Regio- and Stereoselective Synthesis of Novel Dispiropyrrolidine Bisoxindole Derivatives via Multicomponent Reactions

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Received December 25, 2009

A convenient and efficient method for the synthesis of novel dispiropyrrolidine bisoxindole derivatives by 1,3-dipolar cycloaddition reaction of azomethine ylides has been developed. The synthesis was achieved by using a one-pot multicomponent procedure. The features of this procedure were characterized by the following: mild reaction conditions, high yields, high regio- and stereoselectivity, one-pot procedure, and operational simplicity.

Introduction

The use of multicomponent reactions (MCRs) is a valuable approach to synthesize novel compounds.[1] The MCRs strategy offers significant advantages over conventional linear-type synthesis, in that three or more simple and flexible molecules are brought together to rapidly introduce structural complexity and diversity.[2−4] Due to the range of readily available starting materials, the simplicity of one-pot procedure, as well as the associated atom economy, MCRs has been extensively employed in the synthesis of heterocyclic compounds.

The 1,3-dipolar cycloaddition reaction of 1,3-dipoles with olefinic or acetylenic dipolarophiles, discovered by Huisgen[5a] and developed by Woodward and Hoffman[5b] and Houk et al,[6] has became an important and general method for the construction of five-membered heterocyclic rings. Furthermore, the reaction has been shown to be regio- and stereoselective.[7,8]

Highly substituted pyrrolidines have gained much prominence because they make up the central skeleton of many natural products.[9] Spirooxindole ring systems are the central skeleton for numerous alkaloids and pharmacologically important compounds. Some spiropyrrolidines are potential antileukemic and anticovulsant agents[10] and possess antiviral and local anesthetic activities.[11] Spiropyrrolidinyloxindole ring systems are also found in a number of alkaloids like horsifiline, spirotryprostatine A and B, elacomine, etc.[12] The derivatives of spirooxindole find very wide biological applications as antimicrobial, antitumoral, antibiotic agents and inhibitors of human NK-1 receptor etc.[13] As a part of our own interest in cycloaddition reactions, we report herein the facile synthesis of novel dispiropyrrolidine bisoxindole derivatives via the one-pot, multicomponent condensation of azomethine ylides (generated in situ from sarcosine and isatin) with the Knoevenagel adduct 2-oxo-(3*H*)-indole-3-ylidine-malononitrile derivatives preformed by reaction of isatins with malononitrile.

Results and Discussion

Azomethine ylides can be generated by a number of methods, including the convenient decarboxylation route as described in the synthesis of substituted pyrrolidines.[14] In this method, an aldehyde and a secondary amino acid are condensed to generate the reactive azomethine ylides, which when using simple amino acids like sarcosine[15a] or proline[15b] produce cycloaddition products in good yield.[15] Here we have chosen sarcosine, isatin and 2-(2-oxoindolin-3-ylidine)-malononitrile for our studies. The reaction of sarcosine with isatin in boiling methanol leads to the formation of an azomethin ylide which readily undergoes 1,3-dipolar cycloaddition reaction with 2-(2-oxoindolin-3-ylidene)- malononitrile (generated in situ from isatin and malononitrile in boiling methanol without using any catalyst) to give a single cycloadduct, in a one-pot pseudo-four-component process (Scheme 1). This reaction afforded a series of novel dispiroheterocycles **4** containing the two oxindole rings system by a regio and stereo controlled cycloaddition of the azomethine ylide to the exocyclic bond of 2-(2-oxoindolin-3-ylidene)malononitrile in all cases.

The choice of an appropriate reaction medium is of crucial importance for successful synthesis. Initially, the pseudo-four-component reaction of isatin **1a**, malononitrile **2**, and sarcosine **3**, as a simple model substrate, was investigated to establish the feasibility of the strategy and optimize the reaction conditions. Different solvents, such as methanol, ethanol, and acetonitrile, as well as ionic liquid [bmim]Br, were screened. As can be seen from Table 1, methanol is the solvent of choice for the reaction, and the desired product is obtained in excellent yields (entry 1).

