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A straightforward stereoselective synthesis of cis-10',14'-diazaspiro [pyrrolidine-3,11'-tetracyclo [8.6.0.0^{2,7},0^{12,16}]hexadecane]-2'(7'),4',6',8'-tetraene-2,5,13',15'-tetrone derivatives under solvent-free condition

PERUMAL PARAMASIVAN THIRUMALAI*, RAMACHANDIRAN KRISHNAN, GIRIJA EMANATHAN and MURALIDHARAN DORAISWAMY
Organic Chemistry Division, CSIR-Central Leather Research Institute, Adyar, Chennai, 600020, Tamilnadu, India
e-mail: ptperumal@gmail.com

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Abstract. A simple way to stereoselective synthesis of pyrrolopyrrolo[2,1-a]isoquinoline derivatives has been developed with mild reaction condition and easily available substrate. A new kind of heterocycles, 10', 14'-diazaspiro[pyrrolidine-3,11'-tetracyclo[8.6.0.0^{2,7},0^{12,16}]hexadecane]-2'(7'),4',6',8'-tetraene-2,5,13',15'-tetrone derivatives is disclosed.

Keywords. Pyrrolopyrrolo[2,1-*a*]isoquinoline; spiroazaheterocycle; azomethine ylide dipolar cycloaddition; stereoselectivity; solvent-free reaction.

1. Introduction

Heterocyclic compounds play a major role in organic chemistry and they are the substructures in numerous natural products and bioactive materials. With the importance of the concept of 'atom economy' and 'green chemistry', multi-component reaction (MCR) as well as cycloaddition under neat condition have become more significant in organic synthesis.[1,2] Pyrrolo[2,1-*a*] isoquinoline skeleton[3] are found in alkaloid families, such as erythrina[4] and lamellarin,[5] and in simple pyrrolo [2,1-*a*]isoquinoline derivatives[6,7] all of them showing enhanced biological activities. Moreover, the application of these heterocyclic systems was further increased by their efficacy as pioneering intermediates for the synthesis of alkaloids.[3] Recently, more attention has been directed to the synthesis of 5,6-dihydro-pyrrolo [2,1-*a*]isoquinoline moiety since they are found in numerous natural and bioactive compounds such as Cryptaustoline **I**, Crispine A (**II**),[8] Lettowianthine (**III**)[9] and Lamellarin D (**IV**)[10] (Figure 1).[8–11]

Aza-heterocycles are associated with diverse biological activities and are therefore formulating new routes for the synthesis of complex aza-system is significant. One of the strategies to prepare fused-aza-heterocycles involves ylide as the synthetic precursor.[12–15] A few reports on the formation of ylide from 1,2-diazine and pyrimidine were published.[16] Mangalagiu *et al.* have reported the formation of spiropyrrolidine-pyrroles[16] derivative using pyrimidine and maleimide derivative in twenty days, at room temperature, in acetic acid.

In continuation of our work in 1,3-dipolar cycloaddition, herein we report a novel method of stereoselective synthesis of *cis*-10',14'-diazaspiro[pyrrolidine-3,11'-tetracyclo[8.6.0.0^{2,7}, 0^{12,16}] hexadecane]-2'(7'),4',6',8'-tetraene-2,5,13',15'-tetrone derivatives *via* azomethine ylide 1,3-dipolar cycloaddition.

2. Experimental

2.1 *General experimental procedure for compounds 3a-i*

A mixture of isoquinoline (1 mmol) and maleimide (3 mmol) was stirred at 70°C for 3 h. The reaction mixture was dissolved in ethyl acetate (30 mL) and washed with water (30 mL). The aqueous phase was extracted with ethyl acetate (3 x 20 mL). The combined organic phase was washed with saturated sodium chloride solution (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by columm chromatography with EtOAc:petroleum ether as eluent to afford the corresponding product. See Supporting Information for details.

