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Simple access to spirooxadiazole compounds containing a quinoxaline moiety using a nitrile imine intermediate generated *in situ*

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Abstract: A convenient method for the synthesis of spiro[indeno[1,2-*b*]quinoxaline-[1,3,4]oxadiazole]s involves a 1,3-dipolar cycloaddition reaction of nitrile imines generated *in situ* with indenoquinoxaline derivatives.

Keywords: 1,3-dipolar cycloaddition; nitrile imine; nitrogen containing heterocycles; quinoxaline.

Introduction

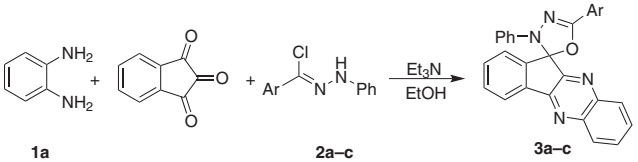
Quinoxaline and its derivatives play a significant role in organic synthesis [1]. Many quinoxalines are antimicrobial [2], anti-hypertensive [3], anti-tubercular [4], antidepressant [5], anti-malarial [6], anti-inflammatory [7], anti-convulsant [8], anti-HIV [9], anti-diabetic and anticancer agents [10, 11]. They are also used in the synthesis of organic semiconductors [12], rigid subunits of macrocyclic receptors for molecular recognition [13] and chemically controllable switches [14].

Spirocyclic molecules are of considerable interest as natural and synthetic products including optoelectronic materials [15]. Spiro frameworks are found in phytochemicals such as alkaloids, lactones and terpenoids [16]. 1,3-Dipolar cycloaddition is a powerful route for the synthesis of five-membered spiro compounds [17, 18]. Nitrile imines are important 1,3-dipoles [19] that are easily generated *in situ* by the treatment of hydrazonoyl chlorides with Et_3N. The reaction of these dipoles with a carbonyl group constitutes an efficient method for the regio- and stereoselective synthesis of structurally complex spirooxadiazole heterocycles from readily available precursors. Although the reactions of 1,3-dipoles with olefinic substrates have been studied extensively [20, 21], methods for the synthesis of oxadiazoles using the reaction of 1,3-dipoles and carbonyl units are rare [22]. In continuation of our efforts on the synthesis of heterocyclic compounds using nitrile imines [23], we describe an efficient procedure for the synthesis of spiro[indeno[1,2-*b*]quinoxaline-11,2′-[1,3,4]oxadiazole] derivatives **3** by the reaction of ninhydrin, phenylenediamines **1** and hydrazonoyl chlorides **2** in the presence of Et_3N in EtOH at room temperature.

Results and discussion

A mixture of phenylenediamine **1a** (Table 1) and ninhydrin was stirred in ethanol under reflux conditions for 1 h followed by the addition of hydrazonoyl chloride **2a** (Ar = Ph) and Et_3N. After an additional stirring at room temperature for 2 h, the product **3a** was obtained in an 80% yield. Other products **3b**,**c** were obtained in high yields in a similar way. The structural determination of **3a–c** was achieved by analysis of ^{1}H NMR, ^{13}C NMR and IR spectroscopic data. The mass spectra of all products display a molecular ion peak and their ^{1}H NMR spectra are fully consistent with the assigned structures. A characteristic peak for a spiro carbon at 99.6–99.9 ppm appears in the ^{13}C NMR spectra of compounds **3a–c**. Additional compounds **3d–f** synthesized using methyl-substituted 1,2-benzenediamines are listed in Table 2. As expected, mixtures of two isomers

Table 1 Synthesis of spiro[indeno[1,2-*b*]quinoxaline-[1,3,4]oxadiazole]s **3a–c** using **1a**.



