

SCIENTIFIC REPORTS



OPEN

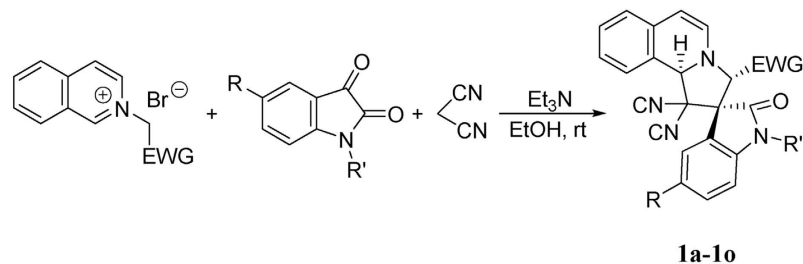
Formation of diverse polycyclic spirooxindoles via three-component reaction of isoquinolinium salts, isatins and malononitrile

Jing Sun, Guo-liang Shen, Ying Huang & Chao-Guo Yan

The triethylamine promoted three-component reaction of *N*-(4-nitrobenzyl), *N*-ethoxycarbonylmethylisoquinolinium bromide, isatins and malononitrile in ethanol afforded spiro[indoline-3,2'-pyrrolo[2,1-*a*]isoquinolines] in good yields and with high diastereoselectivity. The similar reaction of *N*-cyanomethylisoquinolinium chloride mainly gave complex indolo[2'',3'':2',3']pyrrolo[3',4':4,5]pyrrolo[2,1-*a*]isoquinoline derivatives. However, the three-component reaction of *N*-cyanomethylisoquinolinium chloride, isatins and ethyl cyanoacetate mainly resulted in functionalized spiro[indoline-3,8'-pyrido[2',3':4,5]pyrrolo[2,1-*a*]isoquinolines].

The cyclic nitrogen *N*-ylides such as pyridinium, thiazolium, quinolinium, isoquinolinium methylides are a special group of reactive azomethine ylides, which can be easily generated from the deprotonation of imidazolium, thiazolium, pyridinium salts and their benzo-fused analogs with reactive *N*-methyl group connecting with stronger electron-withdrawing groups¹⁻⁸. Because of cyclic nitrogen *N*-ylides have heterocyclic aromatic character, basicity, electron-attracting positive nitrogen atom, and the strongly electron-withdrawing substituent like carbonyl, cyano, or nitro groups connecting with methylene group, they have been become one of practical potential synthons in synthetic reactions⁹⁻¹⁸. The most common reaction is 1,3-dipolar cycloaddition of cyclic nitrogen *N*-ylides such as pyridinium ylide with various electron-deficient acetylene and alkenes to give indolizine derivatives, in which the pyridyl ring is retained¹⁹⁻²⁶. The second widely used reaction is the reaction of cyclic nitrogen *N*-ylides with alkenes bearing electron-withdrawing groups to give the corresponding cyclopropanes, 2,3-dihydrofurans and other heterocyclic compounds, in which the pyridyl unit is eliminated²⁷⁻³⁴. According to the structures of the substrates and the reaction conditions, the reaction of the cyclic nitrogen *N*-ylides showed very interesting molecular diversity^{26,35-39}. In the past few years, we investigated the multicomponent reactions by employing easily generated cyclic nitrogen ylides as the main substrates and have successfully developed a number of highly efficient protocols for synthesis of some biologically important nitrogen-containing heterocyclic compounds⁴⁰⁻⁴⁸. Recently, we successfully found that the cycloaddition reaction of the cyclic nitrogen *N*-ylides with reactive 3-phenacylideneoxindoles resulted in diverse spirooxindole systems including spiro[indoline-3,1'-pyrrolo[2,1-*a*]isoquinolines], spiro[cyclopropane-1,3'-indolines], 3-furan-3(2H)-ylideneindolin-2-ones, spiro[benzo[d]pyrrolo[2,1-*b*]thiazole-3,3'-indolines], and complex cyclopentyl dispirooxindoles⁴⁹⁻⁵⁷. We also found that three-component reactions of *N*-benzylbenzimidazolium salts, isatins and malononitrile or ethyl cyanoacetate gave a series of the novel zwitterionic salts and the unexpected products with opening of the imidazole ring⁵⁸. These results together with the previously reports⁵⁹⁻⁶⁴ indicated that the 1,3-dipolar cycloaddition reactions of cyclic nitrogen *N*-ylides with 3-methyleneoxindoles have fruitful chemistry. Due to the spirooxindole existing in a large number of naturally occurring and medicinally relevant substances, the development of efficient method for constructing the spirooxindole motif is of great importance in synthetic organic and medicinal chemistry⁶⁵⁻⁷². Against this background and in continuation of our efforts to develop new efficient synthetic methods for complex spirooxindoles⁷³⁻⁸³, herein we wish to report the interesting results of three-component

College of Chemistry & Chemical Engineering, Yangzhou University, Yangzhou 225002, China. Correspondence and requests for materials should be addressed to C.-G.Y. (email: cgyan@yzu.edu.cn)



Entry	Compd	EWG	R	R ¹	Yield (%) ^b
1	1a	<i>p</i> -O ₂ NC ₆ H ₄	Cl	<i>n</i> -C ₄ H ₉	84
2	1b	<i>p</i> -O ₂ NC ₆ H ₄	Cl	CH ₂ C ₆ H ₅	90
3	1c	<i>p</i> -O ₂ NC ₆ H ₄	CH ₃	<i>n</i> -C ₄ H ₉	78
4	1d	<i>p</i> -O ₂ NC ₆ H ₄	CH ₃	H	81
5	1e	<i>p</i> -O ₂ NC ₆ H ₄	CH ₃	CH ₂ C ₆ H ₅	88
6	1f	<i>p</i> -O ₂ NC ₆ H ₄	H	CH ₂ C ₆ H ₅	85
7	1g	<i>p</i> -O ₂ NC ₆ H ₄	F	<i>n</i> -C ₄ H ₉	83
8	1h	<i>p</i> -O ₂ NC ₆ H ₄	F	CH ₂ C ₆ H ₅	87
9	1i	CO ₂ C ₂ H ₅	H	CH ₂ C ₆ H ₅	62
10	1j	CO ₂ C ₂ H ₅	Cl	<i>n</i> -C ₄ H ₉	70
11	1k	CO ₂ C ₂ H ₅	Cl	CH ₂ C ₆ H ₅	72
12	1l	CO ₂ C ₂ H ₅	CH ₃	<i>n</i> -C ₄ H ₉	86
13	1m	CO ₂ C ₂ H ₅	CH ₃	CH ₂ C ₆ H ₅	80
14	1n	CO ₂ C ₂ H ₅	CH ₃	H	53
15	1o	CO ₂ C ₂ H ₅	F	<i>n</i> -C ₄ H ₉	76

a. Reaction conditions: isoquinolinium salt (1.2 mmol), isatin (1.0 mmol), malononitrile (1.0 mmol), Et₃N (2.0 mmol), EtOH (15.0 mL), rt, 12 hrs. b. Isolated yield.

