 1731, 1730, 2924, 3287 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.22 (s, 3H), 2.96 (s, 3H), 3.29 (s, 3H), 3.38 (s, 3H), 3.49 (d, 1H, $J = 9$ Hz), 3.59 (d, 1H, $J = 9$ Hz), 4.33 (d, 1H, $J = 9$ Hz), 4.65 (d, 1H, $J = 9$ Hz), 6.48–6.59 (m, 2H), 6.78–6.79 (m, 1H), 6.93–6.94 (m, 1H), 7.09–7.13 (m, 2H), 7.23–7.28 (m, 1H), 7.49 (d, 1H, $J = 9$ Hz), 8.11 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 25.8, 34.6, 51.9, 58.0, 59.1, 60.3, 63.5, 78.5, 107.5, 107.0, 109.2, 121.5, 121.8, 124.1, 124.8, 127.2, 128.1, 129.6, 130.5, 141.8, 143.3, 171.5, 172.6, 177.1; FAB mass: calcd for $C_{24}H_{25}N_3O_5$ is 435.47; found: $M^+ = 435.35$.

3.1.4. Compound **18**

FTIR (CH_2Cl_2): ν_{max}: 753, 1222, 1359, 1459, 1469, 1614, 1723, 2951, 3272 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.24 (s, 3H), 3.33 (s, 6H), 3.46 (d, 1H, $J = 9$ Hz), 4.12 (d, 1H, $J = 9$ Hz), 4.28 (d, 1H, $J = 9$ Hz), 4.66 (d, 1H, $J = 9$ Hz), 4.91–4.95 (m, 1H), 5.35–5.42 (m, 1H), 6.51 (d, 1H, $J = 6$ Hz), 6.59 (d, 1H, $J = 6$ Hz), 6.78 (t, 1H, $J = 6$ Hz), 6.92 (t, 1H, $J = 6$ Hz), 7.05–7.13 (m, 2H), 7.22 (d, 1H, $J = 6$ Hz), 7.29 (d, 1H, $J = 6$ Hz), 7.50 (d, 1H, $J = 6$ Hz), 8.01 (s, 1H); ^{13}C NMR($CDCl_3$/TMS, 75.3 MHz): δ 35.2, 47.7, 51.4, 58.1, 58.4, 59.2, 60.3, 63.4, 76.5, 78.4, 108.1, 109.2, 116.8, 121.6, 122.1, 124.3, 125.1, 127.2, 128.5, 129.4, 130.7, 141.9, 142.4, 171.5, 172.2, 177.3; FAB mass: calcd for $C_{26}H_{27}N_3O_5$ is 461.51; found: $M^+ = 461.89$.

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