Encouraged by this success, we extended this reaction of isatins **1a**−**f** with malononitrile **2** and sarcosine **3** under similar conditions, and corresponding dispiropyrrolidine bisoxindole derivatives **4a**−**f** were synthesized in high yield (Table 2). We have shown that pseudo-four-component

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10.1021/cc900195t
Published on Web 02/15/2010

Scheme 1. Pseudo-Four-Component Reaction of Isatin, Malononitrile, and Sarcosine

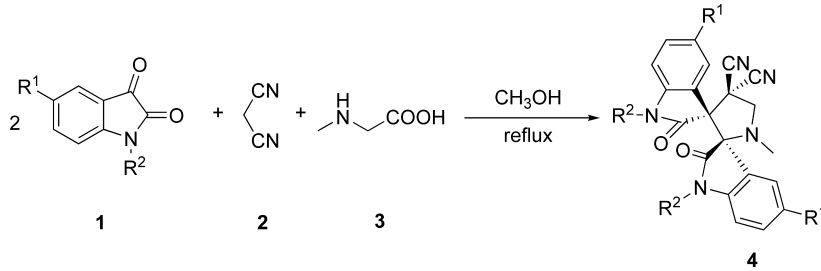


Table 1. Synthesis Results of **4a** under Different Reactions Conditions

entry	temp/°C	solvent	time/h	yield/%
1	reflux	methanol	4	82
2	reflux	ethanol	5	76
3	reflux	acetonitrile	4	77
4	80	[bmim]Br	10	76

Table 2. Synthesis of Dispiropyrrolidine Bisoxindole **4** via Pseudo-Four-Component Reaction

entry	R^1	R^2	products	time/h	yield/%
1	H	H	**4a**	4	82
2	H	CH_3	**4b**	3	93
3	CH_3	H	**4c**	4	83
4	F	H	**4d**	4	83
5	Cl	H	**4e**	4	88
6	Br	H	**4f**	4	91

reaction makes possible the synthesis of libraries under similar circumstances.

As expected, when the three-component reaction of 2-(2-oxoindolin-3-ylidene)-malononitrile **5**, isatin **1**, and sarcosine **3** were carried out, the dispiropyrrolidine bisoxindole containing two different indole rings **6** was obtained in good yield under the same reaction conditions (Scheme 2 and Table 3).

Control of the relative stereochemistry at the spiro center was observed. The regio- and stereochemical outcome of the cycloaddition was determined by single crystal X-ray analysis of the cycloadduct (**4a**) (Figure 1). The X-ray structure of the product **4a** reflects that the cycloaddition proceeds via endotransition state[16] (Scheme 3).

In conclusion, a convenient and efficient synthesis of novel dispiropyrrilidine bisoxindole derivatives has been accomplished by 1,3-dipolar cycloaddition methodology. Advantages of this method include the availability of starting materials, mild reaction conditions employed, high yields, as well as the complete regio- and stereoselectivity observed.

Experimental Section

Melting points were determined in open capillaries and uncorrected. IR spectra were recorded on a Varian F-1000 spectrometer in KBr pellet. ^{1}H NMR and ^{13}C NMR spectra were obtained from a solution in DMSO-d_6 with Me_4Si as internal standard using Varian Invoa-400 MHz or Invoa-300 MHz spectrometer. HRMS analyses were carried out using TOF-MS or TOF LC/MS 6220 instrument.

Table 3. Synthesis of Dispiropyrrolidine Bisoxindole **6** via Three-Component Reaction

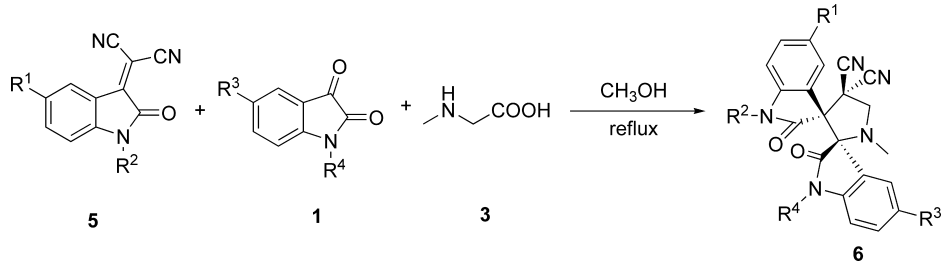
entry	R^1	R^2	R^3	R^4	products	time/h	yield/%
1	H	H	H	CH_3	**6a**	3	91
2	H	H	CH_3	H	**6b**	4.5	85
3	H	H	F	H	**6c**	5	90
4	H	H	Cl	H	**6d**	2	89
5	Br	H	H	H	**6e**	2	91
6	Br	H	CH_3	H	**6f**	3	90
7	Br	H	F	H	**6g**	2	92
8	Br	H	Cl	H	**6h**	2	91

General Procedure for the Synthesis of 4. A dry 50 mL flask was charged with isatin **1** (1 mmol), malononitrile **2** (0.5 mmol), sarcosine **3** (0.5 mmol), and methanol (10 mL). The reaction mixture was stirred at refluxing temperature for 3−4 h. After completion of the reaction, the solvent was removed under vacuum. The solid was recrystallizated from DMF and ethanol, and then dried at 80 °C for 4 h under vacuum to give **4**.

