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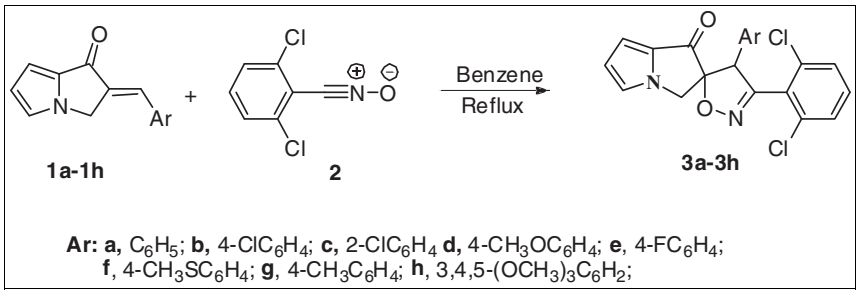


The 1,3-dipolar cycloaddition of nitrile oxide to 2-arylmethylidene-2,3-dihydro-1*H*-pyrrolizin-1-ones afforded new 4-(aryl)-3-(2,6-dichlorophenyl)-1′*H*,4*H*-spiro[isoxazole-5,2′-pyrrolizin]-1′-ones in moderate yields. The structures of all the products were characterized thoroughly by NMR, IR, MS, and elemental analysis together with X-ray crystallographic analysis.

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## INTRODUCTION

Spiro isoxazoline compounds represent an important class of naturally occurring substances characterized by highly pronounced biological properties [1]. One of the most widely used methods for the synthesis of these compounds is via 1,3-dipolar cycloaddition reactions of nitrile oxides to exocyclic double bonds [2].

The pyrrolizinones derivatives are known for their anti-inflammatory and analgesic activities [3]; their pyrrolizidine framework is a frequently encountered structural motif in many alkaloids with important bioactivity [4].

As part of our endeavor to synthesize novel heterocyclic system [5], we herein report the synthesis of a series of new spiro isoxazoline heterocycles containing pyrrolizinone framework (Scheme 1).

## RESULTS AND DISCUSSION

The 1,3-dipolar cycloaddition reaction of 2-arylmethylidene-2,3-dihydro-1H-pyrrolizin-1-ones **1** to the nitrile oxide **2** yields 4-(aryl)-3-(2,6-dichlorophenyl)- 1′H,4H-spiro [isoxazole-5,2′-pyrrolizin]-1′-one **3**.

The structures of all compounds **3a–3h** were established by different spectroscopic techniques (NMR, IR, and MS) and elemental analysis. The IR spectrum of **3a** displayed $\nu_{C=O}$ at 1706.7 $cm^{-1}$. The $^1H$ NMR spectrum of **3a** revealed two doublets at δ 4.09 ($J$ = 12.5 Hz) and 4.42 ($J$ = 12.5 Hz) resulting from $CH_2$ (H-1), which existed in pyrrolizidine ring, several multiplets, and doublets in the range of δ 6.52–7.31 for aromatic protons. The singlet at δ 5.89 is in accord with the proton of Ar–CH (H-4) in isoxazoline ring.

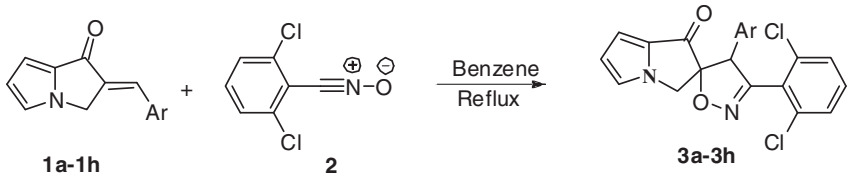
The $^{13}C$ NMR spectrum of the product **3a** exhibited the presence of $CH_2$ carbon (C-1) at δ 51.48 and carbonyl carbon at δ 183.61 (C-3). The signal at δ 59.80 is assignable to the carbon of Ar–CH (C-4) (based on HSQC). The signal at δ 155.66 is in agreement with the carbon of C-5 in isoxazoline ring. The existence of signal at δ 96.25 is assignable for the spiro carbon of C-2.

In the $^1H$–$^{13}C$ HMBC map of **3a** (Fig. 1), protons of H-1 correlate with a spiro carbon (C-2), carbonyl carbon (C-3), and Ar–CH (C-4). Proton of Ar–CH (H-4) existed in isoxazoline ring correlates with the spiro carbon (C-2), C═N (C-5), and carbonyl carbon (C-3). Further, the structure of **3d** was confirmed by X-ray diffraction, supporting the structural assignments of all compounds made using spectroscopic methods (Fig. 2) [6].

