J. Pestic. Sci., **32**(3), 260–263 (2007)
DOI: 10.1584/jpestics.G07-04

Note

Preparation of 5-chloro-6-fluoroimidacloprid analogs and comparison of their insecticidal activity in a laboratory test with a 6-chloro-5-fluoro analog

Shinzo KAGABU,* Yosuke HIEDA and Ikuya OHNO

Department of Chemistry, Faculty of Education, Gifu University, Gifu 501–1193, Japan

(Received February 28, 2007; Accepted May 7, 2007)

Five new neonicotinoid compounds bearing a 5-chloro-6-fluoronicotinyl group were prepared and their insecticidal activity against brown rice planthopper, green peach aphid and common cutworm under laboratory conditions was compared with 1-(6-chloro-5-fluoronicotinyl)-2-nitroiminoimidazolidine. 5-Fluoroimidacloprid controlled the two hemipteras at 0.2 ppm at the same dose level of imidacloprid, while the positional isomers showed far lower activity. None of the tested compounds controlled the lepidoptera at 200 ppm.

Keywords: imidacloprid, neonicotinoid, fluorinated pyridine, aphid, planthopper.

Introduction

A recent report on 6-chloro-5-fluoronicotinyl-2-nitroiminoimidazolidine (**2**) exhibiting comparable insecticidal activity against the American cockroach by injection[1] and nerve-blocking potency on excised cockroach ganglia with imidacloprid (**1**)[2] has encouraged us to examine actual insecticidal activity against agriculturally important pests under laboratory conditions. The high potency of 5-fluoroimidacloprid **2** in the above tests surprised us because the 6-chloropyridyl constituent has been considered as the best activator of ring substituents so far,[3] prompting investigation of its related compounds (Fig. 1).

This note describes the preparation of inversely dihalogenated derivatives, 5-chloro-6-fluoronicotinyl-nitroiminoimidazolidine, -cyanoiminoimidazolidine, -oxazolidine and -thiazolidine, and presents the insecticidal activity of **2** and newly prepared neonicotinoids against three insect species tested in the laboratory.

* To whom correspondence should be addressed.
E-mail: kagabus@gifu-u.ac.jp
Published online June 30, 2007

Materials and Methods

1. Preparation of compounds

All melting points (mp) are uncorrected. IR spectra were measured with a Perkin Elmer FTIR 1600 spectrometer. NMR spectra were obtained using a Varian Gemini 2000 C/H (400 MHz). Chemical shifts were recorded in δ (ppm) and the coupling constant J in Hz. Mass spectra were recorded with a Jeol JMS-700. Compound **2** was prepared according to the published procedures.[1]

*1.1. 2-Amino-3-chloro-5-methylpyridine (**5**)*

A solution of 2-amino-5-methylpyridine (5.0 g, 47 mmol) in conc. HCl (23 ml) was cooled to 0°C in an ice bath and was treated with 30% H_2O_2 (5.2 ml). The resulting mixture was allowed to warm to room temperature and stirred for 2 hr. The reaction mixture was poured into 50 ml of water, made basic to pH 8–9 by the addition of solid Na_2CO_3, and then extracted with isopropyl ether (IPE) (3×30 ml). The combined extracts were dried ($MgSO_4$) and concentrated to afford a yellow solid. The product was separated by chromatography on SiO_2 with IPE. Yield: 1.83 g (28%). Mp: 59–62°C (61–62°C).[4]

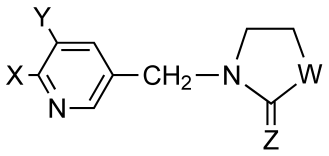
*1.2. 3-Chloro-2-fluoro-5-methylpyridine (**7**)*

Method A. To a suspension of **5** (1.45 g, 10.2 mmol) in 40% tetrafluoroboric acid (9.7 ml) at −5°C was added portionwise $NaNO_2$ (1.76 g, 25.5 mmol) while keeping the temperature in the vessel below 5°C. The resulting mixture was allowed to warm to 45–50°C and stirred for 2.5 hr. The cooled mixture was neutralized with aqueous NaOH and extracted with ether, dried, and evaporated. The brown residue was subjected to chromatography on SiO_2 with hexane. The product was separated as pale yellow solid. Yield: 0.69 g (47%). Mp: 44–46°C. ^{1}H NMR δ ($CDCl_3$): 2.32 (3H, s), 7.62 (1H, dd, J_{H-H}=2.2 Hz, J_{H-F}=8.8 Hz), 7.89 (1H, m); ^{13}C NMR δ ($CDCl_3$): 17.3, 132.4, 141.3, 145.0 (d, J_{C-F}=13.1 Hz), 156.4, 158.2. EIMS *m/z* (%): 145 (M^+, 38), 130 (38), 126 (40), 111 (95), 95 (100). HRMS (EI) *m/z* (M^+): Calcd. for C_6H_5ClFN: 145.0095, Found: 145.0069.

