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Combinatorial Synthesis of Functionalized Spirooxindole-Pyrrolidine/Pyrrolizidine/Pyrrolothiazole Derivatives via Three-Component 1,3-Dipolar Cycloaddition Reactions

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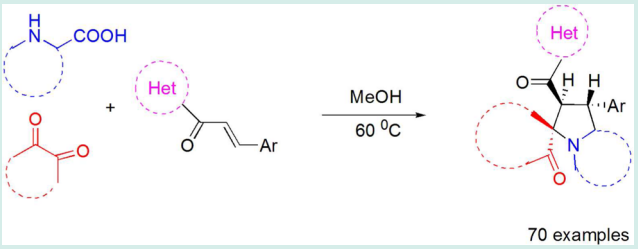
Supporting Information

ABSTRACT: A series of diverse polycyclic heterocycles containing spirooxindole, pyridine/thiophene, and pyrrolidine/pyrrolizidine/pyrrolothiazole rings have been synthesized through the 1,3-dipolar cycloaddition of azomethine ylides generated in situ by the condensation of dicarbonyl compounds (isatin or acenaphthenequinone) and secondary amino acids with dipolarophiles. The method is simple and provides diverse and biologically interesting products with excellent yields.



KEYWORDS: *spirooxindole, pyrrolidine/pyrrolizidine/pyrrolothiazole, 1,3-dipolar cycloaddition, combinatorial synthesis*

INTRODUCTION

In recent decades, combinatorial synthesis has received considerable attention in organic chemistry and chemical biology.[1] This strategy provides an efficient synthetic means for the combination of functionally and regio-chemically diverse small molecules toward the discovery of novel biologically active compounds.[2] According to this method, the products are formed in a straightforward procedure, for example one-pot multicomponent reactions,[3] and diversity can be achieved simply by varying the reacting materials.

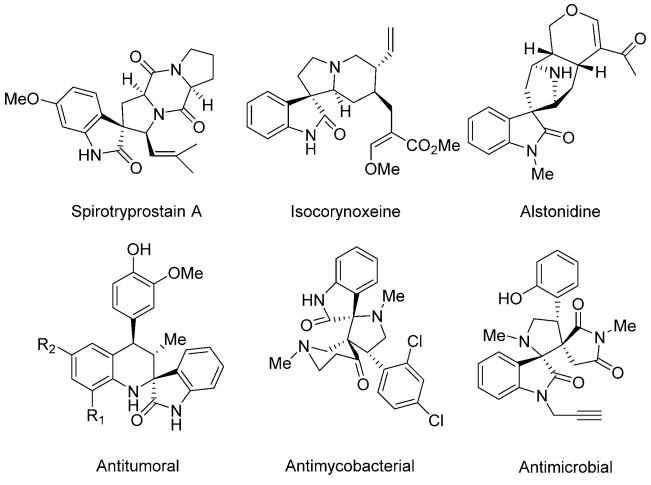


Figure 1. Biologically important molecules containing a spiro-oxindole core.

Spirooxindoles are attractive synthetic targets because of their prevalence in numerous natural products and applications in medicine and therapeutics.[4−6] A great number of new methods for their synthesis[7−9] and related reviews[10−12] have been rapidly developed in recent years. Moreover, functionalized pyrrolidines,[13] pyrrolizidines,[14] and pyrrolothiazoles[15] are the central skeletons for numerous alkaloids and pharmacologically important compounds. As a consequence, the integration of these scaffolds, spirooxindole and pyrrolidine/pyrrolizidine/pyrrolothiazole, into a molecule may result in the discovery of new drug candidates. (Figure 1)

1,3-dipolar cycloaddition of ylidic species, for example azomethine ylides with dipolarophiles, is a useful method for the construction of five-membered heterocycles, such as pyrrolidines and pyrrolizidines.[16−18] The synthesis of spiooxindole via 1,3-dipolar cycloaddition reaction of azomethine

Table 1. Optimizing the Reaction Solvents for the Synthesis of 4{*1,1,1*}

entry	solvent	temp (°C)	time (h)	yield[a] (%)
1	methanol	reflux	2.0	86
2	ethanol	reflux	2.0	80
3	glycol	reflux	2.0	70
4	chloroform	reflux	2.0	58
5	DMF	reflux	2.0	55
6	water	reflux	2.0	31
7	methanol	rt	2.0	56
8	methanol	40	2.0	72
9	methanol	60	2.0	86

[a]Isolated yield.

