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# Spiro indane-1,3-dione pyrrolizidine compounds synthesized by 1,3-dipolar cyclo-addition reaction

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## Abstract

Spiro indane-1,3-dione pyrrolizidine compounds were synthesized by the 1,3-dipolar cyclo-addition reaction of ninhydrin, L-proline and two kinds of alkene (chalcone and (*E*)-*β*-aryl-nitrostyrene). All these reactions proceeded with good yield and with high regio- and stereoselectivity. It was found that the use of two kinds of alkene lead to different regioselectivity. In the structure of **D1** and **D2**, the electron-withdrawing group (EWG; benzoyl group) is attached to C-3 and the phenyl group is at C-4 of the newly constructed pyrrolidine. In the structure of **D3-D7**, the EWG (nitro group) is at C-4 and the phenyl group is at C-3 of the newly constructed pyrrolidine.

**Keywords:** 1,3-dipolar cycloaddition; regioselectivity; spiro compounds.

## Introduction

The 1,3-dipolar cyclo-addition reaction provides a simple and direct entry into a number of five-membered heterocyclic compounds, such as pyrrolidines, pyrrolines and pyrroles (Okino et al., 2005; Chen et al., 2009; Miao et al., 2010). In this reaction, the azomethine ylides are generated *in situ* via decarboxylative condensation of aldehyde or ketone with α-amino acids. The ylides can be trapped by dipolarophiles to form five-membered heterocyclic compounds (Huisgen, 1968). Almost all these reactions proceed with good yield and with high regio- and stereoselectivity (Huisgen, 1968; Okino et al., 2005; Chen et al., 2009; Miao et al., 2010). Until now, very little attention has been paid to regioselectivity of this reaction. In this article, we report two different 1,3-dipolar cyclo-addition reactions between ninhydrin, proline and two different types of alkenes (chalcone and (*E*)-*β*-aryl-nitrostyrene). The reactions are shown in Scheme 1.

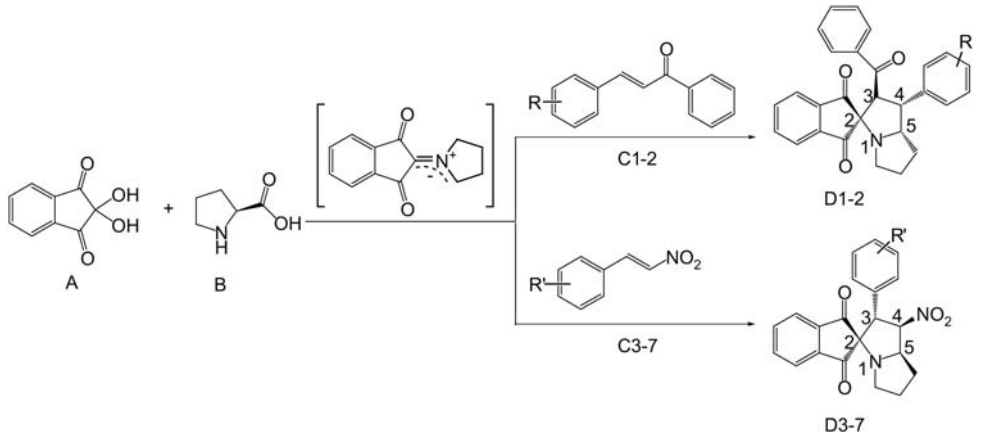
## Results and discussion

The reaction of ninhydrin (**A**), L-proline (**B**), and a chalcone (**C1**–**2**) was conducted in a mixture of methanol and water (3:1). The solvent was distilled off under reduced pressure and the product was purified by silica gel column chromatography and characterized by spectral analysis. In this reaction, azomethine ylide was generated *in situ* via decarboxylative condensation of ninhydrin with L-proline, and was then trapped by the reaction with a chalcone to form a spiro compound. Two products, **D1** and **D2**, were obtained by using two different chalcones.

The $^{1}$H nuclear magnetic resonance (NMR) spectrum of compound **D1** shows multiplet signals in the region $\delta$ 0.85–4.94 for the protons of the pyrrolizidine system. The signals in the region $\delta$ 7.05–7.86 are for the protons of aryl groups. A doublet at $\delta$ 4.94 (1H, d, $J$=7.6 Hz), indicates the presence of a methine proton, next to the benzoyl group at C-3 of the pyrrolidine ring. The benzylic proton at C-4 resonates as a multiplet at $\delta$ 4.19 (1H, m). In the $^{13}$C NMR spectrum of the cyclo-adduct **D1**, the carbonyl carbons of indane-1, 3-dione and the benzoyl group carbons exhibit signals at $\delta$ 202.1, 200.4 and 196.6, respectively. A molecular ion peak at m/z 422 (ESI-MS, M+1) in the mass spectrum confirmed the formation of the cyclo-adduct. The spectra of the cyclo-adduct **D2** showed similar characteristics, indicating identical regiochemistry; there is a precedence in the literature for this type of regiochemistry (Fokas et al., 1998; Amal Raj et al., 2003).

