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Research Article

AN EFFICIENT AND FACILE SYNTHESIS OF SPIROOXINDOLES

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Abstract

Spirooxindoles are important heterocyclic compounds that are found in many natural products having interesting biological activities. At present, this class of compounds is under immense research due to their vast range of bioactive properties such as analgesics and anti-tumor agents etc. In this paper, we report a simple, one-pot approach to spirooxindoles by reacting isatin, pipecolic acid and an unsaturated ester derivative giving an easy access to these polycyclic structures.

Keywords: Isatin, Pipecolic acid, Oxindole, Spirooxindole, one-pot reaction

Introduction

The spirooxindole alkaloids belong to a family of natural products that were first isolated from plants of the Apocynaceae and Rubiacae families (Bindra, 1973). The key structural characteristic of these compounds is the spiro ring fusion at the 3-position of the oxindole core, with varying degrees of substitution around the pyrrolidine and oxindole rings. In addition to the interesting molecular architecture and densely functionalized core, several natural products possessing this heterocyclic motif exhibit significant bioactivity (Chris et al., 2007). A spirocyclic-oxindole moiety is a structural centerpiece found in a number of biologically active synthetic and natural products with activities in a variety of disease areas (Albertshofer et al., 2012, Fensome et al., 2008, Shangary et al., 2008, Bond et al., 1979, Greshok et al., 2008, Mugishima et al., 2005). Few examples of bioactive spirooxindoles are given in figure 1.

As we find in literature, that since past few years, such stunning compounds have fascinated the academic as well as industrial researchers for their broad therapeutical and industrial applications (Jacob et al. 2012, Chunhui et al., 2012, Galliford et al., 2007, Trost et al., 2009). Owing to their immense importance, we report the synthesis of some novel, substituted spiroxindoles by a simple one-pot reaction of isatin and a piperidine-based aminoacid with an unsaturated ester or an unsaturated amido-compound.

Results and Discussion

Oxindole and spirooxindole scaffolds have generated considerable synthetic interest due to their occurrence in diverse natural products and notable biological activity (Badillo et al., 2010, Russel et al., 2011, Lee et al. 2001, Abdel rehman et al., 2004, Millemaggi et al., 2010). Many synthetic routes for the Synthesis of Spiro-Pyrrolidine-Oxindoles have been reported as, Oxidative Rearrangement Reactions (Finch et al., 1962, Shavel et al. 1962), Intramolecular Mannich Reactions (Tamelen et al., 1969, Ban et al., 1963), Dipolar Cycloaddition Reactions (Palmisano et al., 1996), Intramolecular Heck Reactions (Abelman et al., 1987), Radical Cyclization Reactions (Jones et al., 1995, Escolano et al., 2000), and Asymmetric Nitroolefination (Fuji et al., 1995) and so many others. Such type of multicomponent reactions (MCRs) are special types of synthetically useful organic reactions in which three or more different starting materials react to produce a final product in a one-pot procedure. MCRs are powerful tools in the modern drug discovery process and allow the fast, automated, and high-throughput generation of organic compounds. In the

past decade, there have been tremendous developments in three- and four-component reactions and efforts are still being made to find and develop new MCRs (Fontaine et al., 2009, Shanthi et al., 2010). We have developed here an easy approach to reach such structurally and biologically important compounds via a three-component 1,3-dipolar cycloaddition reaction (Yong et al., 2011) involving N-protected isatin, pipecolic acid and an unsaturated ester (scheme 1).