*For correspondence

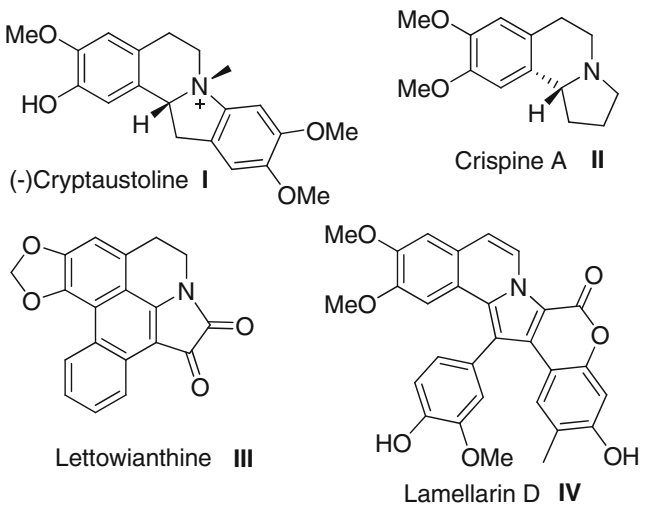


Figure 1. Natural products containing pyrrolo[2,1-*a*]isoquinoline moiety.

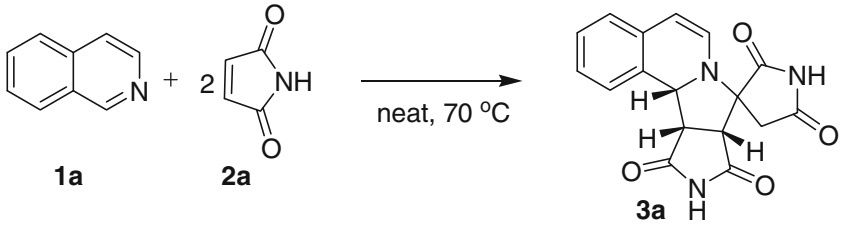
3. Results and Discussion

Although annulated pyrroles of type **II** have been prepared *via* intramolecular cyclization of advanced intermediates using radical,[17] metal-catalyzed,[18] or base- induced processes,[19] few examples of direct synthesis are known.[20] Herein, we report a straightforward one-step synthesis of highly functionalized *cis*-10',14'-diazaspiro[pyrrolidine-3,11'-tetracyclo[8.6.0.$0^{2,7}$, $0^{12,16}$]hexadecane]-2'(7'),4',6',8'-tetraene-2,5,13',15'-tetrone derivatives **3** using readily accessible starting materials **1** and **2**.

Our self-promoted dipolar cycloaddition approach to isoquinoline and maleimide is outlined in scheme 1. We commenced our studies utilizing maleimide and isoquinoline a nitrogen containing cyclic compound, as these readily available compounds have demonstrated ability to form polycyclic compounds under neat condition in one-pot manner. We hypothesized the formation of azomethine ylide from simple isoquinoline **1** and maleimide **2**. We began by exploring the dipolar cycloaddition reaction of substrate **1a** and **2a**. Heating of isoquinoline **1a** in CH_3CN at 70°C in the presence of 2 equivalent of maleimide **2a** delivered the *cis*-10',14'-diazaspiro[pyrrolidine-3,11'-tetracyclo[8.6.0.$0^{2,7}$, $0^{12,16}$]hexadecane]-2'(7'),4',6',8'-tetra-ene-2,5,13',15'-tetrone **3a** in 28% yield.

While the reaction utilizing 2 equiv. of maleimide was successful, reaction using an excess of maleimide (3 equiv) proceeded in higher yield (45%) in CH_3CN as solvent. Having obtained the *cis*-10',14'-diazaspiro[pyrrolidine-3,11'-tetracyclo[8.6.0.$0^{2,7}$, $0^{12,16}$]hexadecane]-2'(7'),4',6',8'-tetra-ene-2,5,13',15'-tetrone **3a**, we next varied the reaction conditions in order to improve the yield of the products from its initial low yield of 45%. Change of solvent from CH_3CN to CH_3OH, THF, ethanol and DMF moderately increased the yield up to 60% (table 1, entries 1–9). Among the various solvents screened, DMF was found to be a better choice, giving higher yield in the cycloaddition reaction (table 1, entry 9). Fortunately the highest yield 88% (table 1, entry 13) was obtained when the same reaction was carried out with excess of maleimide and a much shorter reaction time (3 h). The reaction yield was reduced when the reaction was performed under neat condition for prolonged reaction times. It was observed that the reaction temperature had a significant effect on the reaction. Only a very low amount of the desired product could be detected at rt and an increase in temperature from rt to 70°C led to an increase in yield. But further increase in temperature to 120°C led to a very low yield and at higher temperatures no product was observed (table 1, entry 12–14).