Method B. 2-Fluoro-5-methylpyridine (**6**; 0.50 g, 4.5 mmol) in THF solution was slowly added to a cold (−78°C) solution of LDA in dry THF (4 ml). The resulting mixture was stirred for 4 hr at this temperature, before slowly addition of CCl_4 (1.5 ml, 15.4 mmol). Stirring continued for 2 hr before hydrolysis with water at 0°C. Extraction by ether, drying ($MgSO_4$), and solvent removal afforded a crude solid, which was purified by chromatography on SiO_2 with hexane. Yield: 0.11 g (17%).

*1.3. 5-Bromomethyl-3-chloro-2-fluoropyridine (**8**)*

A mixture of compound **5** (0.50 g, 3.45 mmol) and *N*-bromosuccinimide (0.737 mg, 4.09 mmol) in CCl_4 (15 ml) was stirred with a catalytic amount of benzoyl peroxide at reflux temperature for 6 hr. The solids precipitated on cooling were filtered off, and the filtrate, after evaporation of the solvent, was subjected to chromatography on SiO_2 with hexane/IPE (5 : 1 v/v). The eluted mixture (0.25 g) of the product and the starting compound **5** (ratio of



1 imidacloprid (X=Cl, Y=H, Z=NNO_2, W=NH)
2 (X=Cl, Y=F, Z=NNO_2, W=NH)
3a (X=F, Y=Cl, Z=NNO_2, W=NH)
3b (X=F, Y=Cl, Z=NNO_2, W=S)
3c (X=F, Y=Cl, Z=NCN, W=NH)
3d (X=F, Y=Cl, Z=NCN, W=O)
3e (X=F, Y=Cl, Z=NCN, W=S)

Fig. 1. Imidacloprid and its 5,6-dihalogenated analogs.

5 : 1 based on ^{1}H-NMR) were used to the next step. The following ^{1}H-NMR shifts were assigned for compound **6**. ^{1}H-NMR δ ($CDCl_3$): 4.42 (2H), 7.88 (1H, m), 8.10 (1H, m).

*1.4. 1-(5-Chloro-6-fluoropyridin-3-ylmethyl)-2-nitroiminoimidazolidine (**3a**)*

A solution of 2-nitroiminoimidazolidine (120 mg, 1.0 mmol) in THF+DMF (10 ml+1 ml) was treated with sodium hydride (60% oil dispersion, 40 mg, 1.0 mmol) at 5°C. The mixture was stirred at room temperature until no hydrogen was produced and then cooled again to 0°C before a solution of the crude compound (**6**) (201 mg, 0.72 mmol for **6**) in THF+DMF (4 ml+0.5 ml) was added dropwise. The mixture was stirred at ambient temperature overnight. THF was removed and the resulting liquid was subjected to preparative thin-layer chromatography on SiO_2 with $CHCl_3$/ethanol (9 : 1, v/v). The crude product was recrystallized from ethanol. Yield: 47 mg (18%). Mp: 155–157°C. ^{1}H NMR δ ($CDCl_3$): 3.56 (2H, m), 3.83 (2H, m), 4.55 (2H, s), 7.86 (1H, dd, J_{H-H}=2.2 Hz, J_{H-F}=8.4 Hz), 8.04 (1H, m), 8.21 (1H, bs); ^{13}C NMR δ ($CDCl_3$): 41.6, 44.9, 45.3, 130.3 (d, J_{C-F}=6.0 Hz), 141.0, 144.7 (J_{C-F}=14.4 Hz), 157.9, 159.8, 161.3. EIMS *m*/*z* (%): 273 (M^+, 0.2), 228 (100), 192 (16), 172 (7), 144 (24). *Anal*. Found: C, 39.80; H, 3.50; N, 25.70%. Calcd. for $C_9H_9ClFN_5O_2$: C, 39.50; H, 3.31; N, 25.59%.

Compounds **3b**–**3e** were prepared according to the procedures above.

*1-(5-Chloro-6-fluoropyridin-3-ylmethyl)-2-nitroiminothiazolidine (**3b**)*

Mp: 190°C. ^{1}H NMR δ ($CDCl_3$): 3.23 (2H, m), 3.77 (2H, m), 4.77 (2H, s), 7.87 (1H, dd, J_{H-H}=2.2 Hz, J_{H-F}=8.4 Hz), 8.05 (1H, m); ^{13}C NMR δ (acetone-d_6): 27.1, 47.7, 51.7, 131.2 (d, J_{C-F}=4.8 Hz), 141.5, 145.6 (J_{C-F}=14.4 Hz), 157.3, 159.2, 174.9. EIMS *m*/*z* (%): 290 (M^+, 0.5), 244 (100), 144 (96). HRMS (EI) *m*/*z* (M^+): Calcd. for $C_9H_8ClFN_4O_2S$: 290.0041, Found: 290.0071.

