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Original article

Design, synthesis and insecticidal activity of spiro heterocycle containing neonicotinoid analogs

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ABSTRACT

Spiro heterocycles frequently occur in bioactive molecules. In the pursuit of neonicotinoids with spiro heterocycles, three types of novel neonicotinoids with spirobenzofuranone, spirooxindole or spiroacenaphythylenone framework were designed and synthesized. Insecticidal evaluation showed that some of spirobenzofuranone containing neonicotinoids exhibited moderate activity against cowpea aphid, armyworm or brown planthopper.

1. Introduction

Spiro heterocycles often exist in a number of natural or synthetic molecules [1–3]. A spiro compound in which the spiro carbon is part of cyclic ring has many unique properties, such as spiroconjugation, anomeric effect and axial chirality [4–7]. Therefore, spiro heterocyclic scaffolds have broad applications in many areas [8–12] and are widely used as building blocks for generating biological and pharmaceutical relevance [13–15].

Neonicotinoid is the largest insecticide now [16–18], but its superiority is being challenged due to resistance [19] and severe bee toxicity [20,21]. Thus, there is an urgent need for the development of novel, effective, neonicotinoid replacements. As part of a project aiming at exploring functionality of the spiro heterocycle core in neonicotinoids, we herein report our investigation in spiro heterocycle containing neonicotinoids.

2. Experimental

2.1. Chemistry

Melting points (mp) were recorded on Büchi B540 apparatus (Büchi Labortechnik AG, Flawil, Switzerland) and are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AM-400 (400 MHz) spectrometer with DMSO-d_6 as the solvent and TMS as the internal standard. Chemical shifts are reported in δ (parts per million) values. High-resolution mass spectra were recorded under electron impact (70 eV) conditions using a MicroMass GCT CA 055 instrument. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel 60 F254), and spots were visualized with ultraviolet (UV) light.

The general synthetic methods for compounds **8a–d**, **9a–g** and **10a** and **10b** are depicted in Schemes 1–3. Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Yields were not optimized. All reactions were carried out under a protective atmosphere of drying nitrogen or utilizing a calcium chloride tube.

General synthetic procedure for **8a–d**: Knoevenagel adduct **2** was synthesized according to the reported procedure [8]. A mixture of phthalic anhydride (1.480 g, 10 mmol) and malononitrile (0.66 g, 11 mmol) in THF (25 mL) were stirred at room temperature. Then, diisopropylamine (DIPA) (2.02 g, 20 mmol) was added dropwise. The resulting mixture was stirred at room temperature for 8 h, and then was filtered and the precipitate was washed with THF (10 mL) to afford the white solid. Then, to a solution of the obtained white solid in 1,2-dichloroethane (20 mL) was added $POCl_3$ (10 mmol) dropwise at room temperature. After completion, the mixture was refluxed and the progress of the reaction was monitored by TLC. At last, the reaction mixture was neutralized by saturated dicarbonate solution to pH 7, extracted by dichloromethane (30 mL × 3), concentrated and the residue was purified by flash chromatography eluting with dichloromethane to afford compound **2** (yield 40%).

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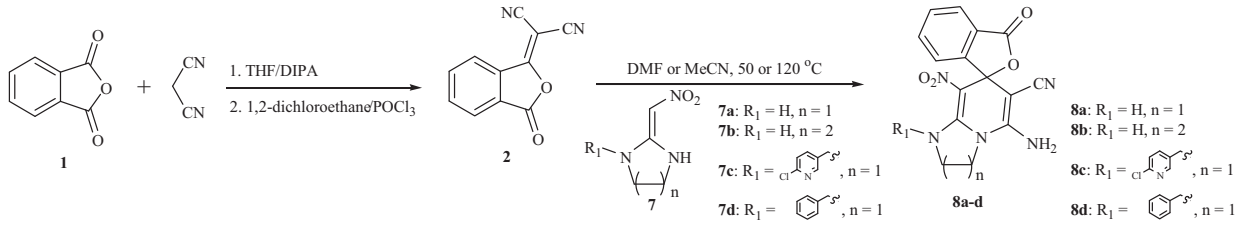
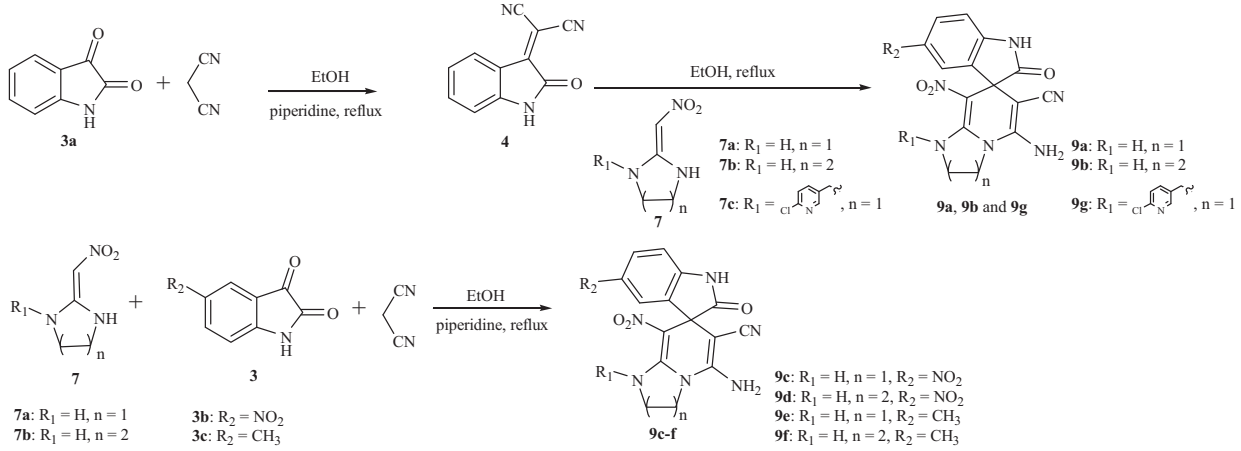


