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A one-pot, three-component regiospecific synthesis of dispiropyrrolidines containing a thiophenone ring via 1,3-dipolar cycloaddition reactions of azomethine ylides

Firouz Matloubi Moghaddam [a,*], Mohammad Reza Khodabakhshi [a], Zahra Ghahremannejad [a], Behzad Koushki Foroushani [a], Seik Weng Ng [b]

[a] Laboratory of Organic Synthesis and Natural Products, Department of Chemistry, Sharif University of Technology, Azadi Street, PO Box 11155-9516, Tehran, Iran
[b] Department of Chemistry, University of Malaya, 50603 Kuala Lumpur, Malaysia

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ABSTRACT

The synthesis of new dispiropyrrolidines containing a thiophenone ring has been achieved by a one-pot, three-component 1,3-dipolar cycloaddition reaction. Unsaturated thiophenone dipolarophiles were reacted with azomethine ylides, generated in situ from sarcosine and cycloketone derivatives (isatin, ninhydrin, acenaphthoquinone), to produce the corresponding cycloadducts in good yields (70–90%). The cycloaddition reaction was found to be highly regio- and diastereoselective.

Multicomponent reactions are very appealing since they can be utilized to prepare combinatorial structures with privileged properties.[1] These types of reactions have advantages over conventional linear syntheses, including reduced number of synthetic steps, shorter reaction times, high degrees of atom economy and environmental friendliness, which allow the preparation of diverse structures in a rapid and cost-effective manner.[2]

One the other hand, the 1,3-dipolar azomethine ylide cycloaddition reaction is a simple and very powerful tool for the construction of pyrrolidine and spiropyrrolidine heterocycles.[3] Spiropyrrolidine compounds exhibit widespread biological activities such as anticonvulsant,[4] potential antileukaemic,[5] local anaesthetic[6] and antiviral.[7] In addition, spiropyrrolidine oxindole skeletons also demonstrate wide biological applications as antibacterial[8] and antiviral[9] agents as well as having local anaesthetic[10] properties, and they are found in the structures of natural alkaloids such as horsfilline, elacomine, MDM2-p53 and spirotryptostatine (Fig. 1). Therefore, the synthesis of newly substituted spiropyrrolidine oxindole derivatives[11] has attracted the attention of synthetic organic chemists.

The thiophenone functionality is found in many compounds. Thiolactomycin is one of the most important biologically active thiophenone-based natural products, which exhibits antibiotic activity against many species of pathogens including gram-positive and gram-negative bacteria,[12] mycobacterium tuberculosis[13] and the malaria parasite, Plasmodium falciparum.[14] Thiolactomycin

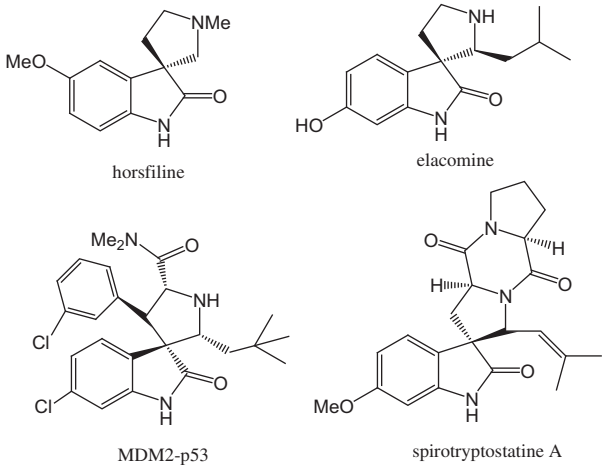

Figure 1. Biologically important molecules containing a spiropyrrolidinyl oxindole skeleton.

* Corresponding author. Tel.: +98 21 66165309; fax: +98 21 66012983.
E-mail address: matloubi@sharif.edu (F.M. Moghaddam).

