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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

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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

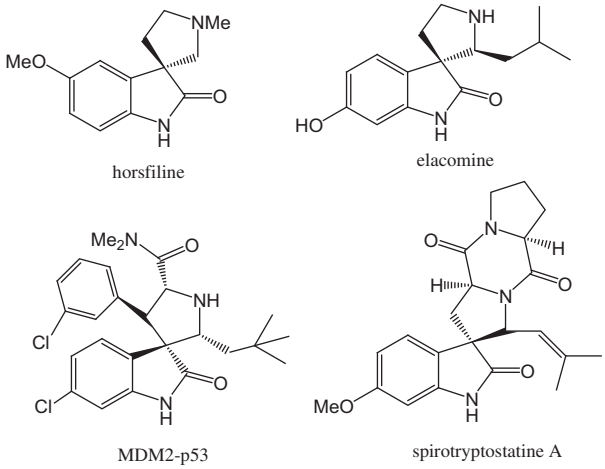

Figure 1. Biologically important molecules containing a spiropyrrolidinyl oxindole skeleton.

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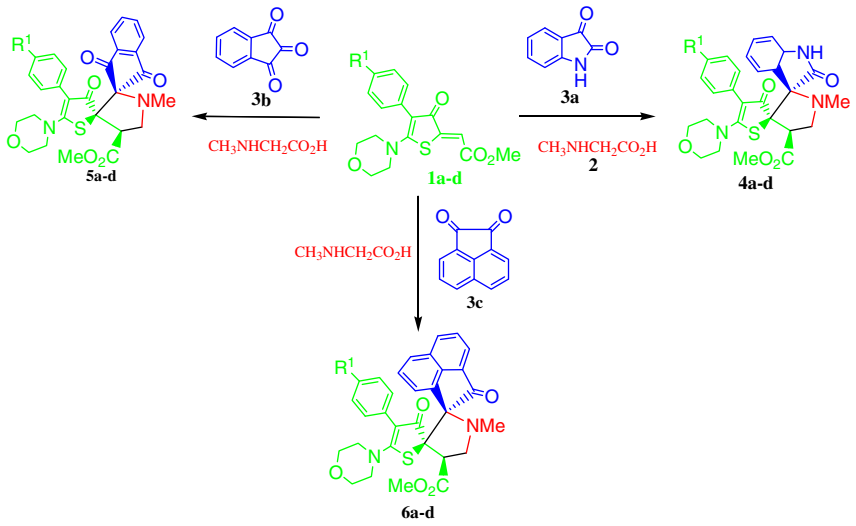
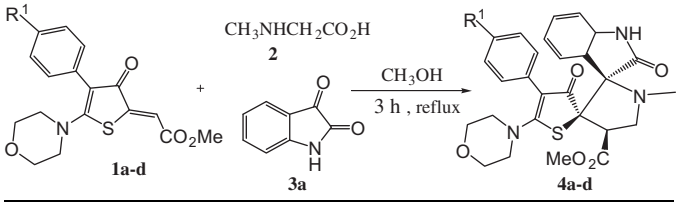
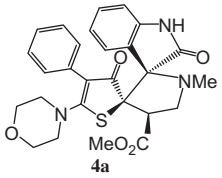
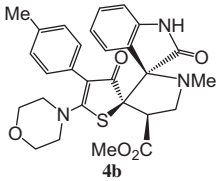
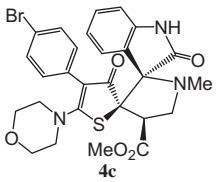
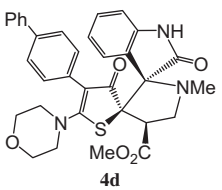


Scheme 1. Synthesis of dispiropyrrolidine-containing thiophenone ring derivatives **4**–**6**.