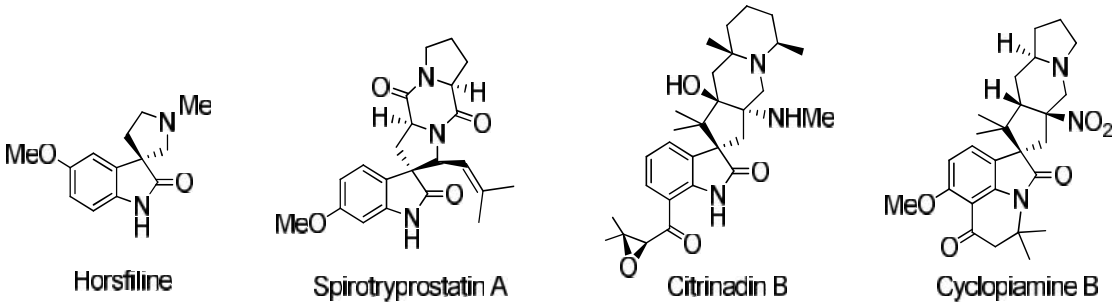
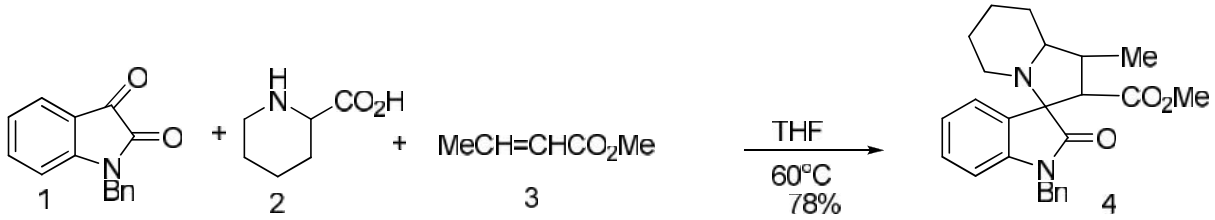
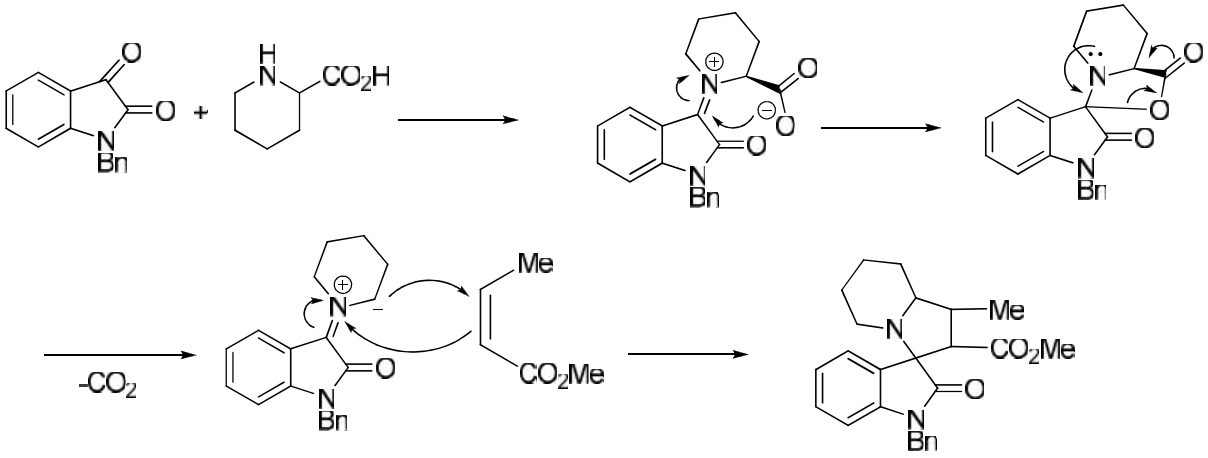


Figure 1. Biologically active Natural Products containing spirooxindole structure



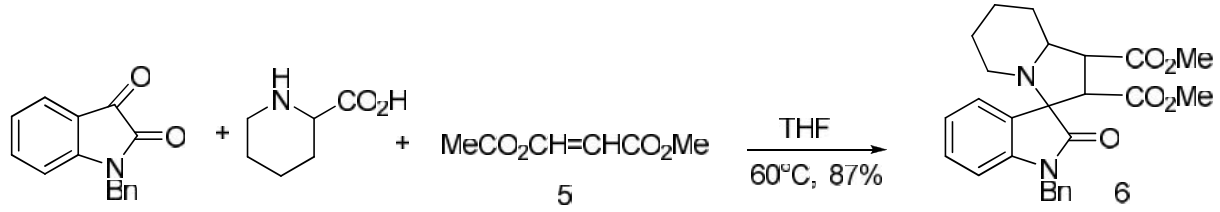
Scheme 1

Thus, a mixture of N-benzylisatin 1, pipecolic acid **2** and dimethylmaleate in THF was stirred at 60°C for 1h, affording spirooxindole **4** as reddish oil (315 mg, 78% yield). The proposed mechanism of the above reaction is given here, scheme 2.



