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Regioselective synthesis of novel spiroindane-1,3-diones through 1,3-dipolar cycloaddition reactions

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ABSTRACT

A facile synthesis of novel spiroindane-1,3-diones has been achieved via 1,3-dipolar cycloaddition of an azomethine ylide, generated in situ from ninhydrin and 1,2,3,4-tetrahydroisoquinoline, with the conjugated double bond of chalcone derivatives. The regiochemistry and structures of the cycloadducts were determined with spectroscopic data and by X-ray crystal structure analysis.

1,3-Dipolar cycloaddition reactions provide an efficient approach for the synthesis of five-membered cyclic heterocycles.[1] The high stereospecificity and stereoselectivity associated with these reactions make them synthetically important.[2–5] Five-membered cyclic heterocycles are an important class of compounds, not only because of their natural abundance, but also for their chemical and biological significance.[6]

Table 1
1,3-Dipolar cycloaddition of chalcones **3a–o** to the in situ generated azomethine ylide

Entry	Product	R	R′	Yield[a] (%)
1	**4a**	H	H	90
2	**4b**	*p*-CN	H	85
3	**4c**	*p*-CH_3	H	92
4	**4d**	*p*-Cl	H	94
5	**4e**	*p*-Br	H	92
6	**4f**	*p*-Cl	*m*-Cl	82
7	**4g**	*p*-NO_2	H	92
8	**4h**	H	*o*-NO_2	79
9	**4i**	*m*-OCH_3	H	83
10	**4j**	*o*-Cl	H	77
11	**4k**	*p*-F	H	92
12	**4l**	*p*-OCH_3	*p*-OCH_3	90
13	**4m**	H	*p*-OCH_3	88
14	**4n**	H	*p*-Cl	85
15	**4o**	*o*-NO_2	H	89

[a] Isolated yield.

Azomethine ylides are reactive and versatile 1,3-dipoles which react readily with various dipolarophiles to afford pyrrolidines and pyrrolizidines.[7] These compounds form the central skeletons of numerous alkaloids and are classes of compounds with significant biological activity.[8]

Spiro compounds, in particular spiropyrrolidines, have gained significant attention as a result of their interesting biological activities such as antimicrobial, antitumor, and antibiotic.[9–18] In addition, they also act as inhibitors of human NK-I receptor activity.[19] Some spiropyrrolidines are potential antileukemic and anticonvulsant agents and possess antiviral and local anaesthetic activities.[20] 1,3-Indanediones possess important pharmacological properties such as anti-inflammatory and anticoagulant.[21] The synthesis and

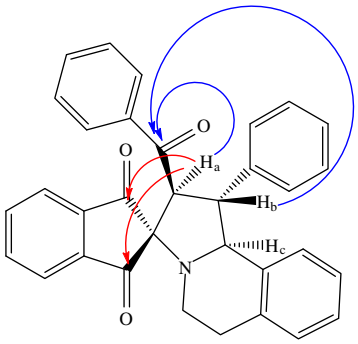

Figure 1. Selected HMBC correlations present in **4a**.