*1-(5-Chloro-6-fluoropyridin-3-ylmethyl)-2-cyanoinoimidazolidine (**3c**)*

Mp: 185–188°C. IR (KBr) cm^{-1}: 2180. ^{1}H NMR δ ($CDCl_3$): 3.52 (2H, m), 3.66 (2H, m), 4.41 (2H, s), 6.65 (1H, bs), 7.83 (1H, dd, J_{H-H}=2.2 Hz, J_{H-F}=8.2 Hz), 8.04 (1H, *m*); ^{13}C NMR δ ($CDCl_3$): 40.5, 44.2, 44.6, 117.4, 132.6 (d, J_{C-F}=4.8 Hz), 141.1, 145.2 (J_{C-F}=14.4 Hz), 157.1, 159.0, 164.3. EIMS *m*/*z* (%): 253 (M^+, 93), 252 (100), 224 (19), 144 (61). HRMS (EI) *m*/*z* (M^+): Calcd. for $C_{10}H_9ClFN_5$: 253.0530, Found: 253.0543.

*1-(5-Chloro-6-fluoropyridin-3-ylmethyl)-2-cyanoiminooxazolidine (**3d**)*

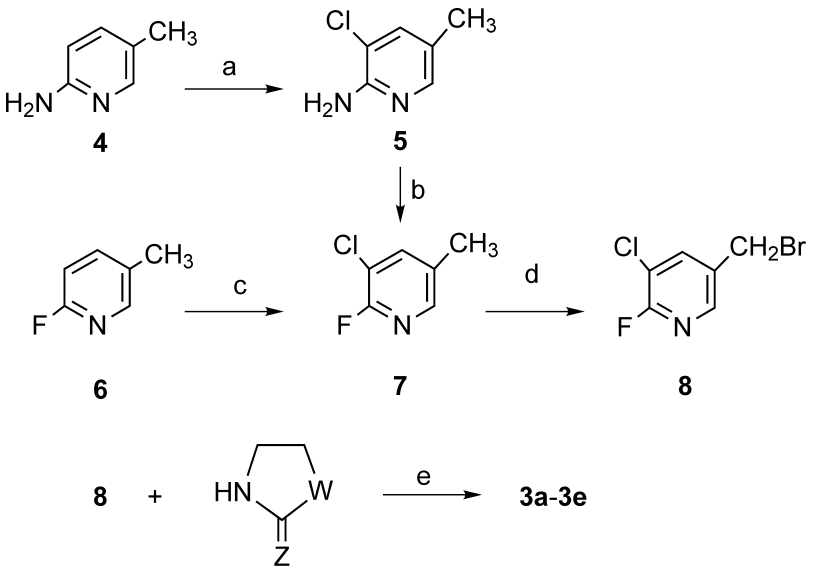
Mp: 183°C. IR (KBr) cm^{-1}: 2345. ^{1}H NMR δ ($CDCl_3$): 3.70 (2H, m), 4.51 (2H, s), 4.64 (2H, m), 7.87 (1H, dd, J_{H-H}=1.8 Hz, J_{H-F}=8.3 Hz), 8.05 (1H, m); ^{13}C NMR δ ($CDCl_3$): 45.4, 46.1, 66.5, 114.5, 129.3 (d, J_{C-F}=4.8 Hz), 141.0, 144.9 (J_{C-F}=14.4 Hz), 158.1, 160.1, 163.3. EIMS *m*/*z* (%): 254 (M^+, 92), 228 (7), 185 (50), 144 (100). HRMS (EI) *m*/*z* (M^+): Calcd. for $C_{10}H_8ClFN_4O$: 254.0371, Found: 254.0381.

*1-(5-Chloro-6-fluoropyridin-3-ylmethyl)-2-cyanoiminothiazolidine (**3e**)*

Mp: 112–115°C. IR (KBr) cm^{-1}: 2180. ^{1}H NMR δ ($CDCl_3$): 3.42 (2H, m), 3.82 (2H, m), 4.62 (2H, s), 7.84 (1H, dd, J_{H-H}=2.2 Hz, J_{H-F}=8.6 Hz), 8.04 (1H, m); ^{13}C NMR δ ($CDCl_3$): 27.3, 46.5, 52.3, 116.7, 129.7 (d, J_{C-F}=6.0 Hz), 141.1, 144.9 (J_{C-F}=13.2 Hz), 158.0, 159.9, 175.2. EIMS *m*/*z* (%): 270 (M^+, 81), 242 (40), 201 (38), 144 (100). HRMS (EI) *m*/*z* (M^+): Calcd. for $C_{10}H_8ClFN_4S$: 270.0142, Found: 270.0149.