## EXPERIMENTAL

Compounds **1** [7] and **2** [8] were prepared according to the reported procedures. All NMR spectra were recorded on a Bruker AV-II 500 MHz NMR spectrometer (Bruker, Switzerland), operating at 500 MHz for $^1H$ and 125 MHz for $^{13}C$. TMS was used as an internal reference for $^1H$ and $^{13}C$ chemical shifts, and $CDCl_3$ was used as solvent. Elemental analysis was performed with an Elementar analyzer (varioEL II; Hessen, Germany). MS was conducted with a Finnigan LCQ Advantage MAX mass spectrometer (San Jose, Ca). IR spectra were recorded on a Perkin-Elmer spectrometer (Spectrum One; Waltham, MA).

**Scheme 1**




**1a-1h** **2** **3a-3h**

**Ar: a,** $C_6H_5$; **b,** 4-$ClC_6H_4$; **c,** 2-$ClC_6H_4$ **d,** 4-$CH_3OC_6H_4$; **e**, 4-$FC_6H_4$; **f**, 4-$CH_3SC_6H_4$; **g**, 4-$CH_3C_6H_4$; **h**, 3,4,5-$(OCH_3)_3C_6H_2$;

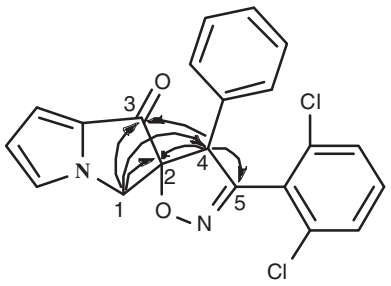



**Figure 1.** Partial HMBC diagram of **3a**.

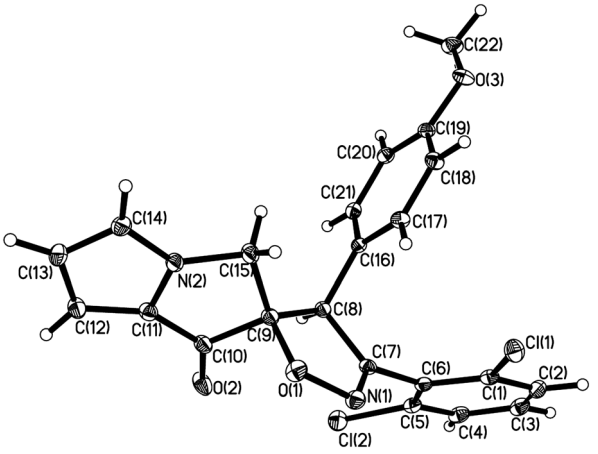



**Figure 2.** ORTEP diagram of **3d**.

Melting points were measured with a Yanaco MP500 melting point apparatus (Tokyo, Japan) and are uncorrected.

**General procedure for the synthesis of 4-(aryl)-3-(2,6-dichlorophenyl)-1′*H*,4*H*-spiro[isoxazole-5,2′-pyrrolizin]-1′-one (3a–3h)**. A mixture of **1** (1 mmol) and **2** (2 mmol) in benzene (15 mL) was refluxed overnight. The solvent was evaporated in vacuum. The residue was purified by column chromatography on silica gel with the use of petroleum ether and ethyl acetate (5:1 v/v) as eluent to afford the corresponding **3a–3h**.

***3-(2,6-Dichlorophenyl)-4-phenyl-1′H,4H-spiro[isoxazole-5,2′-pyrrolizin]-1′-one (3a).*** White solid, yield 64%; mp : 183–185°C; $^1$H NMR ($CDCl_3$, 500 MHz): δ 4.09 (d, $J$ = 12.5 Hz, 1H, H1), 4.42 (d, $J$ = 12.5 Hz, 1H, H1), 5.89 (s, 1H, H4), 6.52–6.54 (m, 1H), 6.89–6.90 (m, 1H), 6.93–6.94 (m, 1H), 7.17–7.20 (m, 3H), 7.25–7.26 (m, 3H), 7.29 (d, $J$ = 4.0 Hz, 1H), 7.31 (d, $J$ = 4.0 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 51.48 (C1), 59.80 (C4), 96.25 (C2), 111.10, 118.04, 124.77, 127.04, 128.77, 128.82, 129.20, 129.27, 129.83, 131.23, 132.40, 135.55, 155.66 (C5), 183.61 (C3); IR (KBr) $v$: 1706.7 cm$^{-1}$; ESI MS $m/z$: 397 $[M+H]^+$. *Anal*. Calcd. for $C_{21}H_{14}Cl_2N_2O_2$: C 63.49, H 3.55, N 7.05; found C 63.30, H 3.61, N 7.18.

