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Regio- and stereoselective synthesis of novel tetraspiro-bispyrrolidine and bisoxindolopyrrolidine derivatives through 1,3-dipolar cycloaddition reaction

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ABSTRACT

An efficient approach to the synthesis of a new class of tetraspiro-bispyrrolidines and tetraspiro-bisoxindolopyrrolidines has been accomplished through 1.3-dipolar cycloaddition reaction. The reported method is a one-pot, three component reaction, that is, run under solvent-free microwave conditions.

Over the past few years, the concept of 'Green Chemistry'[1] has been adopted in organic synthesis to meet the essential challenges for protecting the human health and environment from chemical hazards. Among the most promising ways to attain this objective is to carry out the reaction under solvent-free conditions to enhance the reaction efficiency and to provide rapid access to large libraries of diverse molecules.[2] Microwave-assisted organic synthesis (MAOS) has attracted considerable attention in recent years,[3] especially, microwave reactions under solvent-free conditions have gained popularity because of their simplicity, greater selectivity, enhanced reaction rates, cleaner products, and minimum reaction time.[4]

1,3-Dipolar cycloaddition reactions have been described as 'the most efficient and powerful synthetic tool for the construction of heterocyclic systems, natural products, and alkaloids in organic chemistry.'[5] The 1,3-dipolar cycloaddition reaction of azomethine ylide with olefinic dipolarophiles constitutes a straightforward approach to the synthesis of highly substituted pyrrolidine derivatives.[6] Spiro compounds are elegant targets in organic synthesis because of their significant biological activities.[7] In particular, spirooxindolopyrrolidine and their derivatives have served as potential synthetic intermediates[8] and also act as antiviral, antitumoral, antibiotic agents, local aneasthetics, and inhibitors of human NK-1 receptor etc.[9] Strychnofoline, rhychophylline, elacomine, and pteropodine are some of the alkaloids containing spiropyrrolidinyloxindole-ring system (Fig. 1).[10] Recently, our research group has been largely involved in the synthesis of pyrrolidine derivatives[11d] which are known to possess significant biological activity.[11a–c]

As part of our endeavor to synthesize new bispyrrolidine and bisoxindolopyrrolidine derivatives containing four spiro carbons

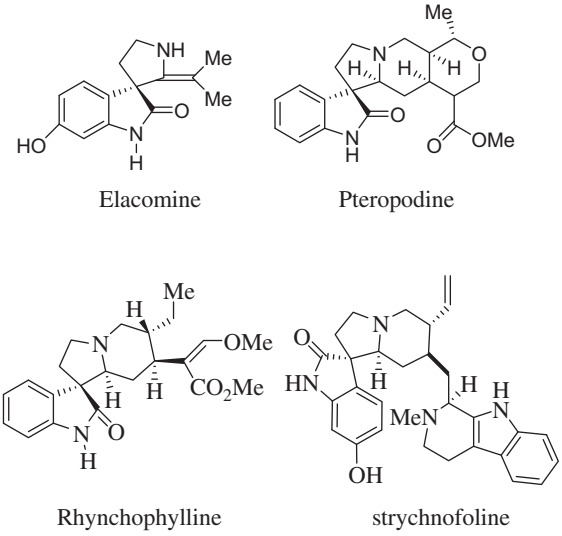

Figure 1. Spiropyrrolidinyloxindole alkaloid natural products.

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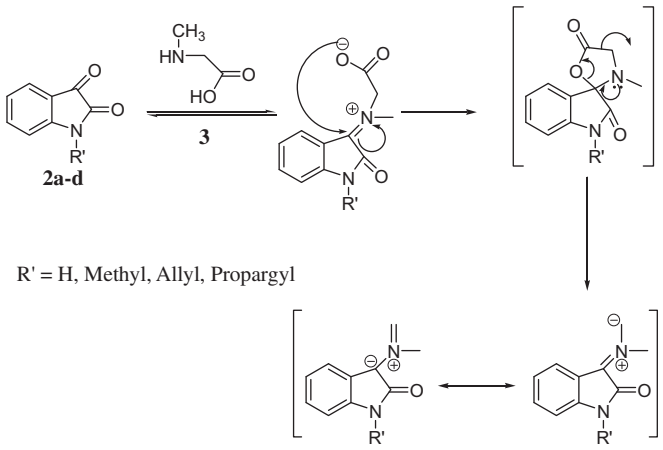


Scheme 1. Mechanism for the generation of azomethine ylide.

