Synthesis and Insecticidal Activity of Neonicotinoids Derivatives

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Abstract:

A new class of compounds- neonicotinoids containing oxadiazole –were synthesized and characterized by using ^{1}H NMR, IR, MS and Elemental Analysis. Their insecticidal activities were tested against *Mythimna separata* Walker and *Aphis rumicis* Linnaeus, some of them showed some insecticidal activity.

Introduction:

Neonicotioids[1] are a novel and distinct class of insecticides. They combine selective activity against insects with a favorable safety profile, and possess contact, stomach and systemic activity, which made these compounds appropriate for foliar, granular and seed treatment application. Neonicotinoids act at the nicotinic acetylcholine receptor.[2] This mode of action has so far not been broadly used for insecticides, and consequently neonicotinoids are important for controlling insects resistant to other commonly used insecticides, such as organophosphates, carbamates, and pyrethroids. The first successful member of this family was imidacloprid **1**,[3](Fig. 1) developed by Nihon Bayer Agrochem KK, Japan. Takeda Chemical Industries, Ltd, has already commercialized the acyclic neonicotinoid, nitenpyram **2**,[4] which is highly active against homopterous and thysanopterous pests. Because of the extremely high activity and the unique properties of these compounds, ones were interested in the synthesis of acyclic nitroenamine, cyanoamidine and nitroamidine derivatives,[5-7] and a molecular-modeling-based approach was for the design of novel structural types of neonicotinoids.[8] However, the real breakthrough was achieved in 1991 with the discovery of nitroimino-[1,3,5]oxadiazinane derivatives.[9]

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After optimization, thiamethoxam **3** was identified as the best one and subsequently selected for development. On the other hand, 1,3,4-Oxadiazole moiety has been investigated with a view to obtaining compounds of biological[10-12] and pesticidal[13,14] interest. Oxadiazoles were shown to inhibit chitin synthesis in *Drosophila* and in *Muscadomestica* in both in vitro and in vivo studies.[15] Symmetrical 1,3,4-oxadiazole and analogs were found to be effective insecticides toward houseflies, faceflies and hornflies.[16] But their limited solubility in polar media made them not to be able to show all intrinsic activity. In our previous work, we made a try to synthesize some compounds containing 1,3,4-oxadiazole[17,18], which showed better activity. Promoted by the above observations, we considered to combine the 1,3,4-oxadiazole with nitroimino-[1,3,5]oxadiazinane in a molecular framework and hoped to find some compounds with better activity.

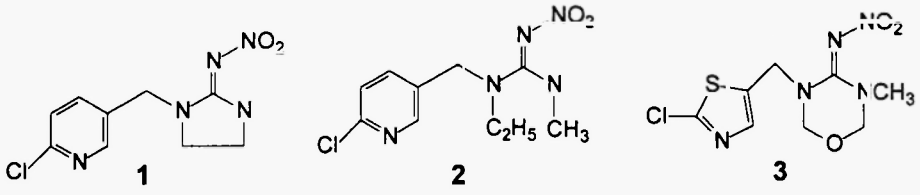
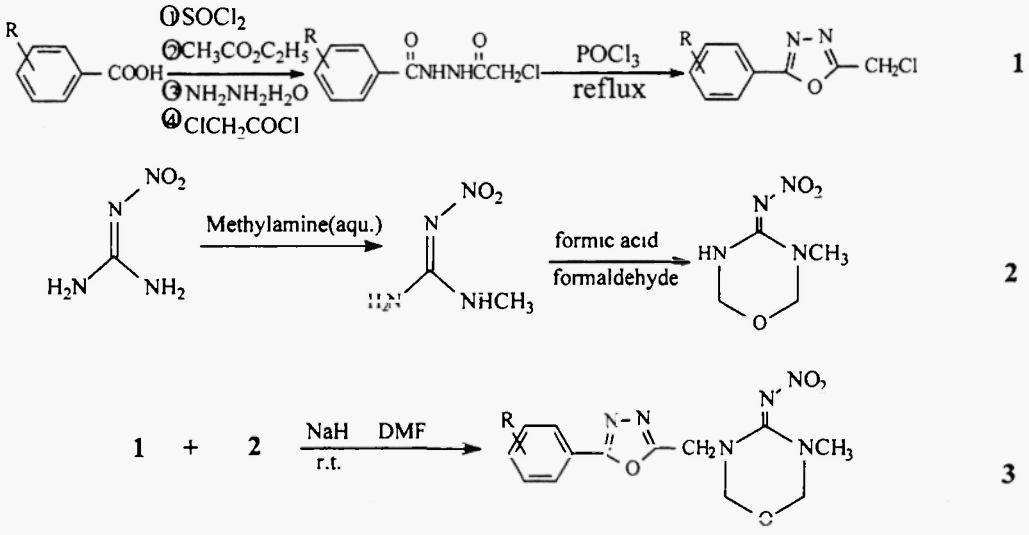