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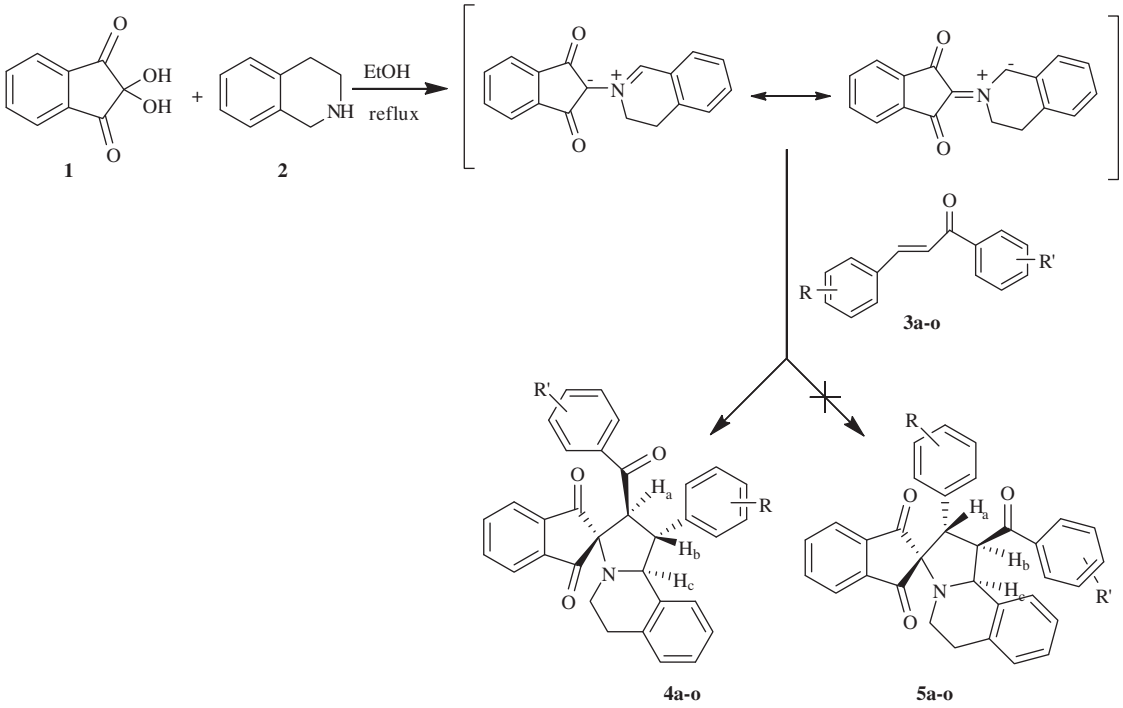


Scheme 1. Regioselective synthesis of spiroindane-1,3-diones **4a–o**.

antimicrobacterial activity of spiro- and dispiroindanediones have been reported recently.[22]

Herein, we report the facile synthesis of novel spiroindane-1,3-diones via a one-pot, three-component condensation of an azomethine ylide, generated in situ from ninhydrin and 1,2,3,4-tetrahydroisoquinoline, with chalcone derivatives.

Various substituted chalcone adducts **3a–o** were synthesized in accordance with the literature.[23] In a first attempt, a mixture of ninhydrin (**1**), 1,2,3,4-tetrahydroisoquinoline (**2**) and chalcone **3a** was heated at reflux in ethanol to afford the corresponding spiroindane-1,3-dione **4a** in good yield (Scheme 1). The extent of reaction was monitored by TLC and the pure cycloadduct