Figure 1. Synthesis of spiro[indoline-3,2'-pyrrolo[2,1-*a*]isoquinolines] **1a-1o**^a.

reactions of *N*-(4-nitrobenzyl), *N*-ethoxycarbonylmethyl and *N*-cyanomethylisoquinolinium salts with isatins and malononitrile as well as ethyl cyanoacetate.

Results and Discussion

According to our previously established reaction conditions⁵⁸, an equivalent amount of *N*-(4-nitrobenzyl) isoquinolinium bromide, isatins and malononitrile in ethanol in the presence of triethylamine as base was stirred at room temperature overnight. The reaction was accomplished to give the expected spiro[indoline-3,2'-pyrrolo[2,1-*a*]isoquinolines] **1a-1h** in satisfactory yields (Fig. 1, entries 1–8). The pure products can be easily obtained after simple filtration of the resulting precipitates and washing with cold ethanol. ¹H NMR and ¹³C NMR spectroscopy clearly indicated that only one isomer exists in the obtained products **1a-1h**. The single crystal structures of the three compounds **1a** (Fig. 2), **1c** (Fig. s1 in SI) and **1e** (Fig. s2 in SI) were successfully determined by X-ray diffraction. The three single crystal structures all showed that the *p*-nitrophenyl group and phenyl group of oxindoline moiety exist in *trans*-configuration. On the basis of spectroscopy and single crystal

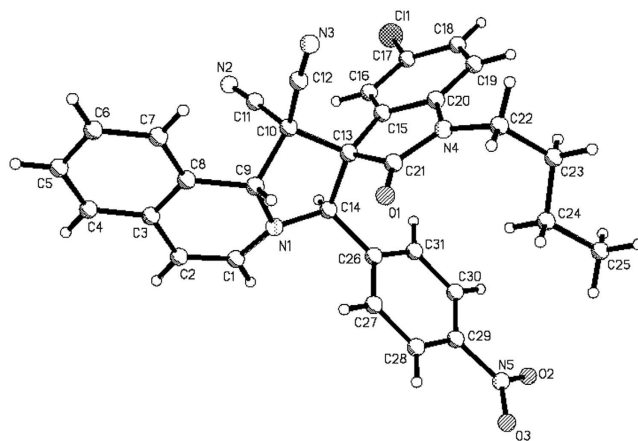


Figure 2. Molecular structure of spiro compound **1a**.

structures, it can be concluded that the thermodynamically stable *trans*-diastereoisomer of spiro[indoline-3,2'-pyrrolo[2,1-*a*]isoquinolines] was predominately produced in this base promoted three-component reaction. Moreover, when *N*-ethoxycarbonylmethylisoquinolinium bromide was employed under the same reaction conditions, the desired spiro products **1i–1o** were also prepared in good yields (Fig. 1, entries 9–15). The crystal structure of the compound **1j** (Fig. s3 in SI) indicated that it has the same configuration to that of compounds **1a**, **1c** and **1e**. Thus, the relative *trans*-configuration of spiro products **1i–1o** were also elucidated on the basis of ^1H NMR spectra and determination of single crystal structure of the compound **1j**. On the other hand, when *N*-phenacylisoquinolinium bromides were employed in the three-component reaction, we were very disappointed to find that the reaction resulted in complex mixtures, which were unable to be separated out. It has been known that *N*-phenacylisoquinolinium bromides usually have higher reactivity than that of *N*-*p*-nitrobenzyl- and *N*-ethoxycarbonylmethylisoquinolinium bromides^{49–57}. In order to get good results, we carefully examined the reaction conditions for *N*-phenacylisoquinolinium bromides and did not get the expected products. This results might be due to the instability of the expected spiro[indoline-3,2'-pyrrolo[2,1-*a*]isoquinolines] with benzoyl groups.

In order to establish the generality of this three-component reaction, we extended the above reaction protocol to *N*-cyanomethylisoquinolinium chloride, which was previously prepared from reaction of isoquinoline and chloroacetonitrile in refluxing acetonitrile. Under similar reaction conditions, the three-component reaction of isatins, malononitrile with *N*-cyanomethylisoquinolinium chloride afforded complex polycyclic compounds **2a–2l** as the main products in moderate to good yields and the corresponding zwitterionic compounds as byproducts in very low yields (Fig. 3). For convenience, only two zwitterionic compounds **3a** and **3b** were successfully separated out in 14% and 10% yields, respectively. The structures of the obtained compounds **2a–2l** and **3a–3b** were fully characterized by IR, HRMS, ^1H and ^{13}C NMR spectroscopy. The single crystal structures of compounds **2d** (Fig. 4), **2e** (Fig. s4 in SI), **2k** (Fig. s5 in SI) and **3b** (Fig. 5) were determined by X-ray diffraction. Comparing the structures of compounds **1a–1o** with that of compounds **2a–2l**, it can be seen that compounds **2a–2l** have two additional pyrrolidine rings on the skeleton of spiro[indoline-3,2'-pyrrolo[2,1-*a*]isoquinolines] **1a–1o**, which suggested that the initially formed spiro compounds **1** underwent further transformations in the reaction system. The byproducts **3a–3b** were obviously coming from a separate reaction mechanism.

In order to explain the formation mechanism of the spiro compounds **1** and **2**, a plausible reaction mechanism was proposed on the basis of the known 1,3-dipolar cycloaddition reactions of the cyclic nitrogen ylides^{49–58} (Fig. 6). Initially, triethylamine promoted condensation of isatin with malononitrile could afford isatylidene malononitrile (**A**). An isoquinolinium ylide was generated *in situ* from basic deprotonation of the isoquinolinium salt. Secondly, Michael addition of the isoquinolinium ylide to isatylidene malononitrile (**A**) resulted in intermediate (**B**). Thirdly, the intramolecular coupling of the cyclic iminium ion with the carbanion to give the spiro compound **1**. On the other hand, the spiro compound **1** might be directly formed by the concerted addition reaction of isoquinolinium ylide with isatylidene malononitrile (**A**). In case of reaction with *N*-(4-nitrobenzyl) and *N*-ethoxycarbonylmethyl isoquinolinium salts, the stable spiro compound **1** was separated out as the final product. In the case of *N*-cyanomethylisoquinolinium salt, further nucleophilic addition of the carbanion of malononitrile to the spiro compound **1** afforded a new intermediate (**C**). Then, the intramolecular attack of one cyano group in intermediate (**C**) to the cyclic imine afforded the obtained polycyclic spiro compound **2**.