Fig. 1



Scheme 1

3a: R= H. 3b: R= 4-OCH_3, 3c: R= 4-F 3d: R= 5-F, 2,4-2Cl
3e: R= 3-NO_2, 3f: R= 4-Cl 3g: R= 4-NO_2, 3h: R= 2-F

Results and Discussion:

The synthetic conditions of the title compounds were investigated. The solvent must have the high polarity. When the substituted oxadiazoles and the nitroimino-[1,3,5]oxadiazinane were dissolved in the acetone and were heated, the TLC results showed that no reaction was happened until 5 hours, but when they were dissolved in the N, N-dimethylformamide (DMF), the TLC results showed that the reactants were almost disappeared completely after 5 hours. The reactive system was very sensitive to aqueous, otherwise, the more by-product would be found. So, the NaH was selected as the base, the title compounds were not obtained when K,CO_3 as base. We think that the reason is the formation of water, which makes the chloromethylene turn into the hydroxymethylene.

All the compounds' ^1H NMR data were in accordance to the structure of the title compounds, respectively. The IR data showed that the main function-group appeared the absorption peak, such as CH_3, C=C and C=N. The MS data indicated that the compounds' nitryl group is easily broken and the peak of molecular ion didn't appeared, as the electron-withdrawing effect of C=N bond make the N-N bond broken easily. The elemental analysis data proved the composition of each compound to be right.

All the compounds' activity was tested against *Mythimna separata* Walker and *Aphis rumicis* Linnaeus by the method of leaf-dip. The compounds of 3d, 3e and 3g showed better activity than others'. They got nearly 20% inhibition rate at the concentration 500 ppm. The bioassay results encouraged us to do more deep research to get the novel compounds with higher activity by the method of molecular-modeling-based approach. The structure-activity relationships for the R group in the benzene ring were also investigated. In the 3-position and 2-position of benzene ring, the electron-withdrawing groups can increase the compound's activity. The activity of 3d, 3e and 3h are higher than that of 3c, 3f and 3g.

Experimental Section:

Infrared spectra were taken on a Nicolet FT-IR-20SX spectrometer using KBr disks; Mass spectra on a Hitachi M80 instrument; and ^1H NMR spectra on a Brucker WP100SY(100 MHz) spectrometer with DMSO-d_6 as solvent and TMS as internal standard. Melting points were measured by a digital melting point apparatus made in Shanghai and were uncorrected. Elemental compositions were obtained by using an Germany elementar vario EL III analyzer. All reactions were followed by TLC.

General Procedure:

Preparation of the title compounds: nitroimino-[1,3,5]oxadiazinane (2mmol) and NaH (2mmol) were solved in DMSO (10mL). The mixture was stirred for 1 hour in the flask (50mL) by magnetic stirrer at the

room temperature. Then, 2-chloromethyl-5-benzyl-1,3,4-oxadiazole (2mmol) was added into the mixture and continued stirring for about 5 hours. The reactive process was monitored by TLC until the starting material nearly disappeared. The reactive mixture was poured into water (30mL), extracted by chloroform (30mL), adding some anhydrous magnesium sulfate, the solvent was filtered and evaporated in the reduced pressure. The residue was washed by the heated ethyl acetate, get the title compounds then crystallized from methanol dried. The following title compounds were prepared:

3a: 3-[5-benzyl-2-methylene-1,3,4-oxadiazole-yl]- nitroimino-[1,3,5]oxadiazinane m.p.:164-165℃yield: 34.5% ^{1}H NMR(d_6-DMSO), δ (ppm): 2.88(s,3H,CH_3), 5.02(s,2H,CH_2), 5.06(s,2H,CH_2), 5.20(s,2H,CH_2), 7.60-8.01(m,5H,ArH). IR(KBr cm^{-1}): υ : 2900-3000(CH_3) 1690(C=N) 1590(C=C). MS (EI,70ev): m/z 274(21), 201(63), 173(10), 160(100), 105(38), 103(17), 77(12). Anal. calcd for $C_{13}H_{14}N_6O_4$: C: 49.06; H: 4.43; N: 26.40. Found: C, 49.11; H, 4.45; N, 26.45.