Remarkably, this 1,3-dipolar cycloaddition proceeded with *cis*-selectivity without any additional reagent or catalyst. We next explored the scope of this self-promoted azomethine ylide 1,3-dipolar cycloaddition utilizing various substituted isoquinolines and maleimides and it was observed that the reaction was significantly affected by electronic effect of the substituents on the isoquinolines. The results are summarized in table 2. The yield of *cis*-10',14'-diazaspiro[pyrrolidine-3,11'-tetracyclo[8.6.0.$0^{2,7}$, $0^{12,16}$]hexadecane]-2'(7'),4',6',8'-tetraene-2,5,13',15'-tetrone derivatives **3a–i** were in the range of 48–88% (table 2; scheme 2). The reaction of isoquinoline with electron-withdrawing substituents on the benzene ring of isoquinoline



Scheme 1. Azomethine ylide dipolar cycloaddition reaction of isoquinoline **1a** with maleimide **2a**.

Table 1. Synthesis of *cis*-10',14'-diazaspiro[pyrrolidine-3,11'-tetracyclo.

Entry	Isoquinoline	Maleimide	Solvent	Temperature (°C)	Time (h)	Product	Yield (%)[a]
1	1a	2a, 2 equiv	CH_3CN	Rt	24	3a	Traces
2	1a	2a, 2 equiv	CH_3CN	70	12	3a	28
3	1a	2a, 3 equiv	CH_3CN	70	12	3a	45
4	1a	2a, 3 equiv	MeOH	Rt	24	3a	Traces
5	1a	2a, 3 equiv	MeOH	70	12	3a	47
6	1a	2a, 3 equiv	THF	70	12	3a	Traces
7	1a	2a, 3 equiv	EtOH	Rt	24	3a	11
8	1a	2a, 3 equiv	EtOH	70	12	3a	40
9	1a	2a, 3 equiv	DFM	70	12	3a	60
10	1a	2a, 3 equiv	Toluene	70	12	3a	15
11	1a	2a, 3 equiv	DMSO	70	12	3a	38
12	1a	2a, 3 equiv	Neat	rt	12	3a	10
13	1a	2a, 3 equiv	Neat	70	3	3a	88
14	1a	2a, 3 equiv	Neat	120	3	3a	22

[a]Isolated yield after column chromatography.

substrate proceeded with low yield (table 2, entry 7–9). The reaction of substrate with no substituent on isoquinoline proceeded efficiently with 88% yield. Table 2 reveals that the electronic effect due to the presence of *N*-substituent on maleimide, has less significant impact on the product formation. Encouraged by the successful

Table 2. Synthesis of *cis*-10',14'-diazaspiro[pyrrolidine-3,11'-tetracyclo[8.6.0.0^{2,7}, 0^{12,16}]hexadecane]-2'(7'),4',6',8'-tetraene-2,5,13',15'-tetrone derivative from isoquinoline **1a** with maleimide **2a**.

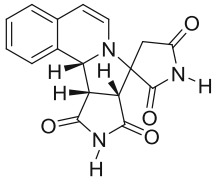
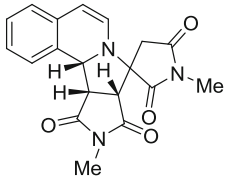
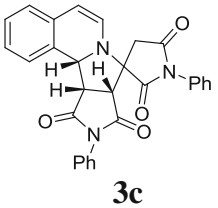
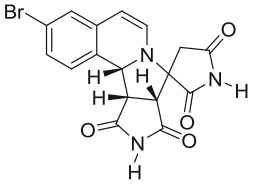
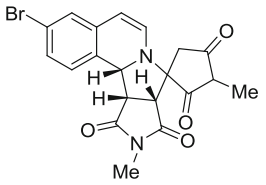
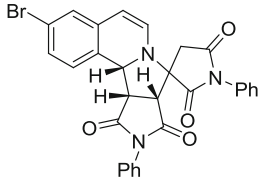
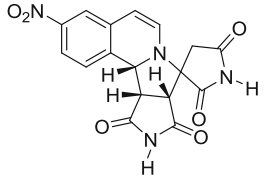
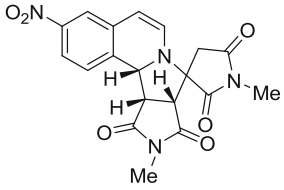
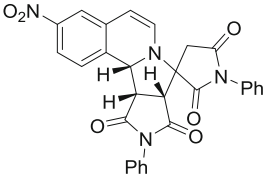
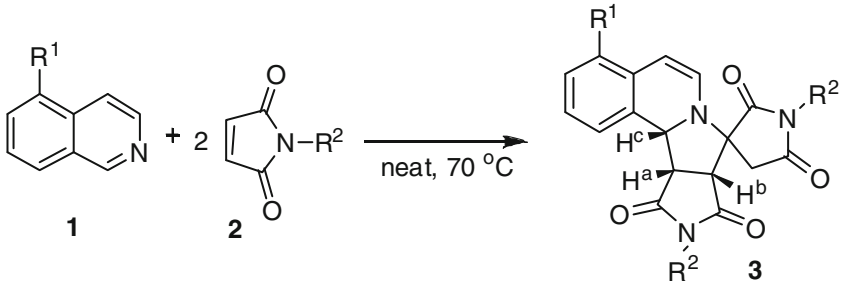
Entry	Isoquinoline	R^1	Maleimide	R^2	Product	Yield (%)[a]
1	1a	H	2a	H	 **3a**	88
2	1a	H	2b	Me	 **3b**	82
3	1a	H	2c	Ph	 **3c**	85
4	1b	Br	2a	H	 **3d**	73