Encouraged by the above results, ethyl cyanoacetate and methyl cyanoacetate were also employed as substrates to replace malononitrile under same reaction conditions. Instead of giving spiro[indoline-3,2'-pyrrolo[2,1-*a*]isoquinolines], new types of polycyclic compounds **4a–4g** were produced in moderate to good yields (Fig. 7). In order to elucidate the structures of the polycyclic compounds **4a–4g**, four single crystal structures of **4b** (Fig. 8), **4c**, **4d** and **4e** (Fig. s6–s8 in SI) were successfully determined by X-ray diffraction. From Fig. 8, it can be seen that the neutral compounds **4a–4g** have similar structural features as zwitterionic compounds **3a–3b**, which suggested that they were produced according to an alternative reaction process.

Although an accurate interpretation of the reaction mechanism remains elusive, according to the experimental observations and the closely related reports⁸⁴, a plausible mechanism for the formation of polycyclic

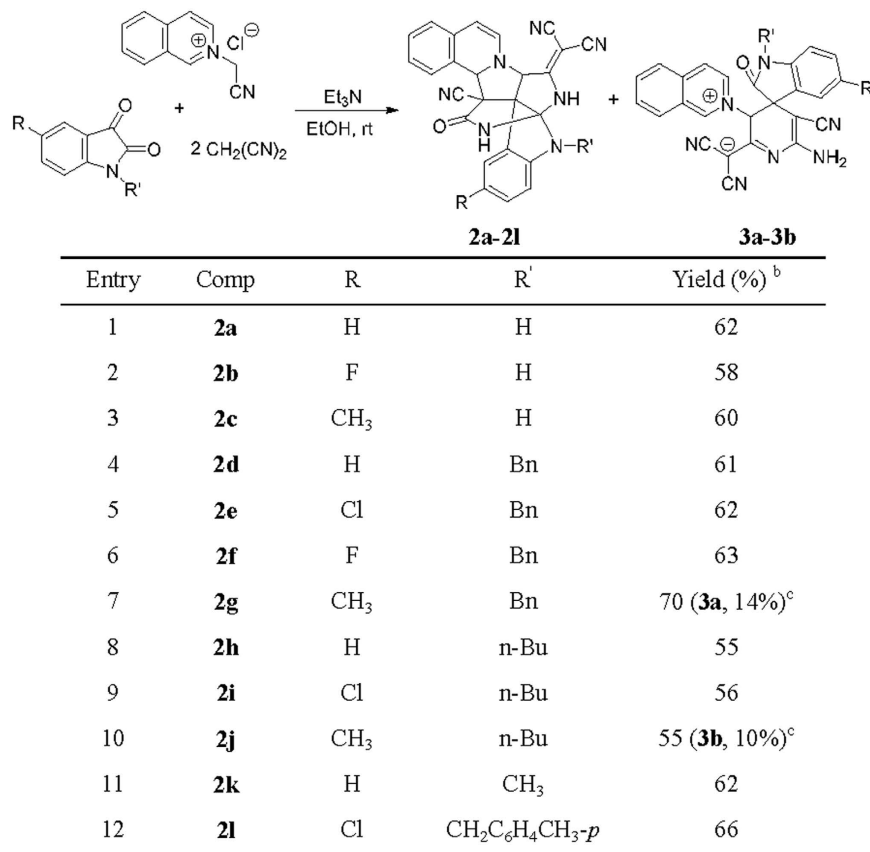


Figure 3. Synthesis of indolo[2'',3'':2',3']pyrrolo[3',4':4,5]pyrrolo[2,1-a]isoquinolines **2a-2l**^a.

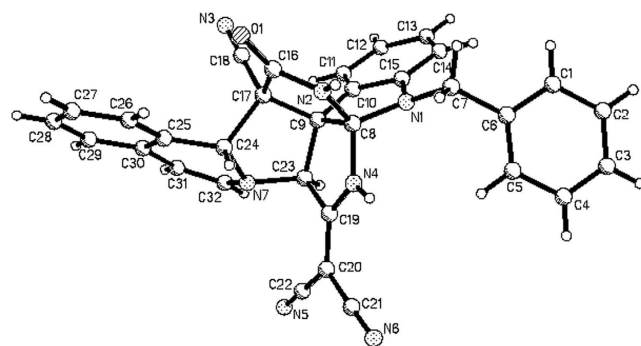


Figure 4. Molecular structure of spiro compound **2d**.

compounds **4** are proposed in Fig. 9. Presumably, the initially formed isatylidene cyanoacetate (**A**) reacts with the isoquinolinium ylide to afford adduct (**B**) as outlined in Fig. 6. Subsequently a Michael addition of second molecule of ethyl cyanoacetate to the adduct (**B**) provides new intermediate (**C**), which was converted to the intermediate (**D**). Then, the polycyclic intermediate (**E**) could be formed by an annulation process, which ultimately provides polycyclic product **4**.

Conclusion

In summary, we have systematically investigated the three-component reaction of various isoquinolinium salts with isatin and malononitrile or ethyl cyanoacetate. The reaction provided a variety of products depending on the structures of the cyclic nitrogen ylides and the functionalized groups in the substrates, from which the expected functionalized spiro[indoline-3,2'-pyrrolo[2,1-a]isoquinolines] and several complex polycyclic spirooxindoles were successfully synthesized in good yields. Possible formation mechanisms accounting for the formation of these complex spiro compounds have been proposed. This protocol has advantages of the mild reaction conditions, easily accessible starting materials, broad substrate scope, satisfactory yields and high diastereoselectivity,

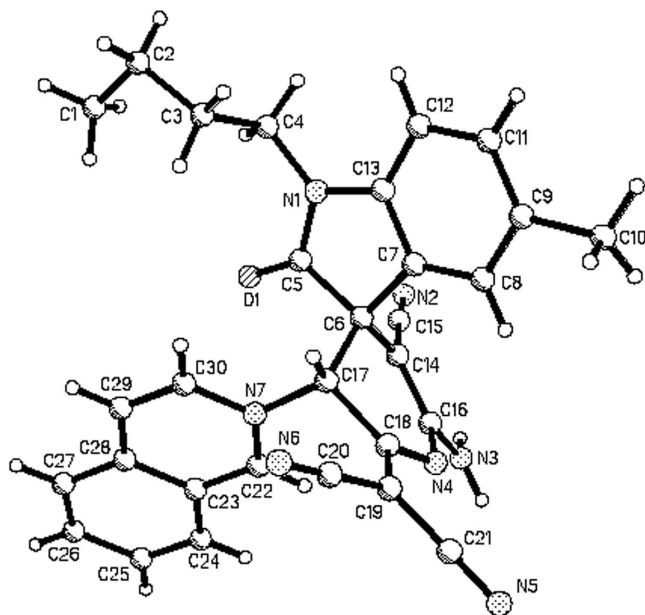


Figure 5. Molecular structure of spiro compound 3b.