3b:3-[5-(4-methoxybenzyl)-2-methylene-1,3,4-oxadiazole-yl]-nitroimino-[1,3,5]oxadiazinane m.p.:203-206 ℃ yield: 42.6% ^{1}H NMR(d_6-DMSO), δ (ppm): 2.87(s,3H,CH_3), 5.04(s,2H,CH_2), 5.05(s,2H,CH_2), 5.20(s,2H,CH_2), 8.24-8.44(m,4H,ArH). IR(KBr cm^{-1}): υ : 2900-3100(CH_3) 1690(C=N) 1590(C=C). MS (EI,70ev): m/z 304(63), 244(10), 231(100), 190(11), 135(23), 133(8). Anal. calcd for $C_{14}H_{16}N_6O_5$: C: 48.28; H: 4.63; N: 24.13. Found: C, 48.37; H, 4.64; N, 24.18.

3c: 3-[5-(4-flurobenzyl)-2-methylene-1,3,4-oxadiazole-yl]- nitroimino-[1,3,5]oxadiazinane m.p. 166-168 ℃ yield: 41.6% ^{1}H NMR(d_6-DMSO), δ (ppm): 2.86(s,3H,CH_3), 5.03(s,2H,CH_2), 5.06(s,2H,CH_2), 5.19(s,2H,CH_2), 7.43-8.01(m,4H,ArH). IR(KBr): υ : 2900-3000(CH_3) 1690(C=N) 1590(C=C). MS(EI,70ev): m/z 290(4), 292(21), 219(41), 178(100), 123(63), 121(49), 95(24). Anal. calcd for $C_{13}H_{13}N_6O_4F$: C: 46.43; H: 3.90; N: 24.99. Found: C, 46.33; H, 3.91; N, 25.04.

3d: 3-[5-(5-fluro-2,4-dichlorobenzyl)-2-methylene-1,3,4-oxadiazole-yl]- nitroimino-[1,3,5]oxadiazinane m.p.:191-194℃ yield: 47.6% ^{1}H NMR(d_6-DMSO), δ (ppm): 2.86(s,3H,CH_3), 5.00(s,2H,CH_2), 5.04(s,2H,CH_2), 5.19(s,2H,CH_2), 7.45-8.07(m,4H,ArH). IR(KBr cm^{-1}): υ : 2900-3000(CH_3), 1690(C=N), 1590(C=C). MS (EI,70ev): m/z 358(15), 287(11), 246(47), 191(100), 163(12), 115(35), 109(8). Anal. calcd for $C_{13}H_{11}N_6O_4FCl_2$: C: 38.54; H: 2.74; N: 20.74. Found: C, 38.60; H, 2.75; N, 20.79.

3e: 3-[5-(3-nitrobenzyl)-2-methylene-1,3,4-oxadiazole-yl]- nitroimino-[1,3,5]oxadiazinane m.p.:228-230 ℃ yield: 36.0% ^{1}H NMR(d_6-DMSO), δ (ppm): 2.86(s,3H,CH_3), 5.00(s,2H,CH_2), 5.04(s,2H,CH_2), 5.20(s,2H,CH_2), 7.68-8.00(m,5H,ArH). IR(KBr cm^{-1}): υ : 2900-3100(CH_3), 1690(C=N), 1590(C=C). MS (EI,70ev): m/z 317(7), 289(16), 246(15), 205(100), 150(32), 115(73). Anal. calcd for $C_{13}H_{13}N_7O_6$: C: 42.98; H: 3.61; N: 26.99. Found: C, 43.04; H, 3.62; N, 27.05.

3f: 3-[5-(4-chlorobenzyl)-2-methylene-1,3,4-oxadiazole-yl]- nitroimino-[1,3,5]oxadiazinane m.p.:222-225 ℃ yield: 34.4% ^{1}H NMR(d_6-DMSO), δ (ppm): 2.87(s,3H,CH_3), 5.04(s,2H,CH_2), 5.05(s,2H,CH_2), 5.75(s,2H,CH_2), 8.04-8.15(m,2H,ArH). IR(KBr): υ : 2900-3100(CH_3), 1690(C=N), 1590(C=C). MS (EI,70ev): m/z 352(M^+, 2), 308(30), 235(48), 194(67), 137(100), 111(23). Anal. calcd for $C_{13}H_{13}N_6O_4Cl$: C: 44.27; H: 3.71; N: 23.83. Found: C, 44.35; H, 3.72; N, 23.88.