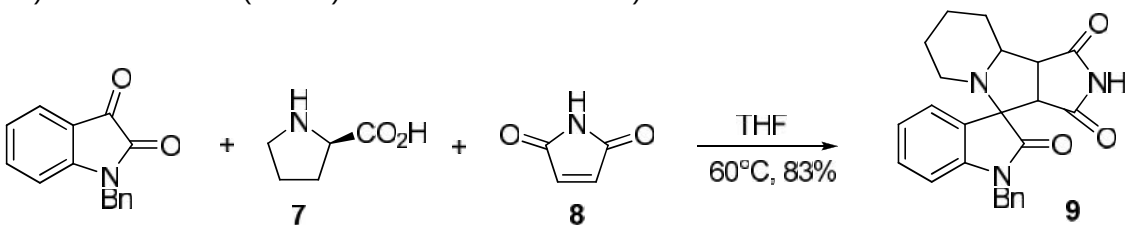
Scheme 2 : Proposed mechanism for spiroindolizine oxindole

In order to check the scope of this synthetic pathway, some other reagents were also used in same manner and as expected, afforded cleanly the new spiroindolizine oxindole compounds. The treatment of N-protected isatin (237 mg, 1mmol) with pipecolic acid (1mmol) dimethyl maleate (1mmol) **5** in THF at 60°C afforded spiro compound **6** as yellow oil (389 mg, 87%) (scheme 3)



Scheme 3

Similarly, spirooxindole **9** was synthesized by treating isatin (1mmol) with L-Proline **7** (1mmol) and maleimide **8** (1mmol) as pale yellow oil (332 mg, 83%) (scheme 4).



Scheme 4

The synthesis of these new spirooxindoles was achieved in good yields and under mild reaction conditions. These results show that such multi-component Reactions (MCRs) offer a diverse and wider scope to reach the novel spiro polycyclic heterocycles that are getting the greater attention of chemists and pharmacists for their wider and potential biological activities. The reaction conditions are moderate and tolerant to the variety of functionalities and are free from metal or any other catalysts. As above synthesized compounds contain different functional groups so, they may be subjected to further transformations to get more complex and preferred molecules to be used in pharmaceutical and/or agrochemical industry

Experimental

***General*:** Solvents were distilled prior to use. Other reagents were used as received. Product organic solutions were dried over sodium sulfate prior to evaporation of the solvents under reduced pressure on a rotary evaporator. Thin layer chromatography were performed on TLC pre-coated aluminium backed silica plates Kieselgel 60 F_{254} (Merck) or glass backed silica Duracil 25 UV_{254} (Macherey nagel). Spots were visualized using UV light (254 nm) before using an ethanolic solution of phosphomolybdic acid (heating). Purifications by column chromatography were carried out on silica gel (70-230 mesh). The Infra-Red spectra were recorded on a Perkin Elmer Paragon 500 spectrophotometer in the form of film in between NaCl plates (liquids). The characteristic band positions are expressed in cm^{-1}. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance spectrometer at 400.13 and 100.61 MHz respectively

***General Procedure**:* A mixture of isatin (1 mmol), pipecolic acid (1 eq.), an unsaturated ester (1 eq.) in THF (10 mL) under argon,was stirred for 1 h at 60 °C. After completion of the reaction (TLC monitoring), the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel using CH_2Cl_2- ethyl acetate (2:1) as the eluent to give the corresponding spirooxindole.

Spectral Data.

(±)-Methyl-1-benzyl-1'-methyl-2-oxo-2',5',6',7',8a'-hexahydro-1'H-spiro[indoline-3,3'-indolizine]-2'-carboxylate 4.

IR (neat) cm^{-1}: 1022, 1098, 1108, 1196, 1425, 1478, 1685, 2869, 3012, 3160, 3227, 3351. ^{1}HNMR($CDCl_3$, 400 MHz) δ ppm: 1.08 (d, J = 8.4, 3H), 1.38-.1.42 (m, 2H), 1.55-1.57 (m, 2H), 1.86-1.90 (m, 2H), 2.55 (dd, J = 7.8 and J = 3.0 Hz, 1H), 2.75 (dd, J = 6.8 and J = 3.0, 1H), 2.83 (s, 2H), 3.52 (s, 1H), 3.73 (s, 3H), 4.62 (s, 2H), 7.12 (dd, J = 8.2 and 4.6 Hz, 1H), 7.29-7.32 (m, 1H), 7.36-7.42 (m, 2 H), 7.47 (dd, J = 7.6 and 4.8 Hz, 1H), 7.48-7.52 (m, 1H), 7.55-7.58 (m, 1H),), 7.68 (dd, J = 4.0 and 8.8 Hz, 1H), 7.71 (dd, J = 7.8 and 3.6 Hz, 1H). ^{13}C NMR($CDCl_3$, 100 MHz) δ ppm : 19.8, 26.5, 27.4, 32.0, 44.6, 51.8, 52.4, 52.8, 54.6, 63.5, 75.9, 116.2, 122.8, 124.5, 126.3, 126.7, 126.9, 128.5,

128.7, 136.2, 140.4, 145.8, 175.9, 180.1 HR-ESI-MS : Calculated (for $C_{25}H_{28}N_2O_3$) 404.5014 and found 404.2123.