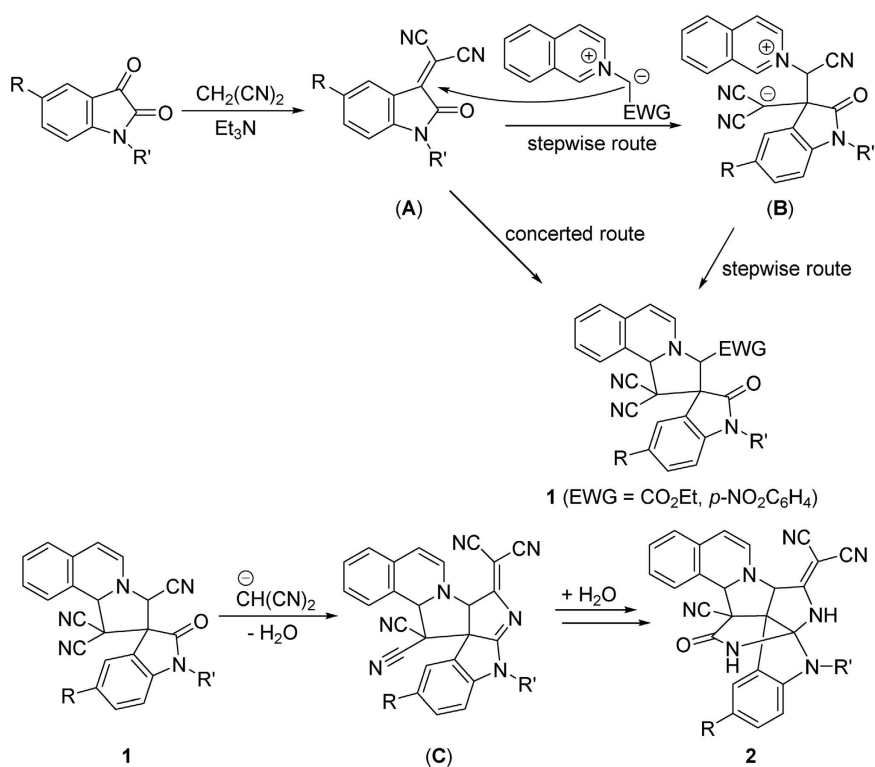
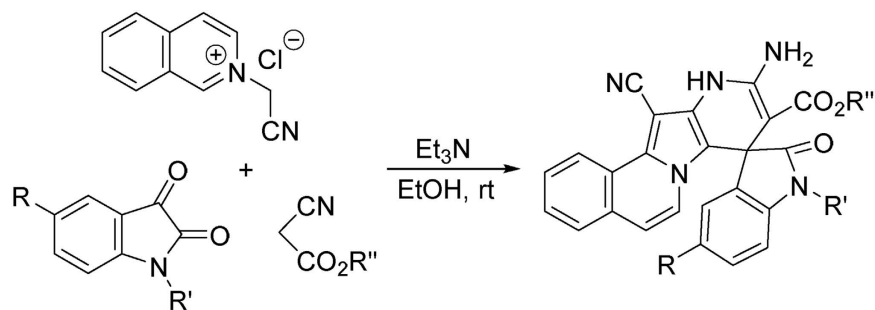


Figure 6. Proposed formation mechanism for spiro compounds 1 and 2.

which makes it a useful and attractive method for the synthesis of the complex heterocyclic spirooxindole systems in synthetic and medicinal chemistry.

Methods

Materials. All reactions were performed in atmosphere unless noted. All reagents were commercially available and use as supplied without further purification. NMR spectra were collected on either an Agilent DD2400 MHz spectrometer or a Bruker AV-600 MHz spectrometer with internal standard tetramethylsilane (TMS) and signals as internal references, and the chemical shifts (δ) were expressed in ppm. High-resolution Mass (ESI) spectra were obtained with Bruker Micro-TOF spectrometer. The Fourier transform infrared (FTIR) samples were prepared as



Entry	Comp	R	R'	R''	Yield (%) ^b
1	4a	H	Bn	Et	71
2	4b	F	Bn	Et	72
3	4c	Cl	Bn	Et	75
4	4d	Cl	n-Bu	Et	68
5	4e	CH ₃	n-Bu	Et	66
6	4f	Cl	Bn	Me	66
7	4g	CH ₃	Bn	Me	67

Figure 7. Synthesis of spiro[indoline-3,8'-pyrido[2',3':4,5]pyrrolo[2,1-a]isoquinolines] **4a-4g**^a.

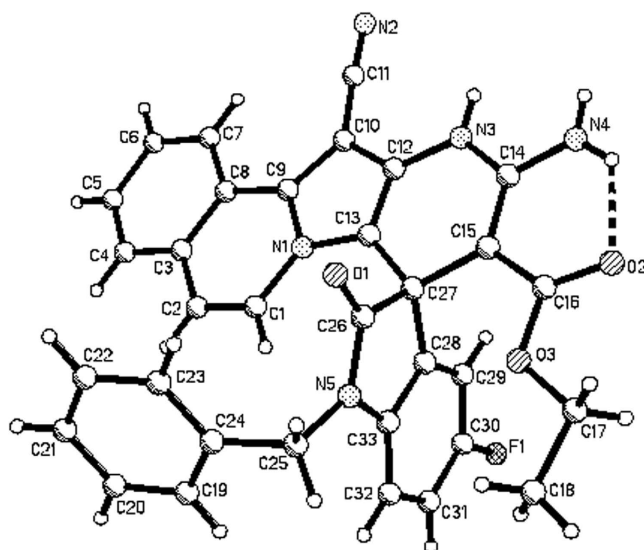


Figure 8. Molecular structure of spiro compound **4b**.

thin films on KBr plates, and spectra were recorded on a Bruker Tensor 27 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). X-ray data were collected on a Bruker Smart APEX-2 CCD diffractometer.

General procedure for the three-component reaction of N-4-nitrobenzyl and N-ethoxycarbonylmethylisoquinolinium salts with isatin and malononitrile. To a 50 mL round flask was added N-(4-nitrobenzyl) or N-ethoxycarbonylmethyl isoquinolinium salt (1.0 mmol), isatin (1.0 mmol), malononitrile (1.0 mmol) and triethylamine (2.0 mmol) in ethanol (15.0 mL). The solution was stirred at room temperature for twelve hours. The resulting precipitates were collected by filtration, which were washed with cold ethanol to give the pure products for analysis.