Scheme 1. Synthetic routes for neonicotinoids containing spiro heterocycles **8a–d**.



Scheme 2. Synthetic routes for neonicotinoids containing spiro heterocycles **9a–g**.

Then, a solution of compound **2** (0.190 g, 1 mmol) and compounds **7a–d** (1 mmol) in DMF (4 mL) was heated at 50 °C or 120 °C with the progress of the reaction monitored by TLC. After completion, the mixture was concentrated and the residue was purified by recrystallization with ethanol to afford the pure products **8a–d**.

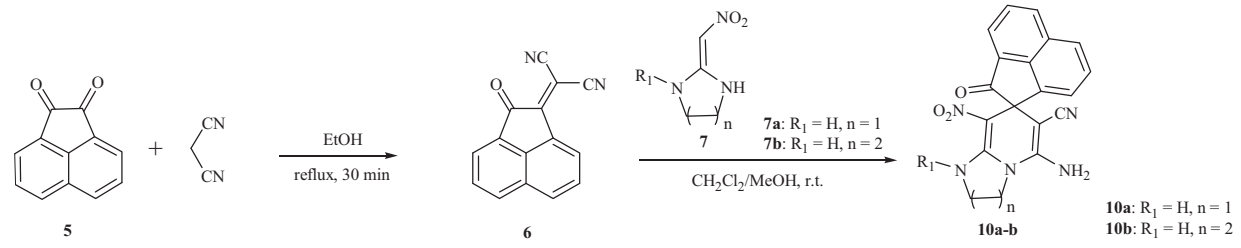
General synthetic procedure for **9a–g**: Method 1 (for **9a**, **9b** and **9g**): A mixture of isatin (1.470 g, 10 mmol), malononitrile (0.60 g, 10 mmol) and piperidine (10 mol%) in absolute ethanol (10 mL) was refluxed for 1 h. The cooled mixture was filtered and the precipitate was washed with ethanol (4 mL) to afford compound **4** (yield 80%). Then, a solution of compound **4** (0.189 g, 1 mmol) and compound **7a–c** (1 mmol) in ethanol (4 mL) was refluxed for 8 h. The mixture was filtered and the precipitate washed with cold ethanol (4 mL) affording the pure products **9a**, **9b** and **9g**. Method 2 (one-pot procedure for **9c–9f**): A solution of **3b** or **3c** (1 mmol), malononitrile (0.060 g, 1 mmol) and piperidine (10 mol%) was refluxed in ethanol (4 mL) for 1 h. Then, **7a** or **7b** was added simultaneously. The resulted mixture was stirred for 8 h under refluxing condition with the progress of the reaction monitored by TLC. After completion, the cooled mixture was filtered and the precipitate was washed with cold ethanol (4 mL) to afford the desired products **9c–9f**.

General synthetic procedure for **10a** and **10b**: A mixture of acenaphthylene-1,2-dione (1.820 g, 10 mmol) and malononitrile (0.60 g, 10 mmol) in absolute ethanol (20 mL) was refluxed for 30 min. The cooled mixture was filtered and the precipitate was washed with cold ethanol (10 mL) to afford compound **6** (yield 85%). Then, a solution of compound **6** (0.230 g, 1 mmol) and **7a** and **7b** (1 mmol) in 5 mL of mixed solvent of dichloromethane and methanol (4:1, v/v) was stirred for 2 h at room temperature. At last, the mixture was filtered and the precipitate was washed with methanol (4 mL) to afford the pure products **10a** and **10b**.

Analytical data of the target compounds are listed in Supporting information.

2.2. Biological assay

All bioassays were performed on representative test organisms grown in the laboratory. The bioassay was repeated at (25 ± 1) °C according to statistical requirements. All compounds were dissolved in *N*,*N*-dimethylformamide (AP, Shanghai Chemical Reagent Co., Ltd., Shanghai, China) and diluted with distilled water containing Triton X-100 (0.1 mg L^{-1}) to obtain a series of concentrations of 500.0, 250.0, 125.0 mg L^{-1} and others for bioassays. The results of bioassay are depicted in Table 1.



Scheme 3. Synthetic routes for neonicotinoids containing spiro heterocycles **10a–b**.