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Facile three-component synthesis and insecticidal evaluation of hexahydroimidazo[1,2-*a*]pyridine derivatives

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ABSTRACT

A series of new hexahydroimidazo[1,2-*a*]pyridine derivatives were synthesized *via* convenient and practical three-component reactions. Preliminary bioassays showed that majority of the target compounds exhibited moderate to excellent insecticidal activity against cowpea aphids (*Aphis craccivora*). Among them, compound **9l** demonstrated significant activity with LC_{50} value of 0.00918 mmol/L which was about 3.8-fold higher than that of imidacloprid (IMI). Furthermore, the study of stereostructure–activity relationship of four isomers of **9k** indicated that configuration played a key role in insecticidal activity of these compounds.

1. Introduction

Neonicotinoids, synthetic agonists selectively acting on the nicotinic acetylcholine receptors (nAChRs) located in the insect central nervous system (CNS) [1,2], are potent broad-spectrum insecticides that possess contact, stomach and systemic activity. By virtue of high efficiency, mammalian safety, low toxicity and unique mode of action, neonicotinoids have replaced those conventional and environmentally less-benign insecticides, such as organophosphorus, carbamates, and pyrethroids [3–6]. In 2011, neonicotinoids accounted for 28.5% of the total global insecticide market which was topmost among all of insecticides [7]. However, an inevitable problem associated with the widespread and frequent use of these insecticides is the occurrence of resistance and cross-resistance [8–11]. It was reported some species exhibited more than 100-fold resistance to imidacloprid (**1**, Fig. 1) [12,13]. Therefore, concerted efforts have to be made to discover potential candidates for the pest controlling in the future.

In previous work, our group reported an innovative neonicotinoid compound **2** that showed excellent insecticidal activity [14]. However, it was unstable and could lead to the formation of compound **3** *via* self-Diels–Alder reaction [15]. Inspired by the facts, a novel series of hexahyroimidazo[1,2-*a*]pyridine neonicotinoids **4** were constructed *via* aza-Diels–Alder cycloaddition reactions [16] and some of those compounds exhibited good insecticidal activity. Whereas the previous structural modifications were only focused on the variations in benzene ring (unit E), other units such as 6-chloropyridin-3-ylmethyl (unit A), five membered ring (unit B), five-membered heterocycle (unit C) and cyano group (unit D) have not been investigated yet. Therefore, as an extension of our previous study and part of ongoing effort to discover potential insecticides, a series of hexahydroimidazo[1,2-*a*]pyridine derivatives **5** with structural diversity at five fragments were envisaged (Fig. 2).

However, the previous method still utilized the step-by-step synthetic strategy which restrained the efficiency of synthesis and bioactivity screening. Therefore, the development of an efficient, convenient and practical protocol to access compounds **5** was also both desirable and valuable. In recent years, multi-component reactions (MCRs) have served as powerful tools for the combinatorial synthesis in organic chemistry [17–24]. MCRs could offer access to large compound library with diverse functionalities with the avoidance purification steps for possible combinatorial surveying of structure variations [25]. Thus, in this paper, we reported the synthesis of hexahydroimidazo[1,2-*a*]pyridine derivatives *via* one-pot, three-component reactions and the insecticidal evaluation of title compounds.

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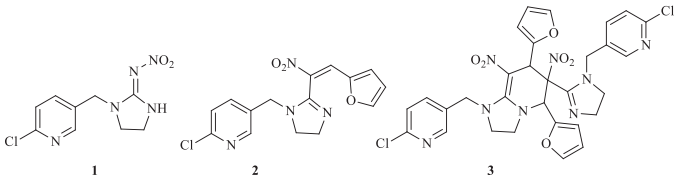


Fig. 1. Structures of neonicotinoids.

2. Experimental

All melting points (mp) were obtained on Büchi Melting Point B540 and uncorrected. NMR spectra were recorded in DMSO-d_6 (^{1}H at 400 MHz and ^{13}C at 100 MHz) using TMS as the internal standard on a Bruker AM-400 spectrometer. High-resolution mass spectra were recorded under electron impact (70 eV) condition using a MicroMass GCT CA 055 instrument. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel 60 F_{254}), and spots were visualized with ultraviolet (UV) light. All other solvents and reagents were used as obtained from commercial sources without further purification.