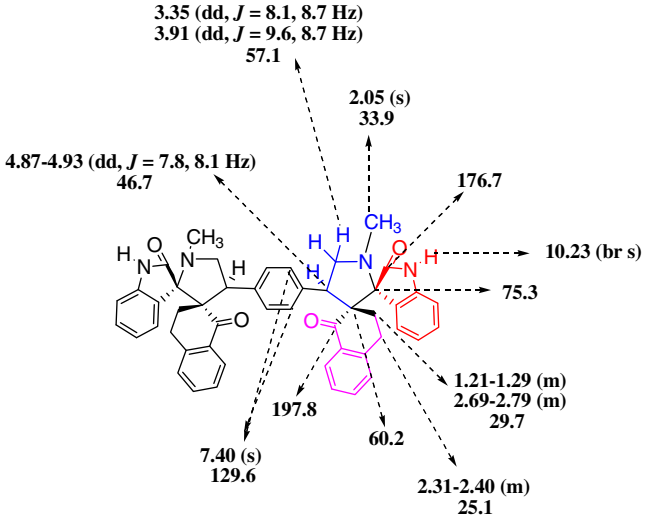


Figure 2. Selected ^{1}H and ^{13}C NMR chemical shifts of **6a**.

which often enhances the biocidal profile or may create new medicinal properties remarkably. Herein we report the facile synthesis of tetraspiro-bispyrrolidine and tetraspiro-bisoxindolopyrrolidine derivatives, in a highly regio- and stereoselective manner through 1,3-dipolar cycloaddition reaction of bis-dipolarophiles (**1a,b**) with the 1,3-dipole generated from 1,2-diketones and secondary amino acids.

The required dipolarophiles 1,4-bis(3′,4′-dihydro-1′-oxonaphthalen-2′-ylidene)benzene **1a** and 1,4-bis(3′,4′-dihydro-6′-methoxy-1′-oxonaphthalen-2′-ylidene)benzene **1b** were prepared by the base-catalyzed condensation of tetralone derivatives with terephthaldehyde according to the literature procedure.[12]

The 1,3-dipole generated from isatin **2a** and sarcosine **3** reacted readily with the bisdipolarophile **1a** under refluxing conditions in toluene[13] to give both mono and bis cycloadducts **4a** and **5a** in 22% and 75% yield, respectively (Schemes 1 and 2).

In an attempt to increase the yield of the bisadduct **5a**, the reaction was performed with excess of reagents **2a** and **3** with increase in reaction time, but we have not observed any change in the yield of the biscycloadduct **5a**. When we subjected the reaction to microwave irradiation in toluene,[13] there was a slight increase in the yield of the **5a**. However, when the reaction was performed in microwave irradiation under solvent-free conditions[13] we obtained the anticipated C_2-symmetric tetraspiro-bisoxindolopyrrolidine **5a** in excellent yield with high regio- and stereoselectivity (Table 1).

The structures of cycloadducts **5a–d** were fully characterized by ^{1}H, ^{13}C, DEPT 135, 2D NMR, and mass spectrometry. In the proton NMR spectrum of **5a** (Fig. 2) a sharp singlet appeared at δ 2.05 for $-NCH_3$ protons of the pyrrolidine ring. The $-NCH_2$ protons and benzylic proton of pyrrolidine ring appeared as doublet of doublets at δ 3.35, 3.91, and 4.87 which explained the regiochemistry of the cycloaddition. In contrast, if the other regioisomer had been formed, the benzylic proton would have appeared as a singlet instead of doublet of doublet in the ^{1}H NMR spectrum. The –NH proton of the oxindole showed a broad singlet at δ 10.23 ppm. For the ^{13}C spectrum of **5a**, the two spiro quaternary carbons resonated at 60.2, 75.3 ppm and the oxindole and tetralone carbonyl carbons resonated at 176.7 and 197.8 ppm and the $-NCH_3$ carbon showed a signal at 33.9 ppm. Finally the formation of the product **5a** was confirmed by mass spectrum analysis, which showed a molecular ion peak at *m/z*: 738.40 (M^+). The C_2-symmetric structure of the compound **5a** was assigned on the basis of ^{1}H and ^{13}C NMR spectra.[14]