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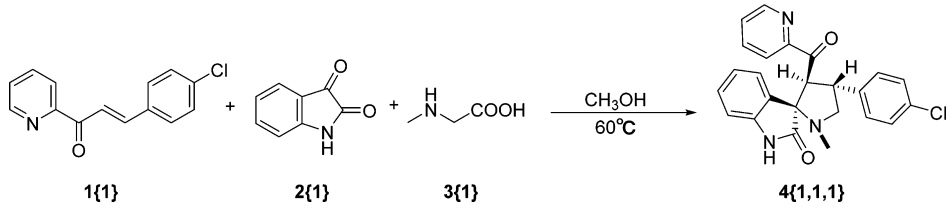
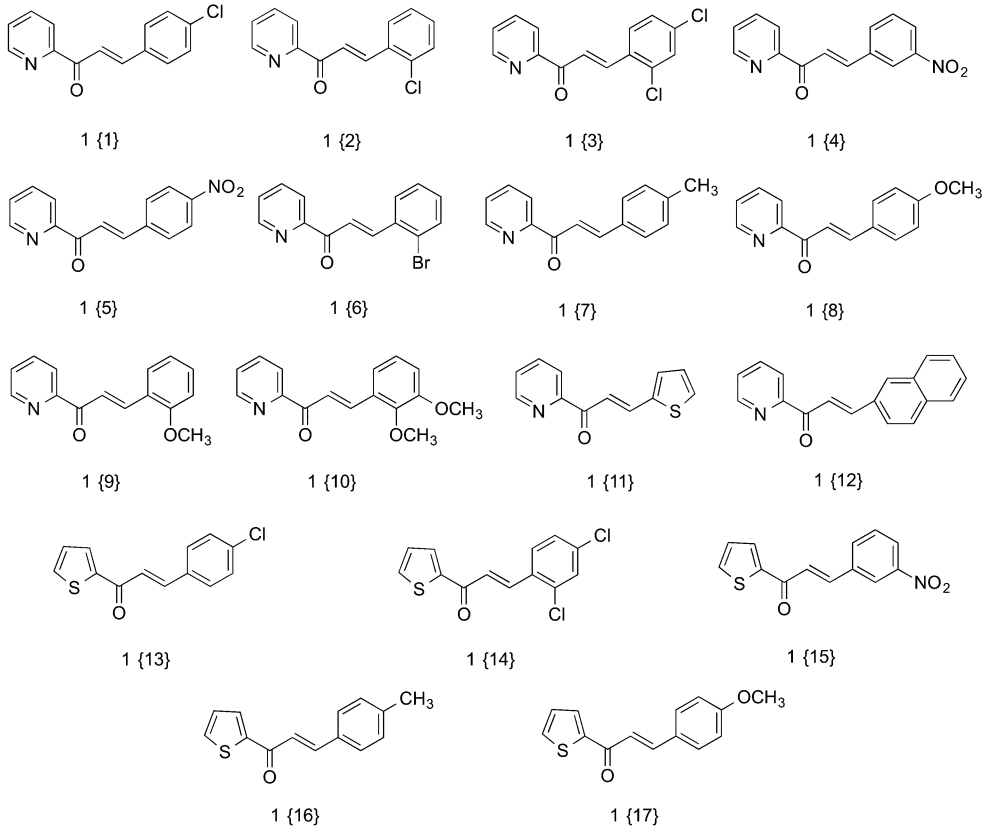
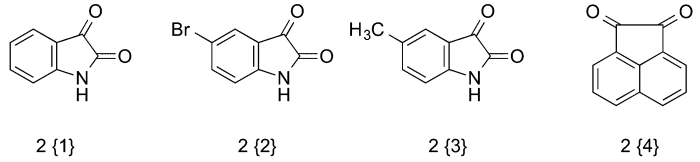
Scheme 1. Synthesis of 4{*1,1,1*}



Dipolarophiles 1



Dicarbonyl compounds 2



Secondary amino acids 3

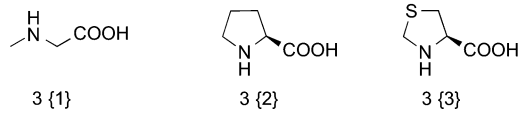


Figure 2. Chemical structures of the reagents.