2.1. General procedure for preparation of **9a–9l**

A solution of ethyl 2-cyanoacetate (3.0 mmol), benzaldehyde (3.0 mmol) and piperidine (0.3 mmol) in 20 mL dichloromethane was stirred for 2 h at room temperature. Then 2-chloro-5-((2-(2-(furan-2-yl)-1-nitrovinyl)-4,5-dihydro-1*H*-imidazol-1-yl)methyl)-pyridine (2.0 mmol) was added to the mixture. The reaction progress was monitored by TLC. On completion of the reaction, the mixture was concentrated under reduced pressure and the crude product was subjected to chromatography on silica gel to afford the pure product **9a**. Compounds **9b–9l** were synthesized analogously.

2.2. General procedure for preparation of **13a–13j**

The solution of 1-benzyl-2-(nitromethylene)imidazolidine (3.0 mmol), furan-2-carbaldehyde (3.6 mmol) and concentrated hydrochloric acid (4.5 mmol) in 30 mL acetonitrile was stirred in ice-bath for 4 h. When the 1-benzyl-2-(nitromethylene)imidazolidine was consumed, triethylamine (4.5 mmol) was added to the solution and stirred for another 3 h. Then 2-(2-fluoro-4-methylbenzylidene)malononitrile was added to the mixture. The reaction progress was monitored by TLC. On completion of the reaction, the mixture was concentrated under reduced pressure the crude product was subjected to chromatography on silica gel to afford the pure product **13a**. Compounds **13b–13j** were synthesized analogously.

Physical and spectroscopic characterization data of compounds **9a–9l** and **13a–13j** were given in Supporting information.

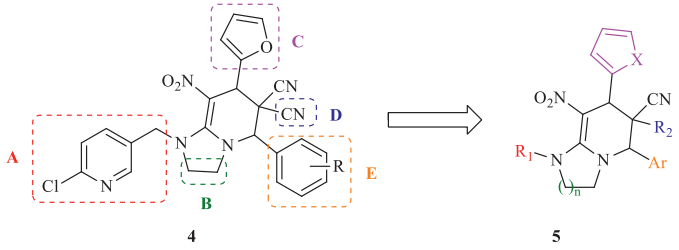


Fig. 2. The molecular design of target compounds.

3. Results and discussion

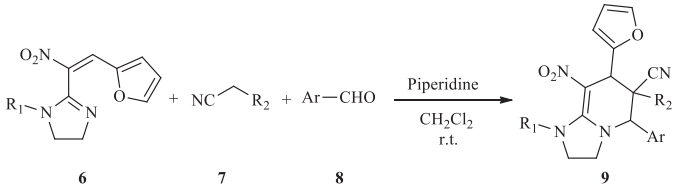
3.1. Synthesis

It was designed that the dienophiles generated by the Knoevenagel condensation of cyano compounds **7** with aromatic aldehydes **8** in the presence of catalyst reacted *in situ* with the diene compounds **6** to yield the target compounds *via* three-component reactions. The diene compounds **6** were synthesized according to the reported procedure [14]. Then the reaction condition was investigated to realized the one-pot preparation of hexahydroimidazo[1,2-*a*]pyridine derivatives. The examination of catalyst, solvent and temperature led to the following informative observations: (i) piperidine was the optimal catalyst; (ii) dichloromethane was the suitable solvent; (iii) the product yield was highest at room temperature. Finally, the target compounds **9** were furnished in moderate to good yields catalyzed by piperidine in dichloromethane at room temperature as showed in Scheme 1.

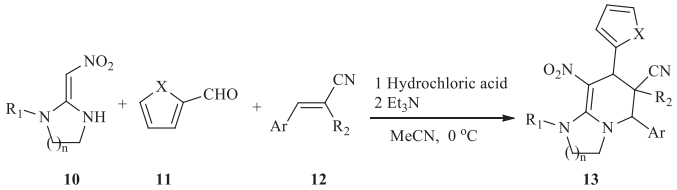
When R_1 was replaced by benzyl, phenyl, or ethyl and $n = 1$ (Fig. 2), the analogs of compounds **6** were very difficult to be isolated and unstable. Thus, an alternative approach was proposed based on an aza-hydro-allyl addition of compounds **10** on the five-membered aromatic heterocyclic aldehydes **11**, followed by aza-Diels–Alder cycloaddition with the prepared electrondeficient dienophiles **12** [16] *in situ*. The reaction condition was reinvestigated to come true the draft. The beneficial results were concluded after the research: (i) acetonitrile was the suitable solvent; (ii) low temperature was necessary to the good yield of products. Then the title compounds **13** were generated from compounds **10**, **11** and **12** in acetonitrile at 0 °C in one-pot as depicted in Scheme 2.