On the other hand, different regiochemistry was observed when ninhydrin, L-proline and (*E*)-*β*-aryl-nitroolefin (**C3-7**) were heated under reflux in methanol. The structure and stereochemistry of the cyclo-adducts **D3**–**D7** were confirmed by their spectral data. Thus, in the $^{1}$H NMR spectrum of **D3**, a doublet at $\delta$ 4.69 (1H, d, $J$=12.8 Hz) indicated the presence of a benzylic proton at C-3 of the newly constructed pyrrolidine. The $CHNO_2$ proton exhibited a doublet of doublets at $\delta$ 6.27 (1H, dd, $J$=12.8, 9.8 Hz), which is consistent with the presence of a nitro group at C-4 of the newly constructed pyrrolidine. The aromatic protons gave resonance in the region of 7.11–7.76 and the pyrrolizidine methylene and methine protons gave rise to multiplets in the region 1.45–4.65. The spectra of other cyclo-adducts **D3**–**D7** showed similar characteristics. Furthermore, the structure of **D4** was corroborated by X-ray diffraction analysis (Figure 1). A similar regioselectivity pattern has been previously reported (Amal Raj and Raghunathan, 2001; Rehn et al., 2004).

In conclusion, two different regioselectivity patterns were observed for the 1,3-dipolar cyclo-addition reactions between ninhydrin, proline and chalcone or (*E*)-*β*-aryl-nitrostyrene. In the structure of **D1** and **D2**, the benzoyl group of the starting chalcone was attached to C-3 and the phenyl group was at C-4 of the newly constructed pyrrolidine. In products **D3**–**D7**, the nitro group of the starting alkene was at C-4 and the phenyl group was at C-3 of the pyrrolidine ring.




**Scheme 1** The 1,3-dipolar cycloaddition reactions between ninhydrin, L-proline and olefins.
**C1, D1**: R=H; **C2**, **D2**: R=*ortho*-Cl; **C3**, **D3**: R=H; **C4**, **D4**: R=*ortho*-Cl; **C5**, **D5**: R=*para*-OMe; **C6**, **D6**: R=*para*-Me; **C7**, **D7**: R=*para*-$NMe_2$.

## Experimental

### General remarks

All starting materials and solvents (A.R. grade) were commercially available and were used without further purification. NMR spectra were recorded in deuteriochloroform solutions on a Bruker DPX 300 spectrometer, operating at 400 MHz for $^1$H and 100 MHz for $^{13}$C. Mass spectra were recorded on a Micromass Platform II spectrometer using the direct-inlet system operating in the electron impact (ESI) mode. The elemental analyses were obtained on a Carlo Erba 1106 element analysis instrument.

### General procedure for the synthesis of spiro indane-1,3-dione pyrrolizidine compounds

A solution prepared from ninhydrin (10 mmol), L-proline (10 mmol) and chalcone or (*E*)-*β*-aryl-nitrostyrene (12 mmol), methanol (100 ml) and water (10 ml) was stirred at room temperature for 1 h. Completion of the reaction was evidenced by thin layer chromatography (TLC) analysis (about 1 h). The solvent was then distilled off under reduced pressure and the residue was separated by column chromatography on silica gel eluting with a mixture of petroleum ether and ethyl acetate (4:1).

**Spiro[2.2′]indane-1′,3′-dione-3-benzoyl-4-phenylpyrrolizidine (D1)** Yellow solid; yield 75%; $^1$H NMR: δ 7.86 (1H, d, *J*=7.6 Hz), 7.34 (1H, t, *J*=7.6 Hz), 7.30(1H, t, *J*=7.6 Hz), 7.05–7.24 (11H, m), 4.94 (1H, d, *J*=12.0 Hz), 4.19 (1H, m), 4.05 (1H, m), 2.75 (2H, m), 2.16 (1H, m), 1.98 (1H, m), 1.25 (1H, m), 0.85 (1H, m); $^{13}$C NMR: δ 202.1, 200.4, 196.6, 140.9, 140.3, 138.9, 136.6, 136.3, 135.7, 133.0, 128.6, 128.1, 127.9, 127.8, 127.1, 123.1, 122.7, 73.1, 64.5, 52.8, 47.8, 30.6, 28.4; ESI-MS: m/z 422 (M+1).