1a 2a–c 3a–c

Entry	Ar
3a	Ph
3b	*p*-Cl-Ph
3c	*p*-OMe-Ph

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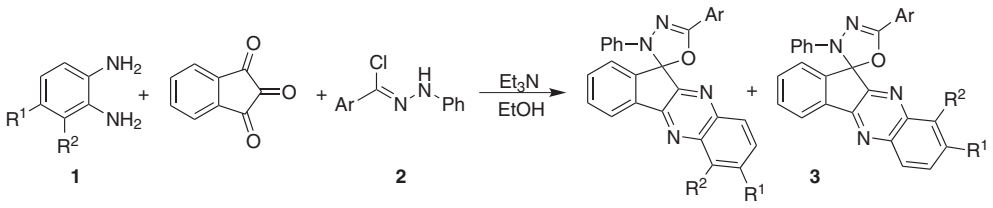
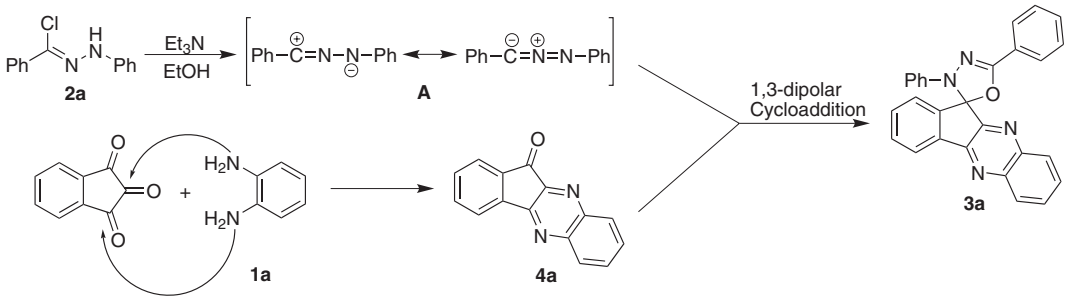
Table 2 Synthesis of compound **3d–f**.



Entry	R^1	R^2	Ar
3d	Me	H	Ph
3e	Me	H	*p*-Cl-Ph
3f	H	Me	Ph



Scheme 1 Proposed mechanism for the synthesis of compounds **3a–f** using **3a** as an example.

were obtained in each case because the starting diamines contained two nonequivalent amino groups. A proposed mechanism for this reaction is exemplified in Scheme 1 by the synthesis of product **3a**. Initially, a quinoxaline **4a** is formed by the reaction of phenylenediamine **1a** and ninhydrin. In a parallel reaction, an intermediate nitrile imine **A** is generated from hydrazonoyl chloride **2a**. A 1,3-dipolar cycloaddition reaction of intermediate products **A** and **4a** leads to the formation of the final product **3a**.

Conclusion

A facile synthetic route to spiro[indeno[1,2-*b*]quinoxaline-11,2′-[1,3,4]oxadiazole]s starting with readily available starting materials was developed.

Experimental

^{1}H-NMR (300 MHz) and ^{13}C-NMR (75 MHz) spectra were obtained using a Bruker DRX-300 AVANCE spectrometer in $CDCl_3$ as solvent. IR spectra were recorded on a NICOLET FT-IR 100 spectrophotometer. Electron-impact mass spectra were recorded on a FINNIGAN-MATT 8430 instrument operating at an ionization potential of 70 eV. Melting points were determined with an Electrothermal 9100 apparatus. Hydrazonoyl chlorides **2** were obtained as previously reported [24, 25].

General procedure for the synthesis of 3a–f

A mixture of phenylenediamine **1** (1 mmol) and ninhydrin (1 mmol) in EtOH (4 mL) was stirred under reflux for 1 h. Then, hydrazonoyl chloride **2** (1 mmol) and Et_3N (1 mmol) were added and the mixture was stirred at room temperature for an additional period indicated below. Progress of the reaction was monitored by TLC analysis. After completion of the reaction, the resultant precipitate was washed with acetone to afford the pure product **3a–f**.