ylides derived from dicarbonyl compounds like isatin, and secondary amino acids like sarcosine, L-proline has been reported.[19] Although the scope of 1,3-dipolar cycloaddition reaction in the synthesis of spiro compounds has been broadened by the use of different dipolarophiles,[20−24] to the best of our knowledge, the utilization of heterocyclic

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Table 2. Synthesis of Functionalized Spiro-Oxindole-Pyrrolidine/Pyrrolizidine/Pyrrolothiazole Derivatives 4, 5, and 6

entry	products	yield[a] (%)	time (h)	mp (°C)
1	4{*1,1,1*}	86	2	257−259
2	4{*2,1,1*}	81	2	266−268
3	4{*3,1,1*}	86	2	234−236
4	4{*4,1,1*}	85	2	243−245
5	4{*5,1,1*}	76	2	245−247
6	4{*6,1,1*}	78	3	267−269
7	4{*7,1,1*}	81	3	270−272
8	4{*8,1,1*}	85	2	258−260
9	4{*9,1,1*}	86	2	232−234
10	4{*10,1,1*}	86	2	249−251
11	4{*12,1,1*}	83	2	269−271
12	4{*1,3,1*}	80	3	265−267
13	4{*8,3,1*}	82	2	243−246
14	4{*2,2,1*}	79	3	273−275
15	4{*3,2,1*}	78	3	276−278
16	4{*8,2,1*}	76	3	246−248
17	5{*1,1,2*}	76	3	168−170
18	5{*2,1,2*}	78	3	208−210
19	5{*3,1,2*}	80	3	213−215
20	5{*4,1,2*}	82	3	230−232
21	5{*6,1,2*}	77	2	225−227
22	5{*8,1,2*}	80	2	200−202
23	5{*9,1,2*}	82	3	180−183
24	5{*10,1,2*}	86	3	210−212
25	5{*11,1,2*}	85	3	217−219
26	5{*12,1,2*}	83	3	243−245
27	5{*8,3,2*}	87	2	127−130
28	5{*2,2,2*}	76	2	226−228
29	5{*3,2,2*}	81	2	148−150
30	5{*8,2,2*}	79	3	145−147
31	6{*2,1,3*}	76	3	208−210
32	6{*3,1,3*}	79	3	224−227
33	6{*4,1,3*}	82	3	250−253
34	6{*6,1,3*}	78	3	226−228
35	6{*7,1,3*}	87	3	228−230
36	6{*8,1,3*}	84	3	153−155
37	6{*9,1,3*}	80	2	241−243
38	6{*10,1,3*}	88	2	144−146
39	6{*11,1,3*}	83	3	244−246
40	6{*12,1,3*}	88	3	167−170

[a]Isolated yield.

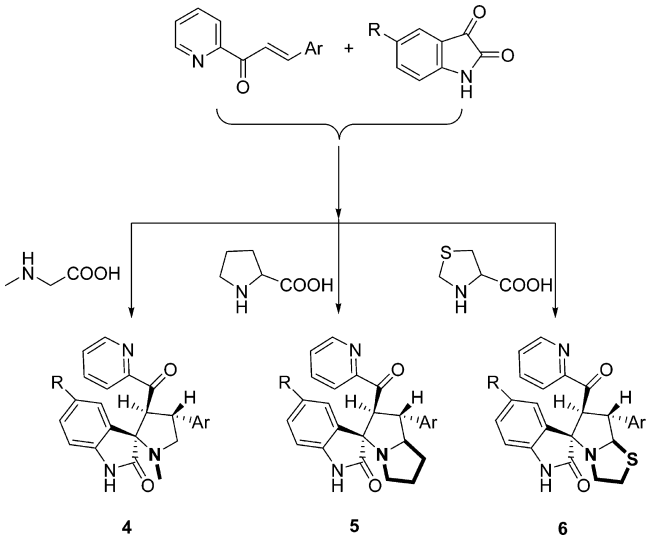

Figure 3. Diverse synthesized spiro-oxindoles **4**, **5**, and **6**.