Analysis: Calcd for $C_{28}H_{23}NO_3$: C, 79.79; H, 5.50; N, 3.32. Found: C, 79.84; H, 5.55, N, 4.28.

**Spiro[2.2′]indane-1′,3′-dione-3-benzoyl-4-(*o*-chlorophenyl) pyrrolizidine (D2)** Yellow solid; yield 80%; $^1$H NMR: δ 7.90 (1H, d, *J*=8.0 Hz), 7.77 (1H, t, *J*=7.2 Hz), 7.67 (2H, m), 7.57 (1H, d, *J*=8.0 Hz), 7.02–7.29 (8H, m), 5.05 (1H, d, *J*=8.8 Hz), 4.72 (1H, m), 4.13 (1H, m), 2.76 (2H, m), 2.16 (1H, m), 2.01 (1H, m), 1.92 (2H, m), 1.24 (1H, m); $^{13}$C NMR: δ 202.1, 200.7, 196.7, 141.4, 140.3, 136.4, 135.6, 134.8, 132.9, 129.8, 128.3, 128.0, 127.9, 127.8, 127.0, 123.1, 122.7, 73.0, 64.4, 48.2, 47.7, 30.5, 28.4; ESI-MS: m/z 456 (M+1).

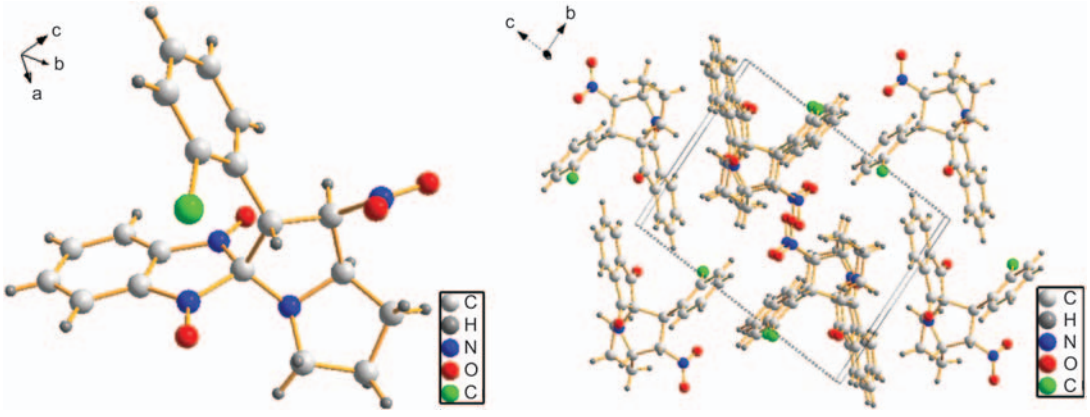



**Figure 1** X-ray crystal structure and the packing of **D4**.

Analysis. Calcd for $C_{28}H_{22}ClNO_3$: C, 73.76; H, 4.86; N, 3.07. Found: C, 73.77; H, 4.88, N, 3.10.

**Spiro[2.2′]indane-1′,3′-dione-4-nitro-3-phenylpyrrolizidine (D3)** Yellow solid: yield 73%; $^1$H NMR: δ 7.76 (2H, m), 7.74 (2H, m), 7.20 (2H, d, *J*=8.0 Hz), 7.11 (3H, m), 6.27 (1H, dd, *J*=12.8, 9.8 Hz), 4.69 (1H, d, *J*=12.8 Hz), 4.65 (1H, m), 3.33 (1H, m), 2.74 (1H, m), 2.03 (2H, m), 1.75 (1H, m), 1.45 (1H, m); $^{13}$C NMR: δ 198.2, 196.2, 142.0, 141.1, 136.5, 136.0, 132.0, 128.8, 128.5, 128.0, 124.0, 123.6, 91.3, 75.0, 65.4, 50.8, 50.0, 27.0, 25.7; ESI-MS: m/z 363 (M+1).

Analysis: Calcd for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.01; N, 7.73. Found: C, 69.65; H, 4.98, N, 7.70.