1-Methyl-4,4-dicyano-2,3-bis(spiro-3′-indolino)-2,3,4,5-tetrahydropyrrole 4a: mp 245−246 °C; IR (KBr) 3346, 3219, 2958, 2285, 2257, 1722, 1621, 1598, 1471, 1390, 1320, 757 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 2.07 (s, 3H, CH_3), 4.19 (s, 2H, CH_2), 6.62 (d, J = 7.6 Hz, 1H, ArH), 6.74 (d, J = 7.6 Hz, 1H, ArH), 6.97 (t, J = 7.6 Hz, 1H, ArH), 7.06 (t, J = 7.6 Hz, 1H, ArH), 7.16−7.20 (m, 1H, ArH), 7.26−7.30 (m, 2H, ArH), 7.59 (d, J = 7.6 Hz, 1H, ArH), 10.75 (s, 1H, NH), 11.07 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 34.6, 39.5, 61.3, 63.1, 77.0, 110.8, 110.9, 115.4, 116.3, 120.3, 122.2, 122.8, 123.2, 126.8, 127.6, 131.5, 131.8, 143.6, 143.9, 173.1, 176.0; HRMS (*m*/*z*) calcd for $C_{21}H_{15}N_5O_2$ 369.1226, found 369.1224.

General Procedure for the Synthesis of 6. A dry 50 mL flask was charged with 2-(2-oxoindolin-3-ylidene)malononitrile **5** (0.5 mmol), isatin **1** (0.5 mmol), sarcosine **3** (0.5

Scheme 2. Three-Component Reaction of 2-(2-Oxoindolin-3-ylidene)malononitrile, Isatin, and Sarcosine



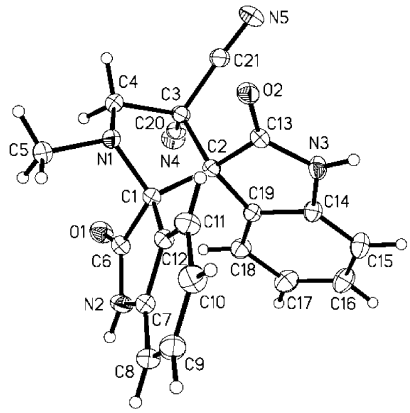
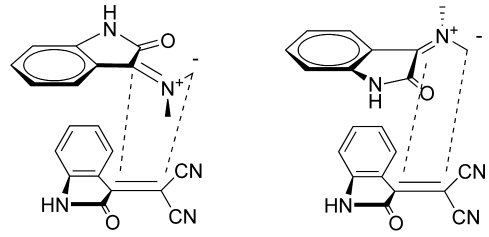


Figure 1. X-ray structure of **4a**.

Scheme 3. Proposed Models for Endo/Exo Cycloaddition



mmol), and methanol (10 mL). The reaction mixture was stirred at refluxing temperature for 2−5 h. After completion of the reaction, the solvent was removed under vacuum. The solid was recrystallizated from DMF and ethanol and then dried at 80 °C for 4 h under vacuum to give **6**.

1-Methyl-4,4-dicyano-2-(1′-methyl-spiro-3′-indolino)-3-(spiro-3″-indolino)-2,3,4,5-tetrahydropyrrole 6a: mp 228−230 °C; IR (KBr) 3332, 3088, 2988, 2943, 2861, 2245, 1732, 1694, 1610, 1494, 1473, 1380, 1199, 1098, 760 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ_H 2.03 (s, 3H, CH_3), 2.96 (s, 3H, CH_3), 4.20 (s, 2H, CH_2), 6.69 (d, J = 7.8 Hz, 1H, ArH), 6.81 (d, J = 7.8 Hz, 1H, ArH), 6.98−7.06 (m, 2H, ArH), 7.21−7.31 (m, 3H, ArH), 7.45 (d, J = 7.8 Hz, 1H, ArH), 11.01 (s, 1H, NH); HRMS (*m*/*z*) calcd for $C_{22}H_{17}N_5O_2$ 383.1382, found 383.1400.

Acknowledgment. We are grateful to the foundation of Key Laboratory of Organic Synthesis of Jiangsu Province for financial support.

Supporting Information Available. Experimental procedures, spectral data of compounds **4a**−**f** and **6a**−**h** and X-ray crystallographic information for **4a**. This material is available free charge via the Internet at http://pubs.acs.org.

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CC900195T