Table 3. Functionalized Spiro-oxindole-pyrrolidine/pyrrolizidine Derivatives 8 Synthesized by the Procedures Shown in Scheme 3

entry	products	yield[a] (%)	time (h)	mp (°C)
41	8{*1,4,1*}	82	3	200−203
42	8{*3,4,1*}	85	3	205−206
43	8{*4,4,1*}	83	3	227−229
44	8{*5,4,1*}	85	3	215−217
45	8{*6,4,1*}	83	3	203−204
46	8{*7,4,1*}	84	4	225−228
47	8{*8,4,1*}	82	4	182−185
48	8{*9,4,1*}	81	3	206−208
49	8{*10,4,1*}	83	3	232−234
50	8{*11,4,1*}	82	3	188−190
51	8{*12,4,1*}	86	3	237−230
52	8{*2,4,2*}	80	4	191−193
53	8{*3,4,2*}	85	3	209−211
54	8{*6,4,2*}	83	3	212−214
55	8{*7,4,2*}	74	4	222−224
56	8{*8,4,2*}	77	4	196−198
57	8{*12,4,2*}	80	3	192−195

[a]Isolated yield.

substituted prop-2-en-1-one as dipolarophlies in cycloaddition of azomethine ylides has been less explored.

As our interest in constructing structural diverse heterocycles via multicomponent combinatorial synthesis and in continuation of our research in the synthesis of spirooxindoles,[25] herein, we report the synthesis of a new class of spirooxindoles through the regioselective cycloaddition reaction of azomethine ylides generated in situ from isatin/acenaphthenequinone and secondary amino acids such as sarcosine, L-proline and L-thioproline with the dipolarophiles 3-aryl-1-(pyridin-2-yl)-prop-2-en-1-one and 3-aryl-1-(thiophen-2-yl)prop-2-en-1-one.

RESULTS AND DISCUSSION

Initially, the three component reaction of 3-aryl-1-(pyridin-2-yl)-prop-2-en-1-one **1**{*1*}, isatin **2**{*1*}, and sarcosine **3**{*1*}, as a simple model substrate (Scheme 1), was investigated to establish the feasibility of the strategy and optimize the reaction conditions. The reaction was examined in different solvents such as methanol, ethanol, glycol, chloroform, DMF and water under refluxing condition. As is shown in Table 1, methanol as a solvent provided higher yield (Table 1, entry 1). Furthermore, the reaction was carried out at different temperatures ranging from room temperature (20 °C) to refluxing (65 °C). The yield of product **4**{*1,1,1*} was improved remarkably as the temperature increased to 60 °C and plateaued when the temperature was further increased to 65 °C. (Table 1, entries 7−9) Therefore, methanol and 60 °C were chosen as optimal conditions for all further reactions.

The optimized reaction conditions were then employed for library construction with diverse dipolarophiles **1**{*1*−*12*}, dicarbonyl compounds **2**{*1*−*3*}, and secondary amino acids **3**{*1*−*3*} (Figure 2). The corresponding functionalized spiro-oxindole- pyrrolidine/pyrrolizidine/pyrrolothiazole derivatives