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

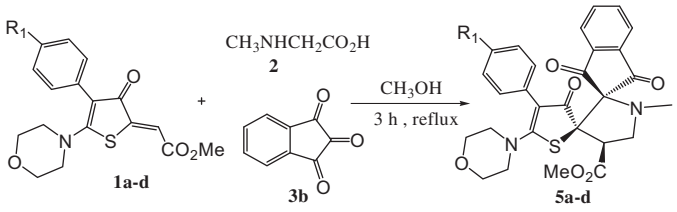
Table 1
Structures of synthesized compounds **4a–d**

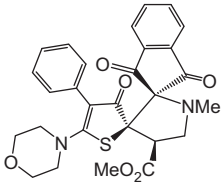
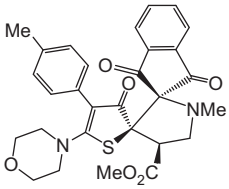
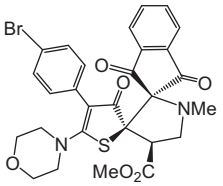
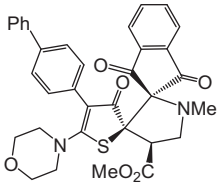


Entry	R^1	Product[a]	Yield[b] (%)
1	H	 **4a**	82
2	Me	 **4b**	87
3	Br	 **4c**	77
4	Ph	 **4d**	80

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

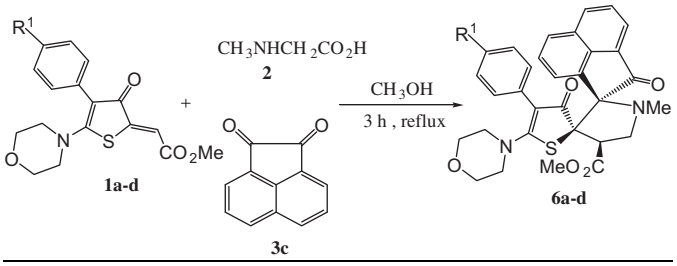
Table 2
Structures of synthesized compounds **5a–d**

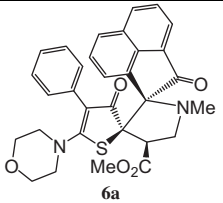
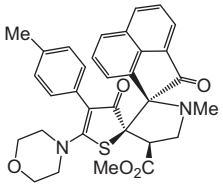
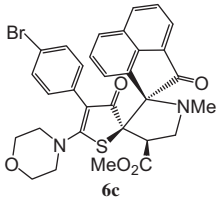
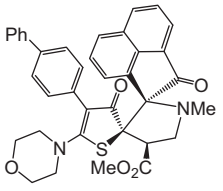


Entry	R^1	Product[a]	Yield[b] (%)
1	H	 **5a**	86
2	Me	 **5b**	91
3	Br	 **5c**	82
4	Ph	 **5d**	87

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

Table 3
Structures of synthesized compounds **6a–d**



Entry	R^1	Product[a]	Yield[b] (%)
1	H	 **6a**	75
2	Me	 **6b**	72
3	Br	 **6c**	70
4	Ph	 **6d**	74

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

To the best of our knowledge, this is the first report in which unsaturated thiophenones are employed as dipolarophiles in cycloaddition reactions of azomethine ylides for the synthesis of dispiropyrrolidines.

In continuation of our research devoted to the development of cycloaddition reactions[16] and the synthesis of heterocyclic systems,[17] we herein report an efficient, highly atom-economic and regioselective preparation of novel dispiropyrrolidine moieties containing a thiophenone ring. The derivatives **4–6** were synthesized via a one-pot, three-component reaction of methyl 2-[(*Z*)-4-aryl-5-morpholino-3-oxo-2,3-dihydrothiophen-2-ylidene]acetate derivatives **1**, sarcosine **2** and various active cycloketones **3** (Scheme 1).

In the first step, we prepared starting materials **1a–d** via the reactions of thioacetomorpholides with dimethyl acetylenedicarboxylate (DMAD) in the presence of K_2CO_3 in toluene as the solvent, according to the method developed in our laboratory.[18]

Next, we examined the three-component reaction of **1a** and sarcosine (**2**) and isatin (**3a**) in various solvents including methanol, toluene, tetrahydrofuran and acetonitrile under reflux conditions. The best results were obtained by refluxing the mixture in methanol to afford the dispiropyrrolidine oxindole **4a**.

To investigate the scope of this procedure, we reacted compounds **1a–d** with sarcosine (**2**) and isatin (**3a**) to give the derivatives **4a–d** in good yields (Table 1).