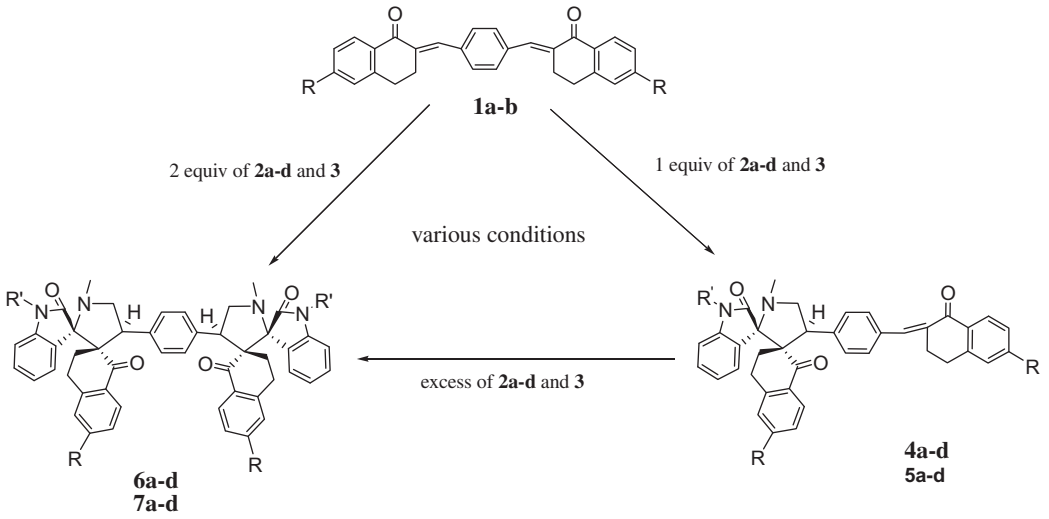
The scope of the reaction was extended by reacting azomethine ylide generated from various isatin derivatives **2b–d**, and sarcosine **3** with bisdipolarophiles **1a** and **1b** to give tetraspiro-bisoxindolopyrrolidine derivatives **5b–d** and **6a–d** in good yields (Scheme 2).

The protocol was extended for the synthesis of **11** and **12** by replacing isatin with acenapthequinone **8**. The dipolarophiles **1a**,**b** reacted with the dipole generated in situ from acenapthequinone and sarcosine to give tetraspiro-bispyrrolidines **11** and **12** in good yield (Scheme 3).

Table 1
Comparative study on the synthesis of tetraspirobiscycloadducts using 1,3-DC reaction