General procedure for the three-component reaction of N-cyanomethylisoquinolinium chloride with isatin and malononitrile. A mixture of N-cyanomethylisoquinolinium chloride (1.0 mmol),

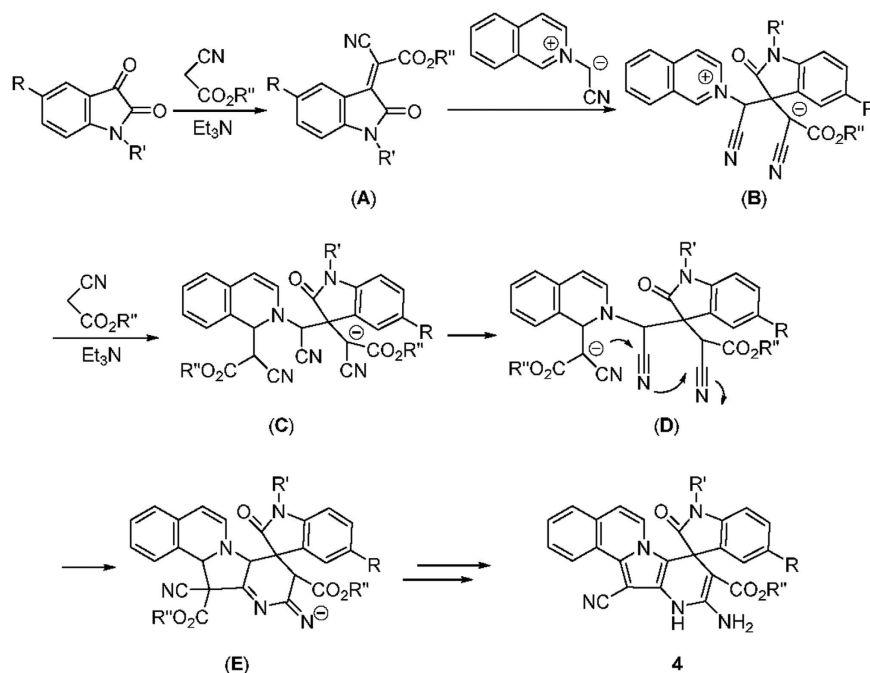


Figure 9. Proposed formation mechanism for spiro compound **4**.

isatin (1.0 mmol), malononitrile (2.2 mmol) and triethylamine (2.0 mmol) in ethanol (15.0 mL). The solution was stirred at room temperature for twelve hours. The resulting precipitates were collected by filtration, which were subjected to preparative thin-layer chromatography with a mixture of light petroleum and ethyl acetate (V/V = 3:1) to give the pure products **2a-2l** and **3a-3b** for analysis.

General procedure for the three-component reaction of *N*-cyanomethylisoquinolinium chloride with isatin and alkyl cyanoacetate. A mixture of *N*-cyanomethylisoquinolinium chloride (1.0 mmol), isatin (1.0 mmol), methyl or ethyl cyanoacetate (2.0 mmol) and triethylamine (2.0 mmol) in ethanol (15.0 mL) was stirred at room temperature for twelve hours. The resulting precipitates were collected by filtration, which were subjected to preparative thin-layer chromatography with a mixture of light petroleum and ethyl acetate (V/V = 3:1) to give the pure products **4a-4g** for analysis.

References

- Kröhnke, F. *et al.* Syntheses Using the Michael Addition of Phridinium Salts. *Angew. Chem. Int. Ed.* **1**, 626–632 (1962).
- Kröhnke, F. Syntheses Using Pyridinium Salts. *Angew. Chem. Int. Ed.* **2**, 225–238 (1963).
- Jacobs, J., Van Hende, E., Claessens, S. & De Kimpe, N. Pyridinium ylides in heterocyclic synthesis. *Current Org. Chem.* **15**, 1340–1362 (2011).
- Bull, J. A., Mousseau, J. J., Pelletier, G. & Charette, A. B. Synthesis of Pyridine and Dihydropyridine Derivatives by Regio- and Stereoselective Addition to *N*-Activated Pyridines. *Chem. Rev.* **112**, 2642–2713 (2012).
- Eryazici, I., Moorefield, C. N., Durmus, S. & Newkome, G. R. Synthesis and Single-Crystal X-ray Characterization of 4,4'-Functionalized 4'-(4-Bromophenyl)-2,2':6',2''-terpyridines. *J. Org. Chem.* **71**, 1009–1014 (2006).
- Tu, S. J. *et al.* Kröhnke reaction in aqueous media: one-pot clean synthesis of 4'-aryl-2,2':6',2''-terpyridines. *Tetrahedron* **63**, 381–388 (2007).
- Constable, E. C., Edwards, A. J., Martínez-Máñez, R. & Raithby, P. R. Metallosupramolecules bearing pendant redox-active domains: synthesis and coordination behavior of the metallocene-functionalized helicand 4', 4''-di(ferrocenyl)-2,2':6',2''-6''-2'''-6'''-2''''-sexiptyridine. *J. Chem. Soc., Dalton Trans.* 3253–3261 (1995).
- Constable, E. C. *et al.* Synthesis and structural characterization of 3,5-[1,1'-ferrocenediyl]-1,7-dioxo-1,7-di(2-pyridyl)-4-(2-pyridylcarbonyl) heptane; an unexpected compound obtained from the reaction of ferrocene-1,1'-dicarbaldehyde with 2-acetylpyridine. *Polyhedron* **14**, 3061–3066 (1995).
- Bora, U., Saikia, A. & Boruah, R. C. A Novel Microwave-Mediated One-Pot Synthesis of Indolizines via a Three-Component Reaction. *Org. Lett.* **5**, 435–438 (2003).
- Armstrong, R. W., Combs, A. P., Tempest, P. A., Brown, S. D. & Keating, T. A. Multiple-Component Condensation Strategies for Combinatorial Library Synthesis. *Acc. Chem. Res.* **29**, 123–131 (1996).
- Domling, A. & Ugi, I. Multicomponent reactions with isocyanides. *Angew. Chem. Int. Ed.* **39**, 3168–3210 (2000).
- Sasaki, T., Kanematsu, K., Yukimoto, Y. & Ochiai, S. Heteroaromaticity. XLIII. Orientation in the 1,3-dipolar cycloaddition reactions of heteroaromatic nitrogen methyldes with dipolarophiles. *J. Org. Chem.* **36**, 813–818 (1971).
- Xia, Z. Q. *et al.* Controlling chemoselectivity; application of DMF di-*t*-butyl acetal in the regioselective synthesis of 3-monosubstituted indolizines. *Tetrahedron. Lett.* **47**, 8817–8820 (2006).
- Katritzky, A. R., Grzeskowiak, N. E. & Alvarez-Buila, J. Preparation of tetrahydroindolizines from pyridinium and isoquinolinium ylides. *J. Chem. Soc. Perkin Trans.* 1180–1185 (1981).
- Druta, I. I., Dinica, R. M., Bacu, E. & Humelnicu, I. Synthesis of 7,7-bisindolizines by the reaction of 4,4'-bipyridinium-ylides with activated alkynes. Original Research Article. *Tetrahedron* **54**, 10811–10818 (1998).
- Dinica, R. M., Druta, I. I. & Pettinari, C. The synthesis of substituted 7,7'-bisindolizines via 1,3-dipolar cycloaddition under microwave irradiation. *Synlett* **7**, 1013–1015 (2000).