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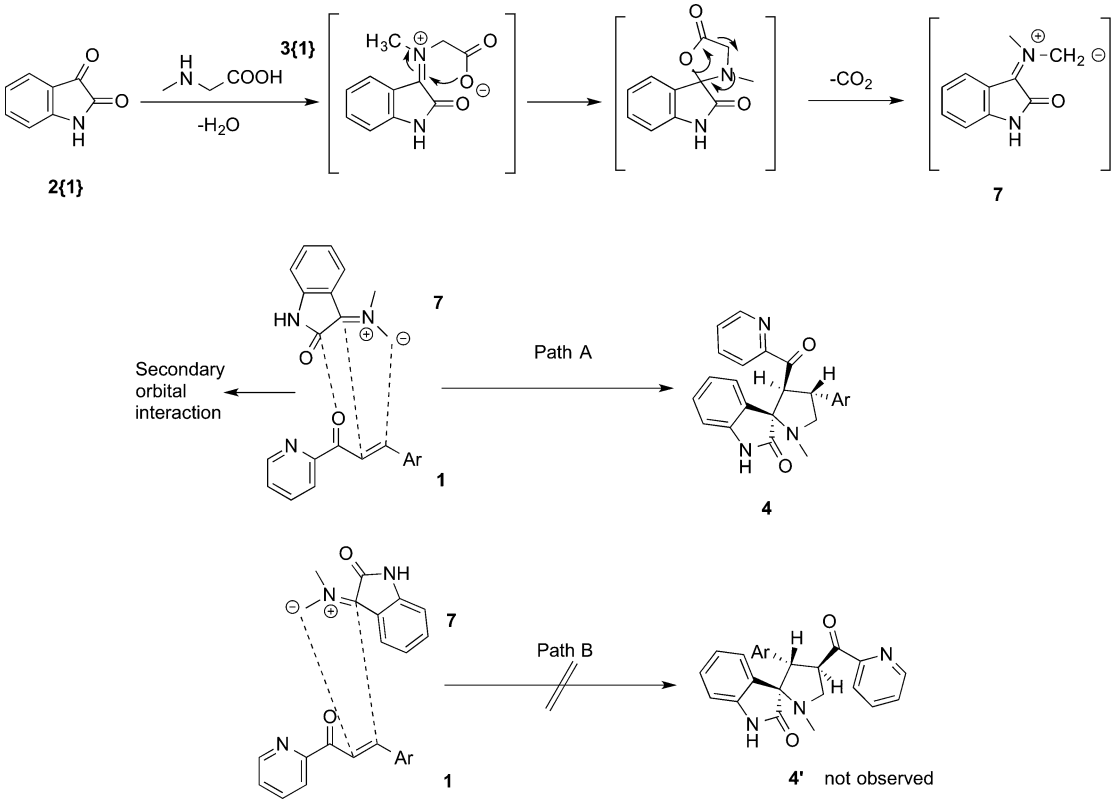
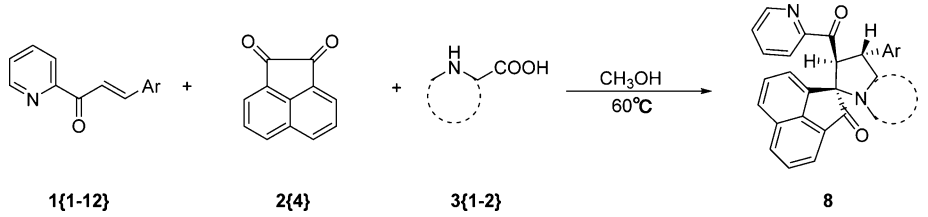
Scheme 2. Proposed Mechanism of the Synthesis of Spirooxindole Derivatives 4



Scheme 3. Synthesis of Functionalized Spiro-oxindole-pyrrolidine/pyrrolizidine Derivatives 8



4, **5**, **6** were obtained in good yields. The results are summarized in Table 2.

As shown in Table 2 and Figure 2, it was found that this method works with a wide variety of substrates. A large range of different substituted aromatic rings including electron-withdrawing groups, electron-donating groups, as well as naphthalene ring and heterocyclic ring can be found in the structures of dipolarophiles for the cycloaddition reactions. Moreover, the reactions with different substituted isatins also proceeded smoothly. In addition, when sarcosine **3**{*1*} was replaced by L-proline **3**{2} or L-thioproline **3**{3}, a series of expected products were obtained with satisfied yields under the same reaction conditions.

Proposed mechanism for the synthesis of spirooxindole derivatives **4** was described in Scheme 2. The reaction proceeds through the generation of azomethine ylide (dipole **7**) via the condensation of isatin **2** with sarcosine **3** and decarboxylation. The dipolarophiles **1** react with azomethine ylides (dipole **7**) in methanol to give the desired products spiro-oxindole-pyrrolidine derivatives **4**.

The regiochemistry of cycloaddition in the product formation can be explained by considering secondary orbital interaction (SOI)[26] of the carbonyl group of dipolarophile **1** with those of the ylide as shown in Scheme 2. Accordingly, the formation of regioisomer **4** via path A is more favorable, which is not possible in path B.[27,28] Hence, only one regioisomer **4**