Table 2. (*continued*.)

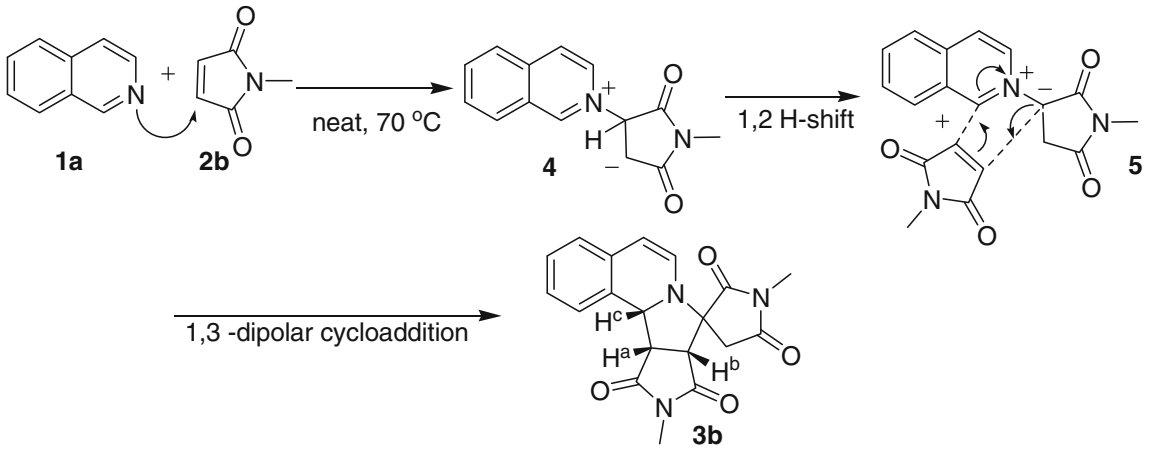
Entry	Isoquinoline	R^1	Maleimide	R^2	Product	Yield (%)[a]
5	1b	Br	2b	Me	 **3e**	78
6	1b	Br	2c	Ph	 **3f**	76
7	1c	NO_2	2a	H	 **3g**	48
8	1c	NO_2	2b	Me	 **3h**	60
9	1c	NO_2	2b	Ph	 **3i**	56

[a] *Isolated yield after column chromatography*

cis-10',14'-diazaspiro[pyrrolidine-3,11'-tetracyclo [8.6.0.0^{2,7}, 0^{12,16}]hexadecane]-2'(7'),4',6',8'-tetraene-2,5,13',15'-tetrone derivatives **3a–i** formation, we next examined quinoline by treating with maleimide.



Scheme 2. Synthesis of *cis*-10',14'-diazaspiro[pyrrolidine-3,11'-tetracyclo [8.6.0.0^{2,7}, 0^{12,16}]hexadecane]-2'(7'),4',6',8'-tetraene-2,5,13',15'-tetrone derivatives.



Scheme 3. Plausible reaction mechanism.

Unfortunately, quinoline failed to add with maleimide under the above optimal reaction conditions. While pyridine was substituted for isoquinoline, a mixture of starting materials and polymeric compounds were obtained. We next tried maleic anhydride to react with isoquinoline, which unfortunately failed to react. The plausible mechanism is outlined in scheme 3. The reaction is believed to involve azomethine ylide cycloaddition[16] of **1a** and **2b** to form adduct **4** which further undergoes 1,2-H shift to form intermediate **5**. Subsequent addition of maleimide **2b** with intermediate **5** *via* 1,3-dipolar cycloaddition gives the product **3b**.