17. Druta, I. I., Andrei, M. A., Ganj, C. I. & Aburel, P. S. Synthesis of indolizine derivatives by the reaction of 2-(2-pyridyl)-pyridinium ylides with ethylenic dipolarophiles Original Research. *Tetrahedron* **55**, 13063–13070 (1999).
18. Furdul, B., Dinica, R., Druta, I. I. & Demeunynck, M. Improved synthesis of cationic pyridinium-substituted indolizines. *Synthesis* **16**, 2640–2642 (2006).
19. Peng, W. M. & Zhu, S. Z. Reactions of N-benzyl-pyridinium or -isoquinolinium ylides with ethyl 3-fluoro-3-(fluoroalkyl)acrylates to give fluoroalkyl-substituted indolizine and pyrrolo[2,1-a]isoquinoline derivatives. *J. Chem. Soc. Perkin Trans. 1*, 3204–3210 (2001).
20. Zhu, S. Z., Qin, C. Y., Wang, Y. L. & Chu, Q. L. Preparation of 1-(trifluoroacetyl)indolizines and their derivatives via cycloaddition of pyridinium N-ylides with 4-ethoxy-1,1,1-trifluorobut-3-en-2-one. *J. Fluorine Chem.* **99**, 183–187 (1999).
21. Zhang, X. C. & Huang, W. Y. A one-step approach to 1-(fluoroalkyl)indolizine derivatives. *Synthesis* **1**, 51–54 (1999).
22. Wu, K. & Chen, Q. Y. Synthesis of fluorinated indolizines and 4H-pyrrolo[1,2-a]benzimidazoles via 1,3-dipolar cycloaddition of fluoroalkenes to N-ylides. *Synthesis* 35–40 (2003).
23. Chuang, C. P. & Tsai, A. I. Pyridinium ylides in the synthesis of 2,3-dihydrofurans. *Synthesis* **4**, 675–679 (2006).
24. Ruano, J. L. G., Fraile, A., Martín, M. R., González, G. & Fajardo, C., Martín-Castro, A. M. Asymmetric synthesis of pyrrolo[2,1-a]isoquinoline derivatives by 1,3-dipolar cycloadditions of stabilized isoquinolinium N-ylides with sulfinyl dipolarophiles. *J. Org. Chem.* **76**, 3296–3305 (2011).
25. Khlebnikov, A. F., Golovkina, M. V., Novikov, M. S. & Yufit, D. S. A Novel Strategy for the Synthesis of 3-(N-Heteryl)pyrrole Derivatives. *Org. Lett.* **14**, 3768–3771 (2012).
26. Brioché, J., Meyer, C. & Cossy, J. Synthesis of 2-Aminoindolizines by 1,3-Dipolar Cycloaddition of Pyridinium Ylides with Electron-Deficient Ynamides. *Org. Lett.* **17**, 2800–2803 (2015).
27. Liu, Y. & Sun, J. W. Copper(II)-Catalyzed Synthesis of Benzo[f]pyrido[1,2-a]indole-6,11-dione Derivatives via Naphthoquinone Difunctionalization Reaction. *J. Org. Chem.* **77**, 1191–1197 (2012).
28. Osyanin, V. A., Osipov, D. V. & Klimochkin, Y. N. Reactions of o-Quinone Methides with Pyridinium Methylenes: A Diastereoselective Synthesis of 1,2-Dihydronaphtho[2,1-b]furans and 2,3-Dihydrobenzofurans. *J. Org. Chem.* **78**, 5505–5520 (2013).
29. Wang, F. Y., Shen, Y. M., Hu, H. Y., Wang, X. S. & Wu, H. & Liu, Y. Copper(II)-Catalyzed Indolizines Formation Followed by Dehydrogenative Functionalization Cascade to Synthesize 1-Bromoindolizines. *J. Org. Chem.* **79**, 9556–9566 (2014).
30. Allgäuer, D. S., Mayer, P. & Mayr, H. Nucleophilicity Parameters of Pyridinium Ylides and Their Use in Mechanistic Analyses. *J. Am. Chem. Soc.* **135**, 15216–15224 (2013).
31. Allgäuer, D. S. & Mayr, H. One-Pot Two-Step Synthesis of 1-(Ethoxycarbonyl)indolizines via Pyridinium Ylides. *Eur. J. Org. Chem.* 6379–6388 (2013).
32. Allgäuer, D. S. & Mayr, H. Electrophilicities of 1,2-Disubstituted Ethylenes. *Eur. J. Org. Chem.* 2956–2963 (2014).
33. Belei, D. et al. A direct synthesis of octahydropyrrolo[2,1,5-cd]indolizin-6-one derivatives. *Synlett* 545–548 (2012).
34. Hopf, H. et al. A Facile Synthesis of Pechmann Dyes. *Chem. Eur. J.* **20**, 5565–5568 (2014).
35. Danac, R. et al. New indolizines with phenanthroline skeleton: Synthesis, structure, antimycobacterial and anticancer evaluation. *Bioorg. Med. Chem.* **23**, 2318–2327 (2015).
36. Schmitz, C., Leitner, W. & Francio, G. Pinene-Derived Monodentate Phosphoramidites for Asymmetric Hydrogenation. *Eur. J. Org. Chem.* 2889–2901 (2015).
37. Shi, F. et al. Transition-Metal-Free Synthesis of Indolizines from Electron-Deficient Alkenes via One-Pot Reaction Using TEMPO as an Oxidant. *Synthesis* **48**, 413–420 (2016).
38. Xiang, J. C., Wang, M., Cheng, Y. & Wu, A. X. Molecular Iodine-Mediated Chemoselective Synthesis of Multisubstituted Pyridines through Catabolism and Reconstruction Behavior of Natural Amino Acids. *Org. Lett.* **18**, 24–27 (2016).
39. Wei, H. P. et al. Three-Component Reaction of 2-Oxoaldehydes, Cyclic 1,3-Dicarbonyl Compounds, and 4-Aminopyridines. *Synthesis* **48**, 1734–1740 (2016).
40. Yan, C. G., Cai, X. M., Wang, Q. F., Wang, T. Y. & Zheng, M. Microwave-assisted four-component, one-pot condensation reaction: an efficient synthesis of annulated pyridines. *Org. Biomol. Chem.* **5**, 945–951 (2007).
41. Yan, C. G. et al. One-step synthesis of polysubstituted benzene derivatives by multi-component cyclization of α -bromoacetate, malononitrile and aromatic aldehydes. *Chem. Commun.* 1440–1442 (2008).
42. Wang, Q. F., Song, X. K., Chen, J. & Yan, C. G. Pyridinium Ylide-Assisted One-Pot Two-Step Tandem Synthesis of Polysubstituted Cyclopropanes. *J. Comb. Chem.* **11**, 1007–1010 (2009).
43. Wang, Q. F., Hou, H., Hui, L. & Yan, C. G. Diastereoselective synthesis of trans-2,3-dihydrofurans with pyridinium ylide assisted tandem reaction. *J. Org. Chem.* **74**, 7403–7406 (2009).
44. Yan, C. G., Wang, Q. F., Song, X. K. & Sun, J. One-Step Synthesis of Pyrido[1,2-a]benzimidazole Derivatives by a Novel Multicomponent Reaction of Chloroacetonitrile, Malononitrile, Aromatic Aldehyde, and Pyridine. *J. Org. Chem.* **74**, 710–718 (2009).
45. Wang, Q. F., Hui, L., Hou, H. & Yan, C. G. Synthesis of Zwitterionic Salts of Pyridinium-Meldrum Acid and Barbiturate through Unique Four-component Reactions. *J. Comb. Chem.* **12**, 260–265 (2010).
46. Han, Y., Chen, J., Hui, L. & Yan, C. G. Synthesis of zwitterionic salts via three-component reactions of pyridacylpyridinium iodide, aromatic aldehydes, and Meldrum acid or N,N-dimethylbarbituric acid. *Tetrahedron* **66**, 7743–7748 (2010).
47. Hou, H., Zhang, Y. & Yan, C. G. One-pot synthesis of 4-substituted isoquinolinium zwitterionic salts by metal-free C-H bond activation. *Chem. Commun.* **48**, 4492–4494 (2012).
48. Liu, L. Z., Wang, X. Y., Sun, J. & Yan, C. G. A facile synthesis of tricyclic skeleton of alkaloid 261C by double [3 + 2] cycloaddition of pyridinium ylide. *Tetrahedron Lett.* **56**, 6711–6714 (2015).
49. Wu, L., Sun, J. & Yan, C. G. Facile synthesis of spiro[indoline-3,3'-pyrrolo[1,2-a]quinolines] and spiro[indoline-3,1'-pyrrolo[2,1-a]isoquinolines] via 1,3-dipolar cycloaddition reactions of heteroaromatic ammonium salts with 3-phenacylideneoxindoles. *Org. Biomol. Chem.* **10**, 9452–9463 (2012).
50. Fu, Q. & Yan, C. G. Molecular diversity of cycloaddition reactions of the functionalized pyridinium salts with 3-phenacylideneoxindoles. *Tetrahedron* **69**, 5841–5849 (2013).
51. Lu, L. J., Fu, Q., Sun, J. & Yan, C. G. Synthesis of complex dispirocyclopentanebisoxindoles via cycloaddition reactions of 4-dimethylamino-1-alkoxycarbonylmethylpyridinium bromides with 2-oxoindolin-3-ylidene derivatives. *Tetrahedron* **70**, 2537–2545 (2014).
52. Wang, X. H. & Yan, C. G. Facile synthesis of spiro[indane-2,1'-pyrrolo[2,1-a]isoquinolines] via three-component reaction of isoquinolinium salts, indane-1,3-dione, and isatins. *Synthesis* **46**, 1059–1066 (2014).
53. Fang, J. & Yan, C. G. Synthesis of 6a,6b,13,13a-tetrahydro-6H-5-oxa-12a-azadibenzo[a,g]fluorene derivatives via cycloaddition reactions of isoquinolinium salts with 3-nitrochromenes. *Mol. Divers.* **18**, 91–99 (2014).
54. Shen, G. L., Sun, J. & Yan, C. G. Diastereoselective synthesis of spiro[benzo[d]pyrrolo[2,1-b]thiazole-3,3'-indolines] via cycloaddition reaction of N-phenacylbenzothiazolium bromides and 3-methyleneoxindoles. *Org. Biomol. Chem.* **13**, 10929–10938 (2015).
55. Lu, L. J. & Yan, C. G. Synthesis of Dispirocyclopentyl-3,3'-bisoxindoles via Domino Cycloaddition Reactions of 4-Dimethylaminopyridinium Bromides with 3-Phenacylideneoxindoles. *Chin. J. Chem.* **33**, 1178–1188 (2015).
56. Lu, L. J. & Yan, C. G. Efficient Synthesis of Complex Oxazatricycles via Three-Component Reaction of Isoquinolinium Salts, Acetone and Cyclic Diketones. *J. Heterocyclic Chem.* **52**, 1513–1517 (2015).