3′,5′-Diphenyl-3′*H*-spiro[indeno[1,2-*b*]quinoxaline-11,2′-[1,3,4]-oxadiazole] (3a) Reaction time 3 h; yield of a yellow powder 80%; mp 232–234°C; ^{1}H NMR: δ 8.38 (d, 1H, J = 4.8 Hz), 8.26 (d, 1H, J = 6.9 Hz), 8.11 (d, 1H, J = 8.1 Hz), 7.94 (d, 2H, J = 6.4 Hz), 7.71–7.80 (m, 4H), 7.60 (t, 1H, J = 6.9 Hz), 7.42–7.46 (m, 3H), 6.98 (t, 2H, J = 7.2 Hz), 6.74–6.76 (m, 3H); ^{13}C NMR: δ 157.2, 152.8, 151.9, 143.2, 142.3, 142.1, 141.6, 136.2, 133.4, 132.5, 131.6, 131.5, 130.4, 130.0, 128.9, 128.6, 128.3, 126.5, 126.1, 125.3, 123.7, 120.7, 114.7, 99.6; EI-MS: *m*/*z* 426 [M$^+$], 306, 106, 91 and 77. Anal. Calcd for $C_{28}H_{18}N_4O$ (426.48): C, 78.86; H, 4.25; N, 13.14. Found: C, 78.92; H, 4.29; N, 13.20.

5′-(4-Chlorophenyl)-3′-phenyl-3′*H*-spiro[indeno[1,2-*b*]quinoxaline-11,2′-[1,3,4]oxadiazole] (3b) Reaction time 5 h; 78% yield of a yellow powder; mp 228–230°C; ^{1}H NMR: δ 8.24 (d, 1H, J = 6.1 Hz), 8.15

(d, 1H, J = 7.2 Hz), 8.08 (d, 1H, J = 6.9 Hz), 7.86 (d, 2H, J = 6.4 Hz), 7.67–7.77 (m, 4H), 7.55 (t, 1H, J = 6.1 Hz), 7.41 (d, 2H, J = 6.4 Hz), 6.97 (t, 2H, J = 7.2 Hz), 6.74–6.76 (m, 3H); ^{13}C NMR: δ 156.7, 153.1, 152.0, 143.6, 142.7, 142.3, 142.1, 137.7, 136.5, 132.9, 132.5, 131.1, 130.5, 129.7, 129.4, 129.1, 129.0, 127.9, 126.2, 124.1, 122.8, 120.9, 114.7, 99.9. Anal. Calcd for $C_{28}H_{17}ClN_4O$ (460.92): C, 72.96; H, 3.72; N, 12.16. Found: C, 72.91; H, 3.80; N, 12.13.

5′-(4-Methoxyphenyl)-3′-phenyl-3′*H*-spiro[indeno[1,2-*b*]quinoxaline-11,2′-[1,3,4]oxadiazole] (3c) Reaction time 6 h; 86% yield of a pink powder; mp 232–234°C; ^{1}H NMR: δ 8.22 (d, 1H, J = 7.5 Hz), 8.14 (d, 1H, J = 8.2 Hz), 8.09 (d, 1H, J = 8.3 Hz), 7.87 (d, 2H, J = 8.5 Hz), 7.62–7.78 (m, 4H), 7.53 (t, 1H, J = 7.5 Hz), 6.93–6.96 (m, 4H), 6.73 (d, 2H, J = 8.5 Hz), 6.66 (t, 1H, J = 7.0 Hz), 3.85 (s, 3H); ^{13}C NMR: δ 161.6, 157.1, 153.2, 152.9, 143.6, 143.1, 142.6, 142.3, 137.4, 132.9, 132.3, 130.9, 130.5, 129.6, 129.4, 129.0, 128.9, 128.4, 126.2, 122.7, 120.5, 118.1, 114.7, 114.1, 99.6, 55.5. Anal. Calcd for $C_{29}H_{20}N_4O_2$ (456.50): C, 76.30; H, 4.42; N, 12.27. Found: C, 76.23; H, 4.36; N, 12.21.