Table 4. Functionalized Spiro-oxindole-pyrrolidine/pyrrolizidine Derivatives 9 Synthesized by the Procedures Shown in Scheme 4

entry	products	yield[a] (%)	time (h)	mp (°C)
58	**9**{*13,1,1*}	76	2	222−224
59	**9**{*14,1,1*}	80	3	243−245
60	**9**{*15,1,1*}	78	2	218−220
61	**9**{*16,1,1*}	78	3	209−211
62	**9**{*17,1,1*}	80	3	223−225
62	**9**{*16,2,1*}	79	3	231−233
64	**9**{*13,1,2*}	82	3	135−137
65	**9**{*14,1,2*}	79	3	158−160
66	**9**{*15,1,2*}	78	3	208−210
67	**9**{*16,1,2*}	79	3	202−204
68	**9**{*17,1,2*}	77	2	138−140
69	**9**{*13,2,2*}	78	2	212−214
70	**9**{*16,2,2*}	79	3	147−149

[a]Isolated yield.

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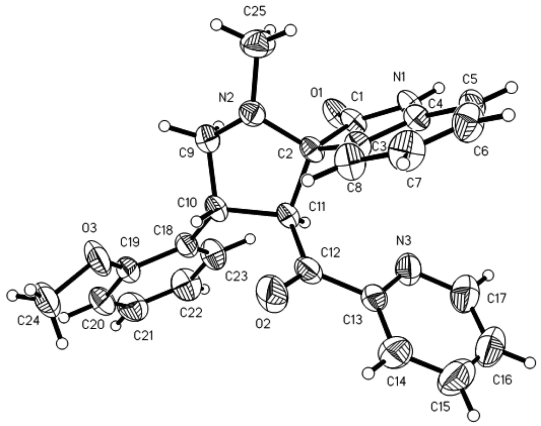


Figure 4. Crystal structure of **4**{*9,1,1*}.

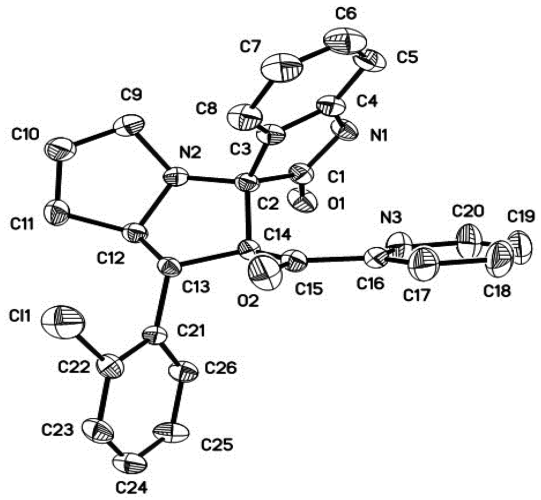


Figure 5. Crystal structure of **5**{*2,1,2*}.

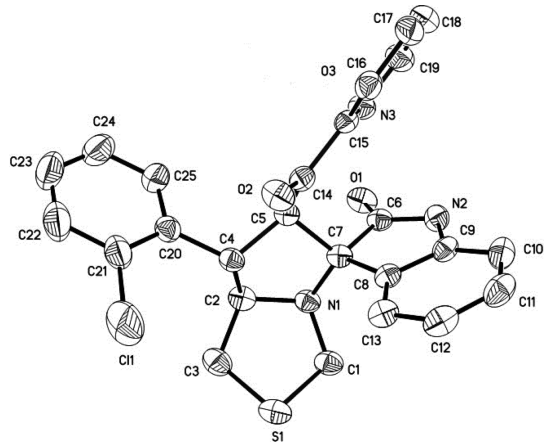


Figure 6. Crystal structure of **6**{*2,1,3*}.

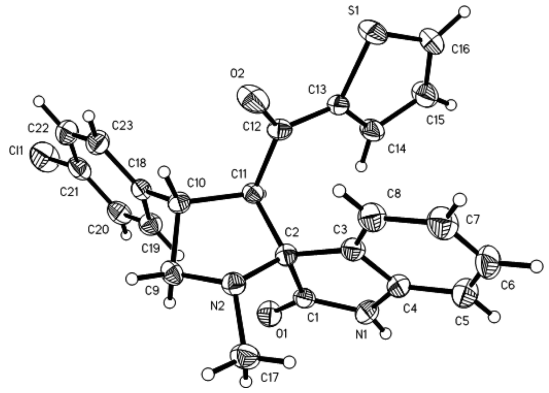


Figure 7. Crystal structure of **9**{*13,1,1*}.

was obtained in the reaction. Further, in these reactions steric factor plays an additional role in the regioselective formation of products.