57. Shen, G. L., Sun, J. & Yan, C. G. Construction of dispirocyclohexyl-3,3'-bisoxindole and dispirocyclopentyl-3,3'-bisoxindole via domino cycloaddition reactions of N-benzylbenzimidazolium salts with 2-(2-oxoindolin-3-ylidene)acetates. *RSC Advances*, **5**, 4475–4483 (2015).
58. Hui, L., Li, H. Y. & Yan, C. G. Molecular diversity of three-component reactions of N-benzylbenzimidazolium salts, isatin, and malononitrile or ethyl cyanoacetate. *Eur. J. Org. Chem.* 3157–3164 (2012).
59. Nyerges, M., Gajdics, L., Szöllösy, A. & Töke, L. 2-Oxoindolin-3-ylidene derivatives as 2 π components in 1,3-dipolar cycloadditions of azomethine ylides. *Synlett*. 111–113 (1999).
60. Fejes, I., Töke, L., Nyerges, M. & Pak, C. S. Tandem *in-situ* generation of azomethine ylides and base-sensitive nitroethylene dipolarophiles. *Tetrahedron*, **56**, 639–644 (2000).
61. Fejes, I., Nyerges, M., Szollosy, A., Blasko, G. & Töke, L. 2-Oxoindolin-3-ylidene derivatives as 2 π components in 1,3-dipolar cycloadditions of azomethine ylides. *Tetrahedron*, **57**, 1129–1137 (2001).
62. Serov, A. B., kartsev, V. G., Aleksandrov, A. Yu. & Dolgushin, F. M. 1,3-Dipolar cycloaddition reaction of heteroaromatic N-ylides with 3-[(E)-2-aryl(heteroaryl)-2-oxoethylidene]indolin-2-ones. *Russ. Chem. Bull.* **54**, 2432–2436 (2005).
63. Velikorodov, A. V., Imasheva, N. M., Kuanchaliev, A. K. & Poddubnyi, O. Yu. Some condensations of methyl 4-acetylphenylcarbamate. *Russ. J. Org. Chem.* **46**, 971–975 (2010).
64. El-Ahl, A. A. S. 1,3-Dipolar cycloaddition reactions in synthesis of spiro 2-oxindoline derivatives. *Pol. J. Chem.* **71**, 27–31 (1997).
65. Kotha, S. B., Deb, A. C. & Lahiri, K. & Manivannan, E. Selected synthetic strategies to spirocyclics. *Synthesis*. 165–193 (2009).
66. Singh, G. S. & Desta, Z. Y. Isatins As Privileged Molecules in Design and Synthesis of Spiro-Fused Cyclic Frameworks. *Chem. Rev.* **112**, 6104–6155 (2012).
67. Liu, Y. Y., Wang, H. & Wan, J. P. Recent Advances in Diversity Oriented Synthesis through Isatin-based Multicomponent Reactions. *Asian. J. Org. Chem.* **2**, 374–386 (2013).
68. Trost, B. M. & Brennan, M. K. Asymmetric syntheses of oxindole and indole spirocyclic alkaloid natural products. *Synthesis*. 3003–3025 (2009).
69. Ball-Jones, N. R., Badillo, J. J. & Franz, A. K. Strategies for the enantioselective synthesis of spirooxindoles. *Org. Biomol. Chem.* **10**, 5165–5181 (2012).
70. Hong, L. & Wang, R. Recent Advances in Asymmetric Organocatalytic Construction of 3,3'-Spirocyclic Oxindoles. *Adv. Synth. Catal.* **355**, 1023–1052 (2013).
71. Cao, Z. Y., Wang, Y. H., Zeng, X. P. & Zhou, J. Asymmetric organocatalytic conjugate addition of dialkyl phosphites to N-unprotected isatylidene malononitriles: access to 3-phospho-2-oxindoles with chiral quaternary stereocenters. *Tetrahedron* **70**, 2406–2415 (2014).
72. Cheng, D. Q., Ishihara, Y., Tan, B. & Barbas, C. B. Organocatalytic Asymmetric Assembly Reactions: Synthesis of Spirooxindoles via Organocascade Strategies. *ACS Catalysis*, **4**, 743–762 (2014).
73. Gao, H., Sun, J. & Yan, C. G. Synthesis of functionalized 2-pyrrolidinones via domino reactions of arylamines, ethyl glyoxylate and acetylenedicarboxylates. *Tetrahedron*, **69**, 589–594 (2013).
74. Sun, J., Gong, H. & Yan, C. G. Diastereoselective synthesis of dispirooxindoline fused [1,3]oxazines via Diels-Alder reaction of functionalized 1,2-dihydropyridines with (E)-1,3-dihydro-3-phenacylidene-2H-indol-2-ones. *Tetrahedron*, **69**, 10235–10244 (2013).
75. Gong, H., Sun, J. & Yan, C. G. Povarov reaction of β -enamino esters and isatin-3-imines for diastereoselective synthesis of spiro[indoline-3,2'-quinolines]. *Synthesis*, **46**, 489–495 (2014).
76. Gao, H., Sun, J. & Yan, C. G. Selective Synthesis of Functionalized Spiro[indoline-3,2'-pyridines] and Spiro[indoline-3,4'-pyridines] by Lewis Acid Catalyzed Reactions of Acetylenedicarboxylate, Arylamines, and Isatins. *J. Org. Chem.* **79**, 4131–4136 (2014).
77. Han, Y., Sheng, Y. J. & Yan, C. G. Convenient synthesis of triphenylphosphanylidene spiro[cyclopentane-1,3'-indolines] and spiro[cyclopent[2]ene-1,3'-indolines] via three-component reactions. *Org. Lett.* **16**, 2654–2657 (2014).
78. Xie, Y. J., Sun, J. & Yan, C. G. Unprecedented formation of 2-oxaspiro[bicyclo[2.2.1]heptane-6,3'-indoline] derivatives from reaction of 3-phenacylideneoxindole with malononitrile or ethyl cyanoacetate. *RSC Adv.* **4**, 44537–44546 (2014).
79. Zhu, D., Sun, J. & Yan, C. G. One-pot synthesis of 6,11-dihydro-5H-indolizino[8,7-b]indoles via sequential formation of β -enamino ester, Michael addition and Pictet-Spengler reactions *RSC Adv.* **4**, 62817–62826 (2014).
80. Yang, F., Zhang, L. J. & Yan, C. G. Four-component reaction of N-alkylimidazoles(N-alkylbenzimidazoles), dialkyl but-2-ynedioate, N-alkylisatins and malononitrile. *RSC Adv.* **4**, 64466–64475 (2014).
81. Shen, G. L., Sun, J. & Yan, C. G. Construction of dispirocyclohexyl-3,3'-bisoxindole and dispirocyclopentyl-3,3'-bisoxindole via domino cycloaddition reactions of N-benzylbenzimidazolium salts with 2-(2-oxoindolin-3-ylidene)acetates. *RSC Adv.* **5**, 4475–4483 (2015).
82. Yang, F., Sun, J., Gao, H. & Yan, C. G. Unprecedented formation of spiro[indoline-3,7'-pyrrolo[1,2-a]azepine] from multicomponent reaction of L-proline, isatin and but-2-ynedioate. *RSC Adv.* **5**, 32786–32794 (2015).
83. Sun, J., Chen, L., Gong, H. & Yan, C. G. Convenient synthesis of functionalized spiro[indoline-3,2'-pyrrolidines] or spiro[indoline-3,3'-pyrrolidines] via multicomponent reactions *Org. Biomol. Chem.* **13**, 5905–5917 (2015).
84. Shakibaei, G. I. & Bazgir, A. A highly efficient one-pot synthesis of indenopyridine-fused spirocyclic systems. *RSC Adv.* **6**, 22306–22311 (2016).