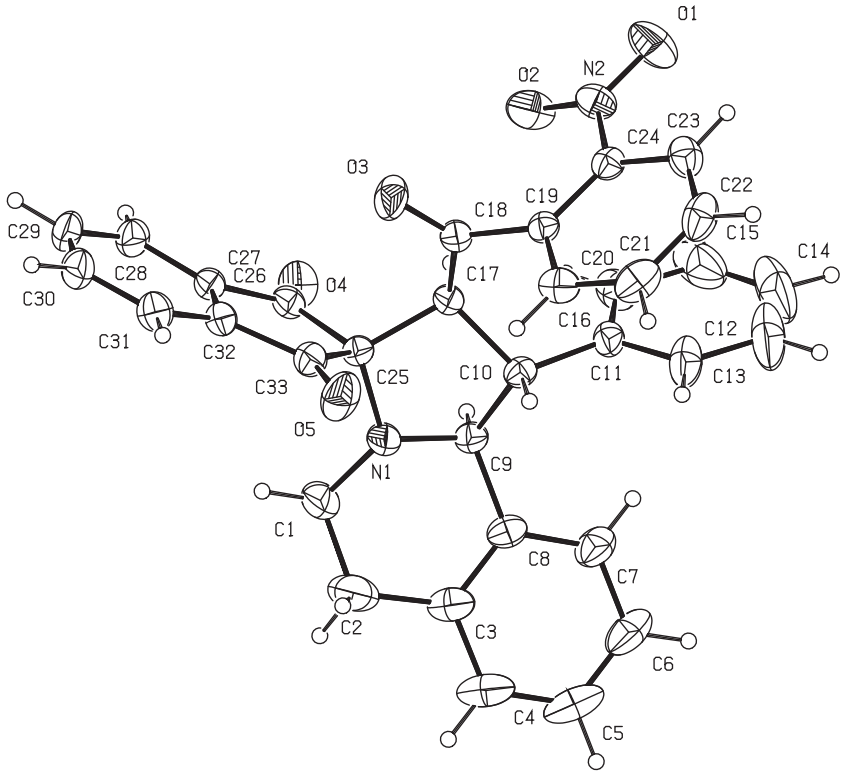
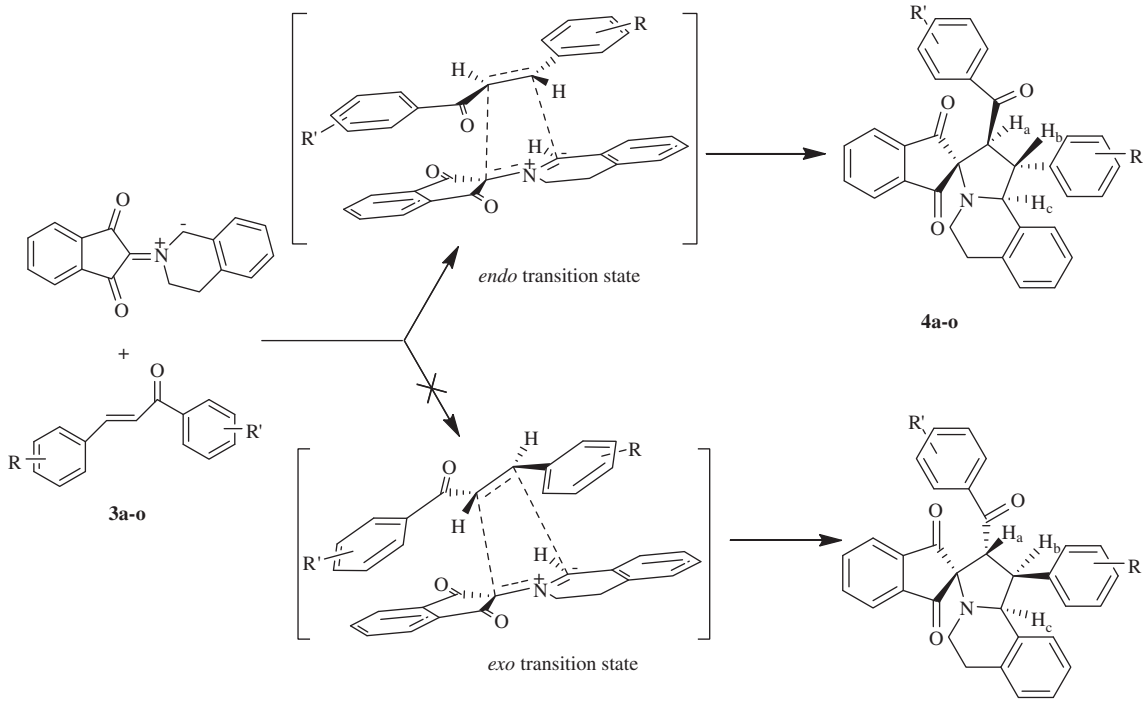


Figure 2. ORTEP diagram of **4h**.



Scheme 2. Proposed mechanism of the cycloaddition of the azomethine ylide with chalcone derivatives.

was obtained by recrystallization from ethanol. The reaction proceeds through the generation of an azomethine ylide via condensation of ninhydrin with 1,2,3,4-tetrahydroisoquinoline followed by a [1,5]-prototropic shift.[24] Next, the generated azomethine ylide undergoes 1,3-dipolar cycloaddition with the chalcone. We applied this protocol to a series of chalcone derivatives in order to obtain the corresponding spirocycloadducts in a regio- and stereocontrolled manner (Table 1).[25] The structures and the regiochemistries of the cycloadducts were confirmed by spectral analysis.[26]