To extend the applicability of the reaction to other cycloketones, sarcosine (**2**) and ninhydrin (**3b**) were reacted with substrates **1a–d** under the same reaction to afford the derivatives **5a–d** in good yields (Table 2).

Moreover, the reactions of **1a–d** with acenaphthoquinone **3c** were accomplished to afford the derivatives **6a–d** (Table 3).

The structures and regiochemistry of products **4–6** were characterized by IR, ^{1}H NMR and ^{13}C NMR spectroscopy and by elemental analysis.[19] For example, the IR spectrum of cycloadduct **4a** showed characteristic absorptions at 3220, 1732, 1685, 1628 and 1544 cm^{-1} corresponding to the NH amide, ester, oxindole ring carbonyl, thiophenone carbonyl and alicyclic double bond, respectively. In the ^{1}H NMR spectrum of **4a** two singlets appeared at δ 2.25 and 3.70 for the –NCH_3 and –OCH_3 methyls, respectively. The methylene protons of the –NCH_2 of the pyrrolidine ring and the –CH proton α to the ester functional group occurred as three doublets of doublets at δ 3.83, 4.58 and 5.10, respectively, confirming the structure of regioisomer **4a**. In contrast, if the other possible regioisomer **4′a** had formed, the proton at the position α to the ester would have appeared as a singlet in the ^{1}H NMR spectrum. In the ^{13}C NMR spectrum of **4a**, the two spiro quaternary carbons resonated at δ

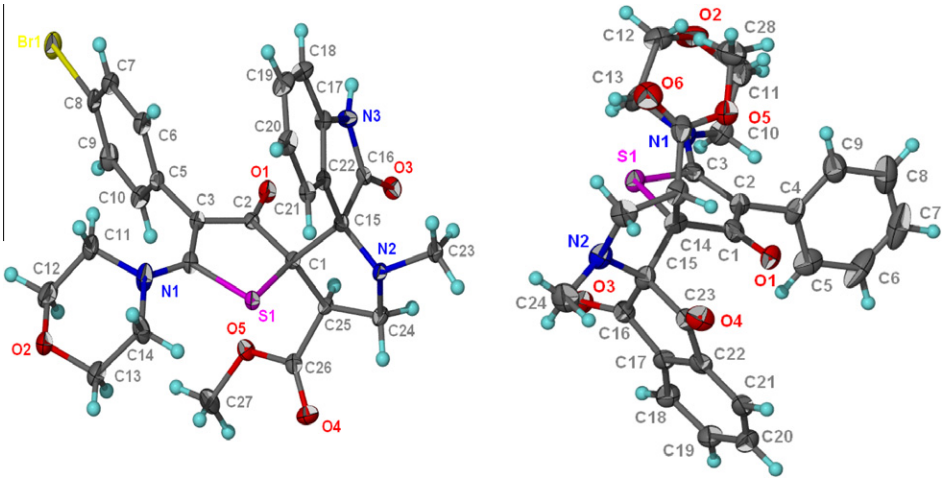
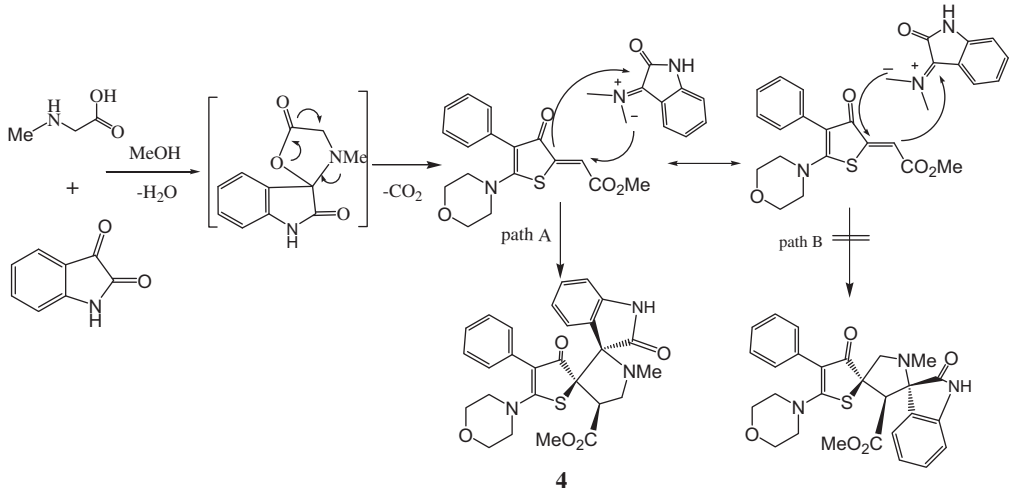


Figure 2. ORTEP diagrams of compounds **4c** and **5a**.