(±)-Dimethyl-1-benzyl-2-oxo-2',5',6',7',8,8a'-hexahydro-1'H-spiro[indoline-3,3'-indolizine]-1'-2'-dicarboxylate6

. IR (neat) cm^{-1} : 1055, 1140, 1196(C-O), 1356, 1425, 1636, 1705 (C=O), 2966, 3024, 3155, 3257, 3312. ^{1}HNMR($CDCl_3$, 400 MHz) δ ppm: 1.46-.1.49 (m, 2H), 1.52-1.57 (m, 2H), 1.92-1.96 (m, 2H), 2.51-2.58 (dd, J = 7.6 and J = 2.9 Hz, 1H), 2.35 (dd, J = 6.8 and J = 3.0 Hz, 1H), 2.75 (s, 2H), 3.59 (s, 1H), 3.71 (s, 3H), 3.75 (s, 3H), 4.58 (s, 2H), 7.02 (dd, J = 7.8 and 4.6 Hz, 1H), 7.26-7.29 (m, 1H), 7.36-7.42 (m, 2 H), 7.46 (dd, J = 7.6 and 4.8 Hz, 1H), 7.48-7.52 (m, 1H), 7.55-7.58 (m, 1H),), 7.68 (dd, J = 3.8 and 8.8 Hz, 1H), 7.72 (dd, J = 2.6 and 8.2 Hz, 1H).^{13}C NMR($CDCl_3$, 100 MHz) δ ppm : 20.4, 27.3, 32.1, 44.6, 51.8, 52.4, 52.8, 54.6, 63.5, 75.9, 116.2, 122.8, 124.5, 126.3, 126.7, 126.9, 128.5, 128.7, 136.2, 140.4, 144.8, 175.2, 175.8, 179.6. HR-ESI-MS : Calculated (for $C_{26}H_{28}N_2O_5$) 448.5109 and found 448.1998.

(±)-1-benzyl-6',7',8,8a'tetrahydro-1'H-spiro[indoline-3,4'-pyrrolo[3,4-a]pyrrolizine]-1',2',3'(2'H, 3a'H,8b'H)-trione 9.

IR (neat) cm^{-1} : 1122, 1235(C-O), 1303, 1470, 1650, 1715 (C=O), 3080, 3155, 3289, 3356. ^{1}HNMR($CDCl_3$, 400 MHz) δ ppm: 1.48-1.1.51 (m, 2H), 1.56-1.60 (m, 2H), 2.20 (dd, J = 8 and J = 3.2 Hz, 1H), 2.35 (dd, J = 7.8 and J = 3.0 Hz, 1H), 2.97 (d, J = 10.2 Hz, IH), 3.56 (s, 1H), 4.90 (s, 2H), 7.02 (dd, J = 5.6 and 7.8 Hz, 1H), 7.21-7.29 (m, 1H), 7.32-7.38 (m, 2 H), 7.35 (dd, J = 7.6 and 4.2 Hz, 1H), 7.34-7.42 (m, 2H), 7.44 (dd, J = 2.8 and 7.2 Hz, 1H), 8.02 (dd, J = 2.8 and 6.8 Hz, 1H). ^{13}C NMR($CDCl_3$, 100 MHz) δ ppm: 22.4, 32.6, 33.1, 49.9, 54.8, 55.7, 82.4, 116.2, 122.9, 126.3, 127.2, 127.8, 128.7, 134.4, 144.2, 152.5, 159.2, 170.9, 178.7. HR-ESI-MS : Calculated (for $C_{23}H_{21}N_3O_3$) 387.4318 and found 387.1676.

Conclusion

In conclusion, we have synthesized spirooxindoles by a 1,3-dipolar cycloaddition reaction, from commercially available starting materials. The method applied is simple, convenient and practical that provides a rapid entry to such structurally complex compounds common to a variety of bioactive molecules, providing good yields. Further studies to explore the diversity of this important structure in terms of applying to a vast range of reagents and exploiting the functionalities is being carried out and detailed results will be communicated very soon.

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