Acknowledgements

This work was financially supported by the National Natural Science Foundation of China (Grant No. 21172189, 21572196) and the Priority Academic Program Development of Jiangsu Higher Education Institutions. We thank Analysis and Test Center of Yangzhou University providing all analytical instruments.

Author Contributions

C.-G.Y. led this research. G.-L.S. and Y.H. performed all the synthetic work and conducted NMR, IR, HRMS. J.S. solved the single crystal X-ray structures. C.-G.Y. wrote the paper.

Additional Information

Accession Codes: Crystallographic data **1a** (CCDC 951518); **1c** (CCDC 951519); **1e** (CCDC 951522); **1j** (CCDC 951520); **2d** (CCDC 1456643); **2e** (CCDC 1456644); **2k** (CCDC 1456645); **3b** (CCDC 1456646); **4b** (CCDC 1456647); **4c** (CCDC 1456648); **4d** (CCDC 1456649), and **4e** (CCDC 1456650) have been deposited at the Cambridge Crystallographic Database Centre and is available on request (<http://www.ccdc.cam.ac.uk>).

Supplementary information accompanies this paper at <http://www.nature.com/srep>

Competing financial interests: The authors declare no competing financial interests.

How to cite this article: Sun, J. *et al.* Formation of diverse polycyclic spirooxindoles via three-component reaction of isoquinolinium salts, isatins and malononitrile. *Sci. Rep.* 7, 41024; doi: 10.1038/srep41024 (2017).

Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



This work is licensed under a Creative Commons Attribution 4.0 International License. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>

© The Author(s) 2017