***4-(4-Chlorophenyl)-3-(2,6-dichlorophenyl)-1′H,4H-spiro[isoxazole-5,2′-pyrrolizin]-1′-one (3b).*** White solid, yield 58%; mp : 179–180°C; $^1$H NMR ($CDCl_3$, 500 MHz): δ 4.09 (d, $J$ = 12.5 Hz, 1H, H1), 4.43 (d, $J$ = 12.5 Hz, 1H, H1), 5.86 (s, 1H, H4), 6.53–6.55 (m, 1H), 6.89–6.90 (m, 1H), 6.96–6.97 (m, 1H), 7.14–7.16 (m, 2H), 7.20–7.26 (m, 3H), 7.31–7.32 (m, 2H); $^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 51.33 (C1), 59.08 (C4), 96.11 (C2), 111.30, 118.19, 124.78, 126.79, 128.90, 129.47, 129.77, 130.62, 130.94, 131.38, 134.84, 135.55, 155.25 (C5), 183.19 (C3); IR (KBr) $v$: 1709.0 cm$^{-1}$; ESI MS $m/z$: 431 $[M+H]^+$. *Anal*. Calcd. for $C_{21}H_{13}Cl_3N_2O_2$: C 58.43, H 3.04, N 6.49; found C 58.58, H 3.15, N 6.29.

***4-(2-Chlorophenyl)-3-(2,6-dichlorophenyl)-1′H,4H-spiro[isoxazole-5,2′-pyrrolizin]-1′-one (3c).*** White solid, yield 60%; mp : 199–200°C; $^1$H NMR ($CDCl_3$, 500 MHz): δ 3.98 (d, $J$ = 12.5 Hz, 1H, H1), 4.36 (d, $J$ = 12.5 Hz, 1H, H1), 6.54–6.55 (m, 1H), 6.57 (s, 1H, H4), 6.90–6.91 (m, 1H), 6.94–6.95 (m, 1H), 7.19–7.25 (m, 3H), 7.30–7.33 (m, 3H), 7.42–7.44 (m, 1H); $^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 51.34 (C1), 55.87 (C4), 95.66 (C2), 111.19, 117.95, 124.27, 126.63, 127.36, 129.01, 129.57, 130.05, 130.31, 130.41, 131.22, 134.76, 135.84, 154.52 (C5), 183.44 (C3); IR (KBr) $v$: 1707.7 cm$^{-1}$; ESI MS $m/z$: 431 $[M+H]^+$. *Anal*. Calcd. for $C_{21}H_{13}Cl_3N_2O_2$: C 58.43, H 3.04, N 6.49; found C 58.56, H 3.20, N 6.32.

***3-(2,6-Dichlorophenyl)-4-(4-methoxyphenyl)-1′H,4H-spiro[isoxazole-5,2′-pyrrolizin]-1′-one (3d).*** White solid, yield 53%; mp : 190–191°C; $^1$H NMR ($CDCl_3$, 500 MHz): δ 4.14 (d, $J$ = 12.5 Hz, 1H, H1), 4.39 (d, $J$ = 12.5 Hz, 1H, H1), 5.83 (s, 1H, H4), 6.52–6.54 (m, 1H), 6.77–6.78 (m, 2H), 6.87–6.94 (m, 2H), 7.11 (d, $J$ = 7.5 Hz, 2H), 7.17–7.20 (m, 1H), 7.28 (d, $J$ = 7.5 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 51.41 (C1), 55.22 (−$OCH_3$), 59.26 (C4), 96.13 (C2), 111.00, 114.51, 117.96, 124.17, 124.64, 127.17, 128.80, 129.92, 130.48, 131.14, 135.57, 155.88 (C5), 183.87 (C3); IR (KBr) $v$: 1713.5 cm$^{-1}$; ESI MS $m/z$: 427 $[M+H]^+$. *Anal*. Calcd. for $C_{22}H_{16}Cl_2N_2O_3$: C 61.84, H 3.77, N 6.56; found C 61.98, H 3.85, N 6.40.

***3-(2,6-Dichlorophenyl)-4-(4-fluorophenyl)-1′H,4H-spiro[isoxazole-5,2′-pyrrolizin]-1′-one (3e).*** White solid, yield 55%; mp : 198–200°C; $^1$H NMR ($CDCl_3$, 500 MHz): δ 4.12 (d, $J$ = 12.5 Hz,

1H, H1), 4.45 (d, $J = 12.5$ Hz, 1H, H1), 5.89 (s, 1H, H4), 6.56–6.57 (m, 1H), 6.92–6.93 (m, 1H), 6.97–7.00 (m, 3H), 7.19–7.23 (m, 2H), 7.24–7.26 (m, 1H), 7.33–7.35 (m, 2H); $^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 51.33 (C1), 59.03 (C4), 96.07 (C2), 111.25, 116.20, 116.37, 118.12, 124.66, 126.90, 128.24, 128.26, 128.86, 129.84, 131.01, 131.08, 131.30, 135.57, 155.45 (C5), 183.36 (C3); IR (KBr) *v*: 1702.4 $cm^{-1}$; ESI MS *m/z*: 415 $[M+H]^+$. *Anal*. Calcd. for $C_{21}H_{13}Cl_2FN_2O_2$: C 60.74, H 3.16, N 6.75; found C 60.99, H 3.26, N 6.52.