**Spiro[2.2′]indane-1′,3′-dione-3-(*o*-chlorophenyl)-4-nitropyrrolizidine (D4)** Yellow solid; yield 75%; $^1$H NMR: δ 7.91 (1H, m), 7.83 (1H, m), 7.75 (2H, m), 7.34 (1H, d, *J*=6.4 Hz), 7.17 (1H, d, *J*=6.4 Hz), 7.06 (1H, m), 7.0 (1H, m), 6.06 (1H, t, *J*=8.0 Hz), 5.46 (1H, d, *J*=8.4 Hz), 4.66 (1H, m), 3.43 (1H, m), 2.82 (1H, m), 2.06 (2H, m), 1.77 (1H, m), 1.57 (1H, m); $^{13}$C NMR: δ 199.2, 195.4, 141.9, 140.8, 136.4, 136.2, 135.4, 130.3, 129.2, 129.1, 127.0, 123.7, 123.2, 92.6, 75.1, 65.9, 49.9, 47.0, 27.8, 25.7; ESI-MS: m/z 397 (M+1).

Analysis: Calcd for $C_{21}H_{17}ClN_2O_4$: C, 63.56; H, 4.32; N, 7.06. Found: C, 63.59; H, 4.33, N, 7.10.

**Spiro[2.2′]indane-1′,3′-dione-3-(*p*-methoxyphenyl)-4-nitropyrrolizidine (D5)** Yellow solid; yield 73%; $^1$H NMR: δ 7.88 (2H, m), 7.75 (2H, m), 7.09 (2H, d, *J*=7.2 Hz), 6.63 (2H, d, *J*=7.2 Hz), 6.19 (1H, t, *J*=8.0 Hz), 4.63 (1H, d, *J*=9.2 Hz), 4.60 (1H, m), 3.63 (3H, s), 3.31 (1H, m), 2.71 (1H, m), 2.01 (2H, m), 1.73 (1H, m), 1.49 (1H, m); $^{13}$C NMR: δ 198.5, 196.4, 159.2, 142.1, 141.2, 136.4, 136.0, 129.6, 124.0, 123.7, 123.5, 114.1, 91.5, 74.9, 65.3, 55.0, 50.2, 50.0, 27.7, 25.7; ESI-MS: m/z 393 (M+1).

Analysis: Calcd for $C_{22}H_{20}N_2O_5$: C, 67.34; H, 5.14; N, 7.14. Found: C, 37.30; H, 5.11, N, 7.17.

**Spiro[2.2′]indane-1′,3′-dione-3-(*p*-methylphenyl)-4-nitropyrrolizidine (D6)** Yellow solid; yield 80%; $^1$H NMR: δ 7.90 (1H, m), 7.78 (1H, m), 7.65 (2H, m), 7.32 (1H, d, *J*=6.4 Hz), 7.15 (1H, d, *J*=6.4 Hz), 7.00 (1H, m), 6.98 (1H, m), 6.25 (1H, t, *J*=8.0 Hz), 4.69 (1H, d, *J*=8.4 Hz), 4.69 (1H, m), 3.34 (1H, m), 2.81 (1H, m), 2.21 (3H, s), 2.02 (2H, m), 1.75 (1H, m), 1.50 (1H, m); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 198.2, 196.3, 142.2, 141.3, 137.8, 136.5, 136.1, 129.5, 128.9, 128.5, 124.1, 123.6, 91.4, 74.9, 65.4, 50.4, 50.0, 27.8, 20.9; ESI-MS: m/z 377 (M+1).

Analysis: Calcd for $C_{21}H_{18}N_2O_4$: C, 70.20; H, 5.36; N, 7.44. Found: C, 70.21; H, 5.34, N, 7.49.

**Spiro[2.2′]indane-1′,3′-dione-3-[*p*-(dimethylamino)phenyl]-4-nitropyrrolizidine (D7)** Yellow solid; yield 70%; $^1$H NMR: δ 7.88 (2H, m), 7.75 (2H, m), 7.03 (2H, d, *J*=7.2 Hz), 6.44 (2H, d, *J*=7.2 Hz), 6.19 (1H, t, *J*=8.0 Hz), 4.61 (1H, d, *J*=9.2 Hz), 4.59 (1H, m), 3.33 (1H, m), 2.79 (6H, s), 2.71 (1H, m), 2.01 (2H, m), 1.73 (1H, m), 1.50 (1H, m); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 198.9, 196.6, 149.9, 142.3, 141.3, 136.3, 135.9, 129.3, 124.0, 123.5, 118.9, 112.4, 91.6, 74.9, 65.3, 50.3, 50.0, 40.2, 27.7, 25.8; ESI-MS: m/z 406 (M+1).

Analysis. Calcd for $C_{23}H_{23}N_3O_4$: C, 68.13; H, 5.72; N, 10.36. Found: C, 68.17; H, 5.70, N, 10.33.

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