3g: 3-[5-(4-nitrobenzyl)-2-methylene-1,3,4-oxadiazole-yl]- nitroimino-[1,3,5]oxadiazinane m.p.:191-19 ℃ yield: 34.9% ^{1}H NMR(d_6-DMSO), δ (ppm): 2.87(s,3H,CH_3), 3.86(s,3H,CH_3O), 5.00(s,2H,CH_2), 5.05(s,2H,CH_2), 5.20(s,2H,CH_2), 7.14-7.95(m,4H,ArH). IR(KBr cm^{-1}): υ : 2900-3000(CH_3), 1690(C=N), 1590(C=C), MS (EI,70ev): m/z 290(7), 219(18), 178(100), 123(38), 121(21), 95(8). Anal. calcd for $C_{13}H_{13}N_6O_4F$: C: 46.43; H: 3.90; N: 24.99. Found: C, 46.32; H, 3.91; N, 25.05.

3h: 3-[5-(2-flurobenzyl)-2-methylene-1,3,4-oxadiazole-yl]- nitroimino-[1,3,5]oxadiazinane m.p.:238-240 ℃ 25.7% ^{1}H NMR(d_6-DMSO), δ (ppm): 2.87(s,3H,CH_3), 5.26(s,2H,CH_2), 5.27(s,2H,CH_2), 5.43(s,2H,CH_2), 8.13-8.91(m,4H,ArH). IR(KBr cm^{-1}): υ : 2900-3100(CH_3), 1690(C=N), 1590(C=C). MS (EI,70ev): m/z 317(65), 259(51), 205(50), 150(100), 115(32), 109(24). Anal. calcd for $C_{13}H_{13}N_7O_6$: C: 42.98; H: 3.61; N: 26.99. Found: C, 42.06; H, 3.62; N, 27.04.

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Reference:

1. Yamamoto I, Neonicotinoids – mode of action and selectivity. *Agrochem. Jpn* **1996**, 68, 14.
2. Tomizawa M and Yamamoto I, Binding of nicotinoids and related compounds to the insect nicotinic acetylcholine receptor. *Nihon Noyaku Gakkaishi* (*J, Pestic Sci*) **1992**,17, 231.
3. Shiokawa K, Tsuboi S,Iwaya K and Moriya K, Development of a chloronicotinyl insecticide, imidacloprid. *Nikon Noyaku Gakkaishi* (*J, Pestic Sci*) **1994**,19, 329.
4. Minamida I, Iwanaga K, Tabuchi T, Aoki I, Fusaka I, Ishizuka H and Okauchi T, Synthesis and insecticidal activity of acyclic nitroethene compounds containing a heteroarylmethylamino group *Nihon Noyaku Gakkaishi* (*J, Pestic Sci*) **1993**,18, 41.
5. Gsell L, Preparation and testing of [(pyridylmethyl)-amino] nitroethylenes as insecticides, acaricides, and ectoparasiticides. *Eur Pat Appl EP 302833 A2 890208* **1987**.

6. Gsell L, Preparation of pyridylmethylcyanoguanidines as insecticides and acaricides. *Eur Pat Appl EP 306696 A1 890315* **1987**.
7. Kristiansen O, Maienfisch P and Gsell L, Guanidine derivatives as insecticides.*Eur Pat Appl EP 418199 A2 910320* **1989**.
8. Maienfisch P. Gonda J. Jacob O et al. Svnthesis and insecticidal activitv of novel nicotinoids. *Book of Abstracts, 214th ACS National Meeting, Las Vegas, NV, 7-11 September AGRO-018*, American Chemical Society, Washingto, DC **1997**.
9. Maienfisch P, and Gsell L, Preparation of 3-(heterocyclylmethyl)-4-iminoperhydro-1,3,5-oxadiazine derivatives as pesticides. *Eur Pat Appl EP 580553 A2 940126* **1992**.
10. J. J. Piala and H. L. Yale, *U. S. Pat.*, 3141022, 1961, *Chem. Abs.*, **1964**, 61, 8817.
11. B. Hokfelt and a. Jonsson, *J. Med. Chem.*, **1962**, 5, 247.
12. A. P. Swain, *U. S. Pat.*, 2883391, **1959**, *Chem. Abs.*, **1959**,53,16157.
13. K. Hiroshi, H. Isao and O. Shigeki, *Zassokenkyn*, **1969**, 8, 46; *Chem. Abs.*, **1970**,73,108544.
14. C. G. Mario, G. Fulvio and P. Maria, Ric. Sci., **1968**, 38, 205; *Chem. Abs.*, **1968**,69,106628.
15. Cunn, B. M., Synthesis and activity of agrochemicals. Thesis, Univ. of Central Florida, **1985**
16. Arrington, J. P. & Wade, L. L., US Patent 4,215,129, **1980**
17. Qian Xuhong, Zhang R., *J. Chem. Tech. Biotech.* **1996**, 67(2), 124.
18. Zhang Rong, Qian Xuhong. *Ying Yong Hua Xue* **1996**, 13(5), 5.

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