Scheme 2. A plausible mechanism for the formation of compounds.

74.6 and 81.3. Furthermore, there were three carbonyl carbons at δ 171.4, 173.8 and 190.9 corresponding to the oxindole, ester and thiophenone. Finally, the regio- and stereochemical outcome of the cycloaddition reactions was unambiguously ascertained by single crystal X-ray analysis of cycloadducts **4c** and **5a** (Fig. 2).[20]

A proposed reaction mechanism for the formation of the dispiropyrrolidine oxindole containing thiophenone ring system using **4a** as an example, is shown in Scheme 2. The mechanism involves the formation of an azomethine ylide, formed via decarboxylative condensation of isatin and sarcosin, which then undergoes 1,3-dipolar cycloaddition with substrate **1** to produce the cycloadduct **4** via path A (Scheme 2).

In conclusion, we have described an efficient synthesis of dispiropyrrolidine-containing thiophenone ring derivatives through a one-pot, three-component reaction of azomethine ylides with unsaturated thiophenone derivatives. This reaction has several advantages, such as operational simplicity, high atom efficiency, good yields, short reaction times and a catalyst-free procedure. The reaction itself proceeds in a highly regio- and stereocontrolled fashion.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.03.023.

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19. *General procedure for the synthesis of dispiropyrrolidine-containing thiophenones* ***4–6***: A mixture of (*E*)-3-benzylidene-indolin-2-one **1a–d** (1 mmol), sarcosine **2** (98 mg, 1.2 mmol) and cycloketones (isatin, ninhydrin or acenaphtoquinone) **3** (1.2 mmol) was refluxed for 3 h in MeOH (7 ml). After completion of the reaction as monitored by TLC, the solvent was removed under vacuum and the residue was subjected to flash chromatography using petroleum ether/EtOAc (1:2) as eluent. The product was crystallized from EtOH to afford the pure product. Ethyl (3*S*∗,3″*R*∗,4′*S*∗)-1′-methyl-5″-morpholin-4-yl-2,3″-dioxo-1,2-dihydro-3″*H*-dispiro[indole-3,2′-pyrrolidine-3′,2″-thiophene]-4′-carboxylate (**4a**). Yield: 82%, white powder, mp 220–222 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.25 (3H, s), 3.20–3.30 (4H, m), 3.45–3.55 (4H, m), 3.60–3.62 (1H, m), 3.70

(3H, s), 3.83 (1H, dd, J = 6.9, 8.8 Hz), 4.58 (1H, dd, J = 8.7, 10.9 Hz), 5.10 (1H, dd, J = 6.7, 11.1 Hz), 6.71 (2H, d, J = 7.6 Hz, Ar-H), 6.90–6.97 (2H, m, Ar-H), 7.12–7.25 (3H, m, Ar-H), 7.68 (1H, d, J = 6.5 Hz, Ar-H), 8.71 (1H, s, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 35.4, 50.2, 51.5, 52.7, 53.7, 66.6, 74.6, 81.3, 109.6, 120.3, 125.9, 127.2, 128.9, 129.1, 130.4, 131.5, 132.0, 136.5, 137.4, 142.5, 171.4, 173.8, 190.9; IR (KBr): 3220, 1732, 1685, 1628, 1544 cm^{-1}; Anal. Calcd for $C_{27}H_{27}N_3O_5S$: C, 64.14; H, 5.38; N, 8.31. Found: C, 64.05; H, 5.30; N, 8.44.

20. Crystallographic data for **4c** and **5a** have been deposited at the Cambridge Crystallographic Data Centre, with the deposition numbers CCDC 911697 **4c** and 911696 **5a**, respectively.