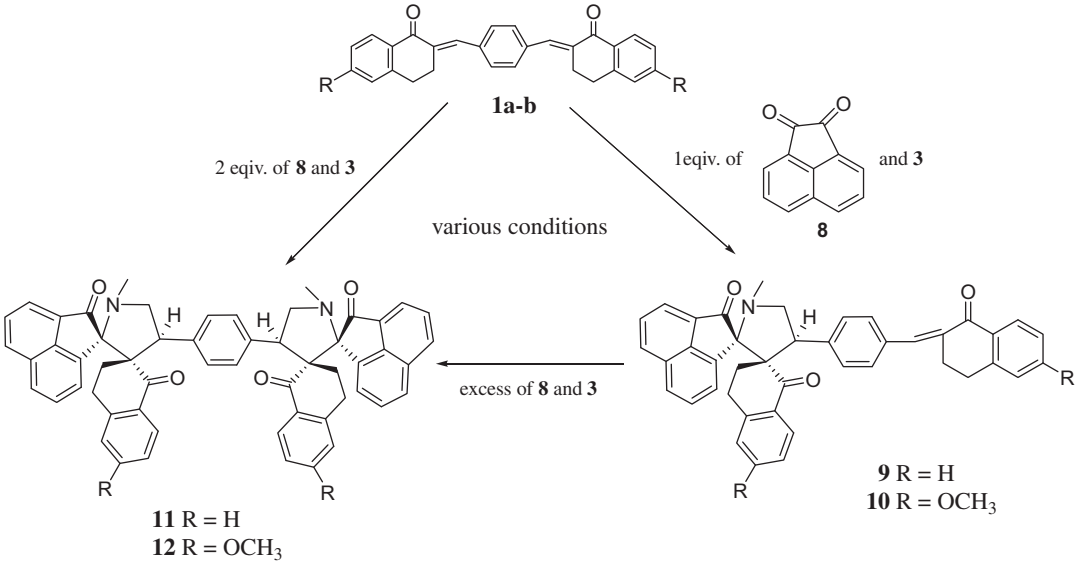
Dipolarophiles	1,2-Diketones	Method A			Method B			Method C		
		T (h)	Y (%)[a]		T (min)	Y (%)[a]		T (min)	Y (%)[a]	
			M	B		M	B		M	B
1a	**2a**	6.5	22	75	6.5	12	84	4.0	–	89
1a	**2b**	7.0	21	73	6.8	15	82	3.5	–	86
1a	**2c**	7.5	26	67	6.5	19	76	3.0	–	83
1a	**2d**	7.2	25	64	7.0	18	77	3.8	–	84
1a	**8**	7.0	25	72	6.0	16	78	4.4	–	85
1b	**2a**	6.0	23	72	6.4	15	80	3.3	–	87
1b	**2b**	6.2	25	68	6.5	16	77	3.4	–	85
1b	**2c**	6.8	26	65	6.7	21	74	3.0	–	83
1b	**2d**	7.5	24	66	6.0	17	73	2.6	–	80
1b	**8**	7.2	25	70	6.8	15	76	6.4	–	81

Method A: toluene/reflux; Method B: toluene/MW; Method C: neat/MW.
M = mono; B = bis.
[a] Isolated yield.



R'	R = H , -OCH_3	
H	**6a**	**7a**
Methyl	**6b**	**7b**
Allyl	**6c**	**7c**
Propargyl	**6d**	**7d**

Scheme 2. Synthesis of tetraspiro-bisoxindolopyrrolidine derivatives 6a–**d** and **7a**–**d**.



Scheme 3. Synthesis of tetraspiro-bispyrrolidine derivatives **11** and **12**.

The formation of cycloadducts was established by various spectroscopic techniques. The C_2-symmetric structure of the biscycloadducts **11** and **12** was assigned on the basis of ^1H and ^{13}C NMR spectra (Fig. 2).

In summary, we have successfully synthesized tetraspiro-bispyrrolidine and tetraspiro-bisoxindolopyrrolidine derivatives by 1,3-dipolar cycloaddition methodology using microwave irradiation under solvent-free conditions. This process is capable of generating four spiro carbons in a single reaction which enhances the biocidal profile or may create new medicinal properties. Studies related to the biological evaluations of these derivatives are currently in progress.

Acknowledgments

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13. Representative procedure for the synthesis of tetraspiro-bispyrrolidine derivatives.
Method A: A solution of isatin **2a** (2.1 mmol), *N*-methylglycine **3** (2.1 mmol), and dipolarophile **1a** (1.0 mmol) was refluxed in dry toluene (Table 1). Completion of the reaction was evidenced by TLC analysis. The solvent was then removed in vacuum and the residue was subjected to column chromatography using hexane/ethyl acetate (6:4) as eluent.
Method B: A mixture of isatin **2a** (2.1 mmol), *N*-methylglycine **3** (2.1 mmol), and dipolarophile **1a** (1.0 mmol) in dry toluene was irradiated under microwave (MODEL = Chem Discover benchmate microwave 300 W) conditions (Table 1).The reaction mixture was concentrated and the product was purified using column chromatography with hexane/ethyl acetate (6:4) as eluent.
Method C: A mixture of isatin **2a** (2.1 mmol), *N*-methylglycine **3** (2.1 mmol), and dipolarophile **1a** (1.0 mmol) was thoroughly ground in a mortar. The reaction mixture was irradiated under microwave (MODEL = Chem Discover benchmate microwave 300 W) conditions (Table 1). The reaction mixture was diluted with dichloromethane, washed with water and the solution was dried over $NaSO_4$. The solvent was removed in vacuum and the residue was subjected to column chromatography using hexane/ethyl acetate (6:4) as eluent.
14. Representative spectral data of the products.