3.2. Insecticidal activity

The insecticidal activity of target compounds against cowpea aphid [26] was evaluated using imidacloprid as control (Table 1). Most of the target compounds exhibited moderate to excellent insecticidal activity. The LC_{50} values of some compounds were approximately equal to that of imidacloprid. In particular, the bioactivity of compound **9l** (LC_{50} = 0.00918 mmol/L) was 3.8-fold more active than that of imidacloprid (LC_{50} = 0.03502 mmol/L). The insecticidal activity varied depending upon R_1, R_2, Ar, the size of ring (n) and the patterns of five-membered heterocycle. For the effect of R_1, it was observed that 6-chloropyridine-3-ylmethyl and 2-chlorothiazol-5-ylmethyl units were favorable to the insecticidal activity, whereas compounds **13a–13f** bearing benzyl, phenyl or



Scheme 1. General synthetic route for title compounds **9**.



Scheme 2. General synthetic route for title compounds **13**.

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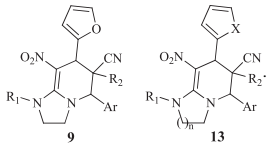
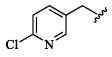
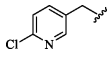
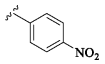
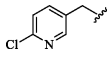
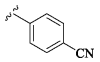
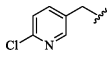
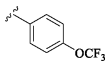
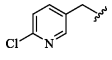
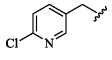
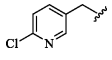
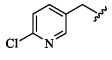
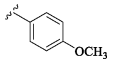
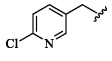
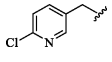
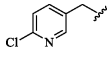
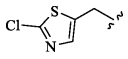
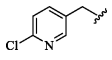
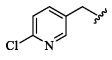
Table 1
Insecticidal activity of compounds **9a–9l**, **13a–13j** and imidacloprid against cowpea aphids.



Compound	R_1	R_2	Ar	*n*	X	Mortality (%) 500 mg L^{-1}	LC_{50} (mmol/L)
9a		CO_2Et				41.2	n.t.[a]
9b		CO_2Et				94.8	0.05287
9c		CO_2Et				82.3	n.t.
9d		CO_2Et				64.5	n.t.
9e		CO_2Et				68	n.t.
9f		CO_2Et				0	n.t.
9g		CO_2Et				80.5	n.t.
9h		CO_2Et				100	0.08298
9i		CO_2Et				82.3	n.t.
9j		CO_2Et				100	0.04657
9k		CO_2Et				100	0.04278
9l		CN				95.0	0.00918
13a		CN		0	O	0	n.t.
13b		CO_2Et		0	O	0	n.t.
13c		CN		0	O	0	n.t.
13d		CO_2Et		0	O	0	n.t.
13e		CN		0	O	0	n.t.
13f		CO_2Et		0	O	0	n.t.
13g		CN		1	O	100	0.02901
13h		CO_2Et		1	O	100	0.02237
13i		CN		1	S	100	0.01418
13j		CO_2Et		1	S	100	0.01974
IMI							0.03502

[a] n.t. = not tested.

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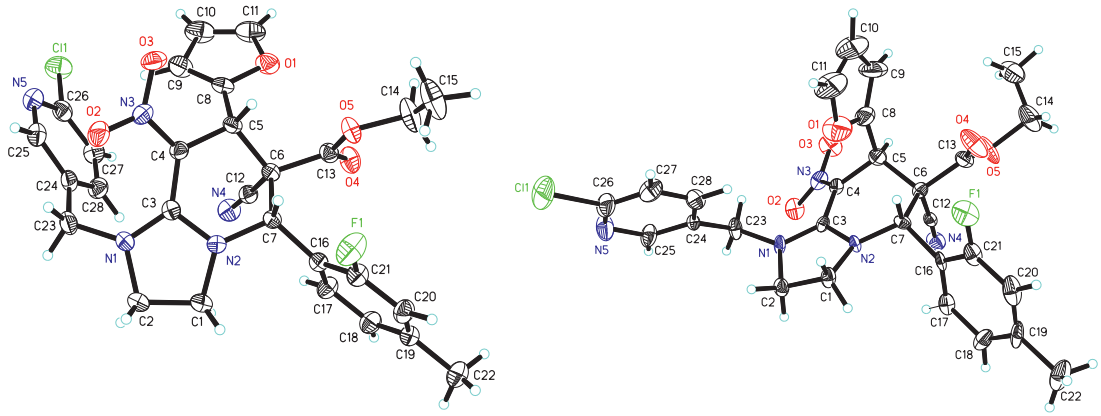

Fig. 3. Crystal structure of the compound **9k–3** (left) and **9k–4** (right).