***3-(2,6-Dichlorophenyl)-4-[4-(methylthio)phenyl]-1′H,4H-spiro [isoxazole-5,2′-pyrrolizin]-1′-one (3f).*** White solid, yield 51%; mp : 175–177°C; $^1$H NMR ($CDCl_3$, 500 MHz): δ 2.40 (s, 3H, –$SCH_3$), 4.11 (d, $J = 12.5$ Hz, 1H, H1), 4.40 (d, $J = 12.5$ Hz, 1H, H1), 5.84 (s, 1H, H4), 6.52–6.53 (m, 1H), 6.88–6.89 (m, 1H), 6.94–6.95 (m, 1H), 7.10–7.11 (m, 4H), 7.18–7.22 (m, 1H), 7.29–7.31 (m, 2H); $^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 15.10 (–$SCH_3$), 51.42 (C1), 59.35 (C4), 96.18 (C2), 111.13, 118.05, 124.68, 126.40, 127.04, 128.66, 128.85, 129.65, 129.88, 131.22, 135.58, 155.57 (C5), 183.54 (C3); IR (KBr) *v*: 1715.8 $cm^{-1}$; ESI MS *m/z*: 443 $[M+H]^+$. *Anal*. Calcd. for $C_{22}H_{16}Cl_2N_2O_2S$: C 59.60, H 3.64, N 6.32; found C 59.43, H 3.58, N 6.51.

***3-(2,6-Dichlorophenyl)-4-(4-methylphenyl)-1′H,4H-spiro [isoxazole-5,2′-pyrrolizin]-1′-one (3g).*** White solid, yield 50%; mp : 188–189°C; $^1$H NMR ($CDCl_3$, 500 MHz): δ 2.25 (s, 3H, –$CH_3$), 4.10 (d, $J = 12.5$ Hz, 1H, H1), 4.39 (d, $J = 12.5$ Hz, 1H, H1), 5.85 (s, 1H, H4), 6.51–6.52 (m, 1H), 6.88–6.89 (m, 1H), 6.93–6.94 (m, 1H), 7.05–7.09 (m, 4H), 7.17–7.20 (m, 1H), 7.28–7.30 (m, 2H); $^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 21.14 (–$CH_3$), 51.49 (C1), 59.52 (C4), 96.22 (C2), 111.04, 117.97, 124.65, 127.18, 128.80, 129.15, 129.28, 129.87, 131.13, 135.59, 138.62, 155.83 (C5), 183.77 (C3); IR (KBr) *v*: 1712.5 $cm^{-1}$; ESI MS *m/z*: 411 $[M+H]^+$. *Anal*. Calcd. for $C_{22}H_{16}Cl_2N_2O_2$: C 64.25, H 3.92, N 6.81; found C 64.44, H 4.03, N 6.99.

***3-(2,6-Dichlorophenyl)-4-(3,4,5-trimethoxyphenyl)-1′H,4H-spiro [isoxazole-5,2′-pyrrolizin]-1′-one (3h).*** White solid, yield 53%; mp : 221–223°C; $^1$H NMR ($CDCl_3$, 500 MHz): δ 3.73 (s, 6H, –$OCH_3$), 3.78 (s, 3H, –$OCH_3$), 4.10 (d, $J = 12.5$ Hz, 1H, H1), 4.38 (d, $J = 12.5$ Hz, 1H, H1), 5.88 (s, 1H, H4), 6.34 (s, 2H, –ArH), 6.54–6.55 (m, 1H), 6.90–6.91 (m, 1H), 6.98–6.99 (m, 1H), 7.25–7.28 (m, 1H), 7.34–7.36 (m, 2H); $^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 51.55 (C1), 56.14 (–$OCH_3$), 59.94 (C4), 60.76 (–$OCH_3$), 96.29 (C2), 105.81, 111.16, 118.05, 124.83, 127.33, 127.87, 128.95, 129.93, 131.33, 135.54, 137.82, 155.23 (C5), 183.65 (C3); IR (KBr) *v*: 1701.3 $cm^{-1}$; ESI MS *m/z*: 487 $[M+H]^+$. *Anal*. Calcd. for $C_{24}H_{20}Cl_2N_2O_5$: C 59.15, H 4.14, N 5.75; found C 58.95, H 4.01, N 5.96.

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[6] CCDC 847145 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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