Mixture of 7-methyl-3′,5′-diphenyl-3′*H*-spiro[indeno[1,2-*b*]quinoxaline-11,2′-[1,3,4]oxadiazole] and its 8-methyl-regioisomer (3d) Reaction time 3 h; 80% yield of an orange powder; mp 221–223°C; ^{1}H NMR: δ 8.22 (d, 2H, J = 7.2 Hz), 7.93–8.05 (m, 6H), 7.87 (s, 2H), 7.43–7.72 (m, 14H), 6.96 (t, 4H, J = 7.6 Hz), 6.75 (d, 4H, J = 7.8 Hz), 6.68 (t, 2H, J = 7.1 Hz), 2.59 (s, 3H, Me of minor isomer), 2.52 (s, 3H, Me of major isomer); ^{13}C NMR of major isomer: δ 156.8; 155.9, 152.4, 143.6, 142.9, 142.3, 140.4, 137.6, 133.2, 132.8, 132.3, 130.5, 130.0, 129.6, 129.0, 128.8, 128.7, 126.6, 126.1, 125.6, 122.7, 120.6, 114.7, 99.86, 22.0; ^{13}C NMR of minor isomer: δ 156.8, 153.2, 152.4, 143.6, 142.7, 141.8, 140.7, 137.6, 133.2, 132.6, 131.9, 130.5, 130.0, 129.6, 129.0, 128.7, 128.5, 126.6, 126.1, 125.6, 122.6, 120.6, 114.7, 99.81, 21.8. Anal. Calcd for $C_{29}H_{20}N_4O$ (440.50): C, 79.07; H, 4.58; N, 12.72. Found: C, 71.11; H, 4.50; N, 12.77.

Mixture of 5′-(4-chlorophenyl)-7-methyl-3′-phenyl-3′*H*-spiro-[indeno[1,2-*b*]quinoxaline-11,2′-[1,3,4]oxadiazole] and its 8-methyl-regioisomer (3e) Reaction time 5 h; 78% yield of an orange powder; mp 240–242°C; ^{1}H NMR: δ 8.16–8.19 (m, 4H), 7.93–7.96 (m, 4H), 7.90 (s, 1H), 7.88 (s, 1H), 7.79–7.82 (m, 4H), 7.65–7.69 (m, 4H), 7.45 (d, 4H, J = 8.1 Hz), 7.20 (t, 4H, J = 7.3 Hz), 6.89–6.93 (m, 6H), 2.65 (s, 3H, Me of major isomer), 2.62 (s, 3H, Me of minor isomer); ^{13}C NMR of major isomer: δ 166.6; 155.1, 154.7, 149.4, 148.6, 147.5, 144.9, 137.6, 136.2, 133.9, 133.8, 132.5, 131.9, 131.3, 130.5, 130.0, 129.2, 128.6, 125.5, 124.1, 122.4, 121.1, 114.6, 99.9, 21.67; ^{13}C NMR of minor isomer: δ 166.6, 155.1, 154.7, 149.4, 148.6, 147.5, 144.9, 137.6, 136.2, 133.9, 133.8, 132.5, 131.9, 131.3, 130.5, 130.0, 129.8, 128.8, 125.6, 124.2, 123.3, 121.1, 113.3, 99.9, 21.68. Anal. Calcd for $C_{29}H_{19}ClN_4O$ (474.94): C, 73.34; H, 4.03; N, 11.80. Found: C, 73.29; H, 4.08; N, 11.71.

Mixture of 6-methyl-3′,5′-diphenyl-3′*H*-spiro[indeno[1,2-*b*]quinoxaline-11,2′-[1,3,4]oxadiazole] and its 9-methyl-regioisomer (3f) Reaction time 5 h; 75% yield of an orange powder; mp 227–229°C; ^{1}H NMR: δ 8.21–8.23 (3H, m), 7.92–7.94 (6H, m), 7.43–7.58 (15H, m), 6.94–6.97 (5H, m), 6.74–6.76 (5H, m), 2.89 (3H, s, Me of minor isomer), 2.87 (3H, s, Me of major isomer); ^{13}C NMR of major isomer: δ_C 156.1, 153.5, 152.7, 142.7, 142.4, 142.3, 142.2, 137.7, 136.6, 132.5, 132.2, 131.3, 130.5, 129.3, 128.9, 128.6, 128.5, 128.3, 126.6, 124.0, 122.7, 120.4, 114.1, 99.7, 17.39; ^{13}C NMR of minor isomer: δ_C 156.1, 153.5, 152.5, 142.7, 142.5, 142.3, 142.1, 137.7, 136.6, 132.7, 132.2, 131.3, 130.6, 129.4, 128.9, 128.7, 128.6, 128.3, 126.4, 124.0, 122.5, 120.5, 114.3, 99.8, 17.40. Anal. Calcd for $C_{29}H_{20}N_4O$ (440.50): C, 79.07; H, 4.58; N, 12.72. Found: C, 79.15; H, 4.63; N, 12.65.

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