The structures were confirmed by NMR and mass spectral studies (figure 2). The ^{1}H NMR spectrum of the *cis*-1,14'-dimethyl-10',14'-diazaspiro[pyrrolidine-3,11'-tetracyclo [8.6.0.0^{2,7}, 0^{12,16}]hexadecane]-2'(7'),4', 6',8'-tetraene-2,5,13',15'-tetrone **3b** showed two

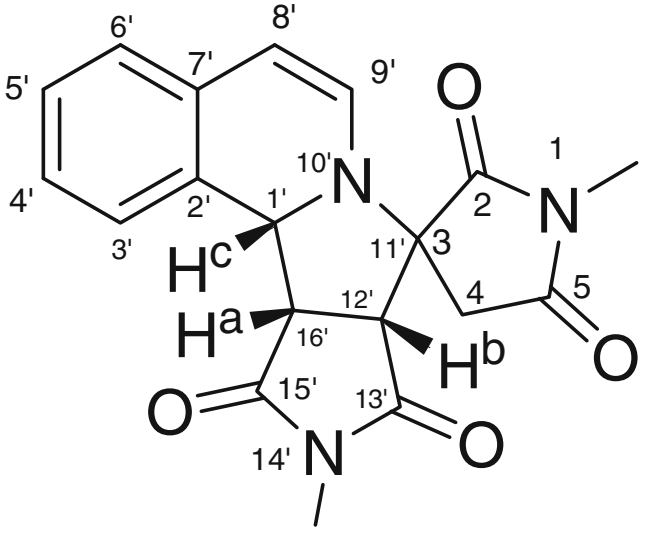


Figure 2. Structure of compound **3b** with number system.

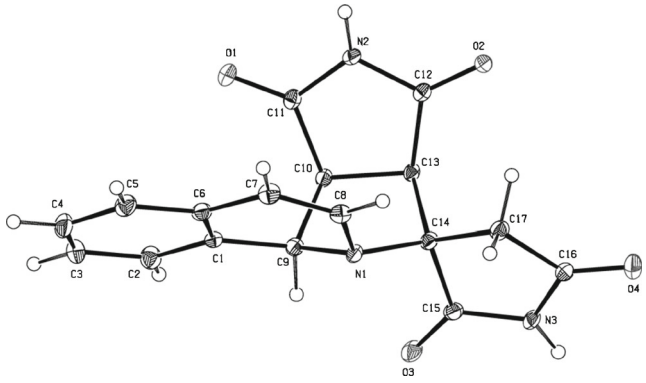


Figure 3. ORTEP diagram of compound **3a**.

doublets at δ 2.69 ppm (J = 19.1 Hz) and 3.87 ppm (J = 18.3 Hz) which were assigned to –CH_2 protons. The triplet at δ 3.85 ppm (J = 7.6 Hz) and a doublet at δ 3.49 ppm (J = 7.6 Hz), were attributed to H^a and H^b protons respectively. The doublet at δ 5.49 ppm (J = 7.6 Hz) was assigned to H^c proton. Moreover in the ^{13}C NMR spectrum a ^{13}C peak at δ 67.5 ppm showed the presence of spiro carbon. The mass spectra revealed the molecular ion peak M^+ at m/z = 351, which confirmed the product formation. The stereochemistry of the compound **3a** was further confirmed by single crystal X-ray diffraction (figure 3).

4. Conclusion

We have developed an efficient and straightforward synthesis of *cis*-10',14'-diazaspiro[pyrrolidine-3,11'-tetracyclo[8.6.0.0^{2,7}, 0^{12,16}]hexadecane]-2'(7'),4',6', 8'-tetraene-2,5,13',15'-tetrone derivatives. The unusual 1,2-hydrogen shift observed in the intermediate resulted

in the formation of 10',14'-diazaspiro[pyrrolidine-3,11'-tetracyclo[8.6.0.0^{2,7}, 0^{12,16}] hexadecane]-2'(7'),4',6',8'-tetraene-2,5,13',15'-tetrone derivative. A privileged medicinal scaffold is synthesized through azomethine ylide 1,3-dipolar cycloaddition reactions of isoquinoline with maleimide in one-pot manner without using any additional reagent or catalyst.

Supplementary Information

Crystallographic data has been deposited at the Cambridge Crystallographic Data Centre as supplemental publication no. CCDC 866905. Copies of the data can be obtained, free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 01223 336033 or email: deposit@ccdc.cam.ac.uk). Supporting information is available at www.ias.ac.in/chemsci.

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