To expand the scope of this three-component 1,3-dipolar cycloaddition reaction, the reaction of acenaphthenequinone **2**{*4*} and secondary amino acids **3**{*1*−*2*} with dipolarophiles **1**{*1*−*12*} was attempted (Scheme 3). To our delight, under the above optimized conditions, the reactions proceeded smoothly and a variety of the desired spiro-pyrrolidine/pyrrolizidine derivatives **8** were obtained in good yields (Table 3).

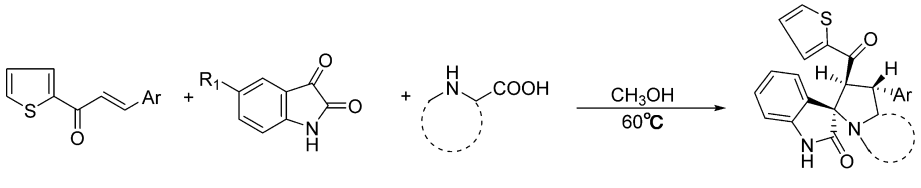
When 3-aryl-1-(thiophen-2-yl)prop-2-en-1-one were used as dipolarophiles to replace 3-aryl-1-(pyridin-2-yl)prop-2-en-1-one, a series of spiro-pyrrolidine/pyrrolizidine derivatives **9** were obtained under the same reaction conditions (Scheme 4). The results are summarized in Table 4.

In this study, all the products were characterized by melting points and IR, HRMS, ^{1}H NMR, and ^{13}C NMR spectral data. Furthermore, the structures of **4**{*9,1,1*}, **5**{*2,1,2*}, **6**{*2,1,3*}, and **9**{*13,1,1*} were established by X-ray crystallographic analysis (Figures 4−7).[29]

CONCLUSION

In conclusion, we have described a simple one-pot three-component reaction involving isatin/acenaphthenequinone, dipolarophlies, and secondary amino acids for the synthesis of a series of spirooxindoles derivatives in methanol. Particularly valuable features of this method include the higher yields of the products, broader substrate scope, mild reaction conditions, and the straightforwardness of the procedure, which make it a useful and attractive process for the synthesis of these important compounds.

Scheme 4. Synthesis of Functionalized Spiro-oxindole-pyrrolidine/pyrrolizidine Derivatives 9



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EXPERIMENTAL PROCEDURES

General. Melting points were recorded on an Electrothermal digital melting point apparatus and uncorrected. IR spectra were recorded on a Nicolet FT-IR500 spectrophotometer using KBr optics. ^{1}H NMR (400 MHz) spectra were recorded on a Varian Mercury MHz spectrometer using DMSO-d_6 or $CDCl_3$ as solvent and TMS as internal standard. HRMS analyses were conducted on a Bruker micro-TOF-Q-MS analyzer. X-ray diffraction data were made on a Rigaku Mercury CCD area detector with graphite monochromated Mo-Ka radiation.

Typical Experimental procedure. A mixture of isatin (1 mmol), 3-aryl-1-(pyridin-2-yl)prop-2-en-1-one (1 mmol), and sarcosine (1 mmol) in methanol (2 mL) was stirred at 60 °C for the given hours in Table 2. Upon completion, monitored by TLC, the reaction mixture was allowed to cool to room temperature. The precipitate was filtered off and washed with water (2 × 20 mL) and cool ethanol (2 × 0.5 mL) to afford the desired product. The pure compounds **4** were obtained by recrystallization from ethanol, and the single crystals for X-ray diffraction were obtained from ethanol solution by slow evaporation at room temperature. This procedure was followed for the synthesis of all the spirooxindoles **5**, **6**, **8**, and **9**.

ASSOCIATED CONTENT

Supporting Information

Additional materials including crystallographic data and NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

§J.L. and J.W. contributed equally to the work.

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Notes

The authors declare no competing financial interest.

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(29) Crystallographic data for the structure of **4**{*9,1,1*}, **5**{*2,1,2*}, **6**{*2,1,3*}, and **9**{*13,1,1*} reported in this paper have been deposited at the Cambridge Crystallographic Data Centre as supplementary publications with CCDC numbers 1003721, 1003908, 1003909, and 1003746, respectively.