The IR spectrum of **4a** showed two peaks at 1742 and 1705 cm^{-1} due to the indanedione and chalcone carbonyl groups. The ^1H NMR spectrum of compound **4a** exhibited two doublets at δ 4.97 (J = 10 Hz) and δ 4.49 (J = 9.2 Hz) for the H_c and H_a protons, respectively, and a triplet at δ 4.15 (J = 9.6 Hz) for H_b. The ^{13}C NMR spectrum of **4a** showed three signals at δ 195.7, δ 199.9, and δ 203.2 for the ketone carbonyl. The spirocyclic carbon atom at δ 74.3 was assigned through ^{13}C NMR and DEPT-135 experiments. The structure of product **4a** was further confirmed by mass spectrometry which showed a molecular ion peak at m/z 483. The regiochemistry of the product was established from the HMBC spectrum. As indicated in Figure 1, the benzoyl C=O group at δ 195.7 correlates with the H_a and H_b protons at δ 4.49 and δ 4.15 and not with proton H_c showing that the correct regiochemistry of the product is as shown in structure **4a**. If the other possible regioisomer **5a** had formed, a long-range coupling between the benzoyl C=O group and H_c would be observed.

The regio- and stereochemical outcome of the cycloaddition was confirmed by X-ray crystallography of the cycloadduct **4h**.[27] The ORTEP diagram of **4h** indicates that the stereochemistry of the product retained the geometry of the starting chalcone and no evidence of isomerization of the starting material was observed (Fig. 2). This is consistent with the cycloaddition reaction following a concerted mechanism via an *endo* transition state. The proposed mechanism of the cycloaddition reaction is shown in Scheme 2.

In summary, a facile and efficient synthesis of a new class of spiroindane-1,3-diones via cycloaddition of an azomethine ylide, generated in situ from ninhydrin and 1,2,3,4-tetrahydroisoquinoline, with the conjugated double bond of various chalcone derivatives has been described. The products were isolated by recrystallization without involving further purification processes such as column chromatography. The structural assignments of the products were deduced by HMBC spectroscopy and X-ray crystallographic analysis.

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Supplementary data

Supplementary data (^1H, ^{13}C of all compounds and the HMBC spectra of compound **4a**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.018.

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25. *Typical experimental procedure for* **4a**: A mixture of ninhydrin (**1**) (1 mmol, 0.178 g), 1,2,3,4-tetrahydroisoquinoline (**2**) (1 mmol, 0.139 g), and chalcone **3a** (1 mmol, 0.208 g) was heated at reflux with stirring in EtOH (10 ml) for 4 h. The resulting orange precipitate was then filtered and recrystallized from EtOH to afford the pure product in good yield (yield 90%, mp: 162 °C).
26. *2′-Benzoyl-1′-phenyl-2′,5′,6′,10′b-tetrahydro-1′H-spiro[indene-2,3′-pyrrole[2,1-a]-isoquinoline]-1,3-dione* (**4a**): Orange crystals; yield: 0.43 g, 90%; mp 162 °C (Anal. Calcd for $C_{33}H_{25}NO_3$: C, 81.97; H, 5.21; N, 2.90. Found: C, 81.93; H, 5.26; N, 2.93.); IR (KBr):1742, 1705 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) 6.58–7.96 (18H, m, Ar), 4.97 (1H, d, J = 10 Hz, H_c), 4.49 (1H, d, J = 9.2 Hz, H_a), 4.15 (1H, t, J = 9.6 Hz, H_b), 2.81–2.86 (2H, m, H-isoquinoline), 2.61–2.66 (2H, m, H-isoquinoline); ^{13}C NMR (100 MHz, DMSO-d_6) 203.2, 199.9, 195.7, 141.6, 141.4, 140.4, 137.9, 137.7, 137.5, 136.7, 134.9, 133.8, 129.6, 129.2, 129.1, 128.8, 128.2, 127.7, 126.9, 125.9, 124.4, 123.3, 123.0, 74.3 (spiro carbon), 65.1, 61.8, 51.3, 43.7, 29.6; MS m/z: 483 (M^+).
27. Crystallographic data for the structure **4h** in this Letter have been deposited with the Cambridge Crystallographic Data centre as supplementary Publication No. CCDC-777612. 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).