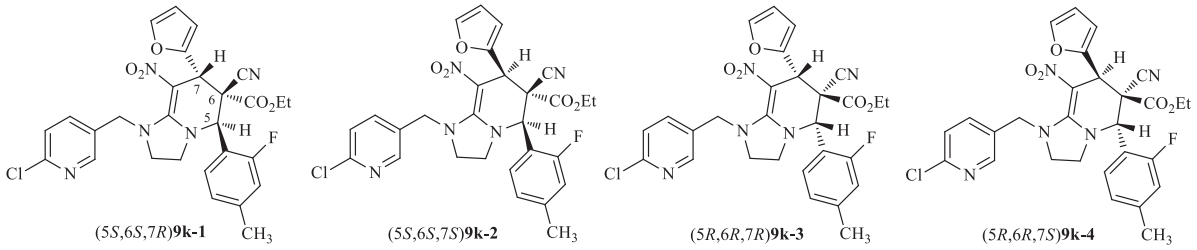

Fig. 4. Configuration of four stereoisomers.

ethyl had no activity. The target compound **9a–9k** ($R_2 = CO_2Et$) exhibited similar insecticidal activity compared with the reported compounds ($R_2 = CN$) [16]. As for the substituent Ar, the introduction of a fluoro group at 2-position was beneficial for the increase of activity. In particular, the compound with 2-fluoro-4-methyl group (**9k**) showed relatively higher insecticidal activity. The insecticidal activity of six-membered ring analogs **13g** and **13h** was higher than that of corresponding five-membered ring counterparts [16]. The replacement of furyl with thienyl (**13i** and **13j**) could not improve the activity dramatically.

3.3. Stereostructure–activity relationship

To our knowledge, isomer chirality has an impact on the bioactivity [15,27]. To explore the stereostructure–activity relationship of this kind of compounds, compound **9k** was resolved by preparative chiral HPLC. The result showed that there were four isomers: **9k–1**, **9k–2**, **9k–3** and **9k–4**. The percentage compositions of them were 27.61%, 22.58%, 20.93% and 28.88%, respectively. By comparing the spectroscopic data, it was found **9k–1** and **9k–4** were a pair of enantiomers and **9k–2** and **9k–3** were another. The establishment of the stereochemistry of four isomers was made possible by the combination of X-ray crystallographic analysis (Fig. 3), principle of enantiomers, *cis*-principle of Diels–Alder reaction [28,29] and NOESY NMR analysis (Fig. 4). Then the insecticidal activity against cowpea aphids of four isomers was tested. The LC_{50} values of **9k–1**, **9k–2**, **9k–3** and **9k–4** were 0.27048, 0.21819, 0.03515 and 0.02273 mmol/L, respectively. Based on the contrast of the LC_{50} value and stereochemistry of **9k–1** and **9k–2** or **9k–3** and **9k–4**, it was speculated that the configuration of stereocenter C(7) did not influence the insecticidal activity. While the discrepancies in activity and stereostructure between **9k–1** and **9k–3** or **9k–2** and **9k–4** illuminated that the configuration of stereogenic carbons C(5) and C(6) had a significant effect on the insecticidal activity. And the (5R,6R)-configuration was more beneficial to the activity. These results would increase our databank of insecticidal activity of hexahydroimizadol[1,2-*a*]pyridine derivatives for further studies.

4. Conclusion

In summary, a series of hexahydroimidazo[1,2-*a*]pyridine derivatives were conveniently synthesized *via* three-component reactions and screened for their insecticidal activity against cowpea aphids. Most of the title compounds exhibited good activities at 500 mg L^{-1}. Among them, compounds **9j–9l** and **13g–13j** were as active as or more than imidacloprid. Especially, the activity of compound **9l** was 3.8-fold higher than that of imidacloprid based on the value of LC_{50}. The stereostructure–activity relation research of four isomers of **9k** expounded that configuration of C(5) and C(6) played more crucial role in the insecticidal activity than that of C(7). Moreover, controlling the C(5) and C(6) of this kind of compounds as R configuration would avail to the activity. Further structure–activity relationship studies of the hexahydroimizadol[1,2-*a*]pyridine derivatives are in progress.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2014.10.019.

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