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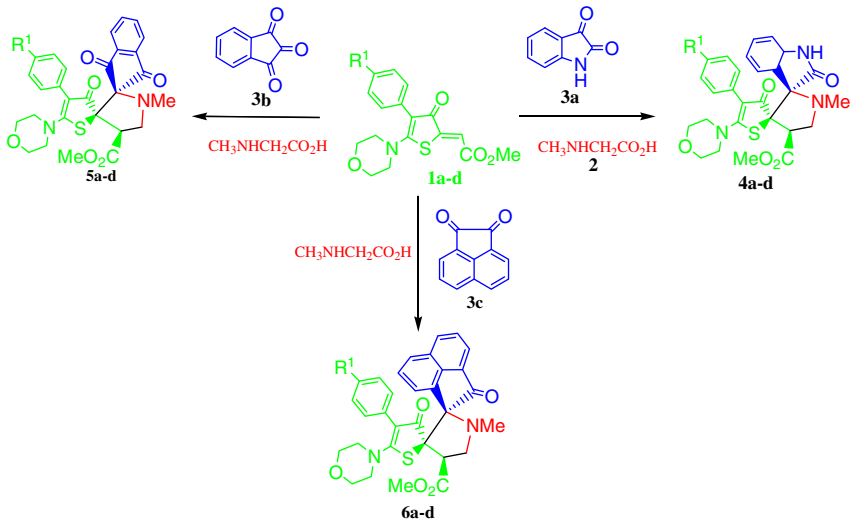
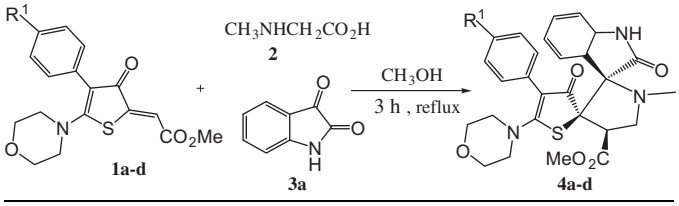
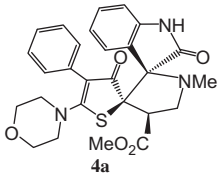
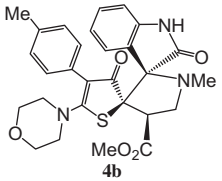
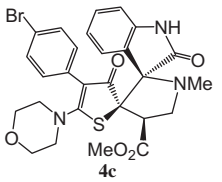
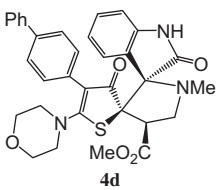


Scheme 1. Synthesis of dispiropyrrolidine-containing thiophenone ring derivatives **4**–**6**.

also exhibits inhibitory activity against fatty acid synthase FAS I and FAS II systems.[15]

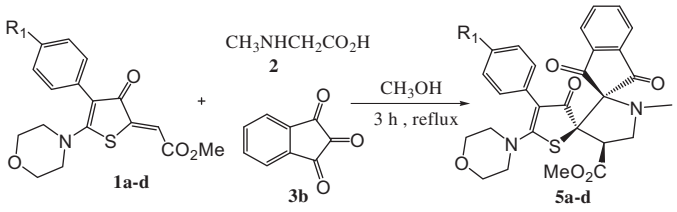
Table 1
Structures of synthesized compounds **4a–d**

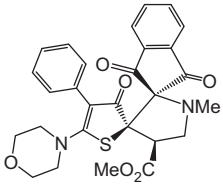
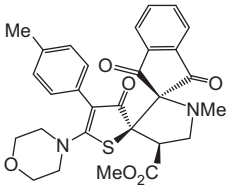
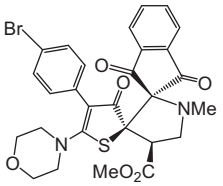
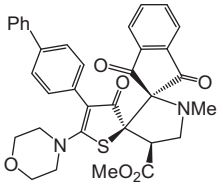


Entry	R^1	Product[a]	Yield[b] (%)
1	H	 **4a**	82
2	Me	 **4b**	87
3	Br	 **4c**	77
4	Ph	 **4d**	80

[a] The products were characterized by IR, NMR, MS and elemental analysis.
[b] Isolated yield after recrystallization.

Table 2
Structures of synthesized compounds **5a–d**



Entry	R^1	Product[a]	Yield[b] (%)
1	H	 **5a**	86
2	Me	 **5b**	91
3	Br	 **5c**	82
4	Ph	 **5d**	87

[a] The products were characterized by IR, NMR, MS and elemental analysis.
[b] Isolated yield after recrystallization.