2. Insecticidal tests

Three species of insects, brown rice planthopper, *Nilaparvata lugens* Stål, green peach aphid, *Myzus persicae* Sulzer, and common cutworm, *Spodoptera litura* Fabricius, were used to evaluate insecticidal activities. The insects were reared in an insect rearing room under a 16 hr : 8 hr (light : dark) cycle and a temperature of 25°C. Acetone solutions containing 1600 ppm test compounds and 1% Triton X-100 were diluted with water containing a small amount of wetting agent (Shin-Rinoh®) to prepare the test solutions. Five to seven concentrations between 200 ppm and 0.0125 ppm of the test solution were used for all three species of insects. Ten nymphs of 2nd or 3rd instar of the planthopper were released on a rice seedling, which was put in a test tube after dipping in the test solution and dried. About twenty 1st instar nymphs of the aphid were placed on eggplant seedling or a leaf of Japanese radish after dipping in the test solution. Ten 2nd instar larvae of the common cutworm were released on a cabbage leaf, which was put in a plastic dish after dipping in the test solution and dried. All treatments were performed at room temperature and the treated insects were cultured at 25°C. On the fifth day after treatment, dead and alive insects were counted for all tests. Mortality was evaluated as a percentage and the minimum concentration which showed ≥90% mortality was determined.



Reagents and conditions
a) HCl/H_2O_2, 0°C to room temperature, 2 hr.
b) $HBF_4/NaNO_2$, 5°C then 45-50°C, 2.5 hr.
c) LDA, -78°C then CCl_4.
d) NBS, $(C_6H_5CO_2)_2$, CCl_4, reflux, 6 hr.
e) NaH / DMF, 0°C to room temperature.

Fig. 2. Preparation scheme for 5-chloro-6-fluoroimidacloprid analogs.

3. Hydrophobicity parameter

Log P, where P is the partition coefficient of a compound in the 1-octanol/water partitioning system, was determined as previously reported.[2)]

Results and Discussion

1. Synthesis

Figure 2 outlines the preparation of 6-fluoro-5-chloronicotinyl derivatives. The key starting compound (**7**) was prepared by two routes. One represented the chlorination of aminopyridines using HCl and hydrogen peroxide,[5)] followed by Schiemann fluorination. The second applied deprotonation at the *ortho* position to the fluorine atom in arylfluorides with a strong base. Thus, commercially available 6-fluoro-3-methylpyridine was treated with LDA and subsequently chlorinated with CCl_4. NBS bromination and the following coupling with the corresponding azolidine were carried out according to the described procedures.[6)]

2. Insecticidal activity

Insecticidal activity 5 days after treatment to three representative insects with neonicotinoids is shown in Table 1. The activity of 6-chloro-5-fluoronicotinyl-nitroiminoimidazolidine (**2**) against brown rice planthoppers and green peach aphids was noticeable; it controlled two hemipteras at as low as 0.2 ppm. Similar high potency comparable with that of imidacloprid has also been observed for the nerve-blocking activity of central nerve cord of American cockroaches.[2)] In contrast, 5-chloro-6-fluoro derivatization resulted in reduced activity, irrespective of the type of the azolidine ring conjugated with $=NNO_2$ or NCN. The activity of all tested compounds, including imidacloprid, was low against lepidopteran common cutworms, which is a typical symptom of neonicotinoid insecticides.[3)]

The presented definitive activity differences between 6-chloro-5-fluoro (**2**) and 5-chloro-6-fluoro nicotinyl derivatives (**3**) suggest a question about the factors responsible for the results. A

Table 1. Insecticidal potency[a)]

Compound	Brown rice planthopper	Green peach aphid	Common cutworm
2	0.2	0.2	>50
3a	50	200	>200
3b	>200	>200	>200
3c	>200	200	>200
3d	>200	200	>200
3e	>200	50	>200
1[b)]	0.2	0.2	>50

[a)] 90% lethal dose in ppm evaluated by testing twice; testing procedures, see the text. [b)] Imidacloprid.

CoMFA on neonicotinoid insecticides[8] has suggested the existence of a forbidden region near the pyridyl nitrogen atom.[7] Spatial crowding in this respect will not be different between 5-chloro-6-fluoro and 6-chloro-5-fluoro nicotinyl moieties. On the other hand, MNDO-PM3 analysis with a similarity index has indicated characteristic negative potential around pyridyl nitrogen in active neonicotinoid molecules.[8] Here either, we cannot calculate any significant stereoelectronic differences between these inversely dihalogenated derivatives, considering the equivalent potency against green rice leafhoppers of 6-chloronicotinyl-nitromethyleneimidazolidine and 6-fluoro derivative.[9]

One of the remarkable features of neonicotinoids is their excellent activity against sucking insects,[3] and it is undeniable that the notable systemicity shown by the log P value of 0.53 of imidacloprid[6] contributes to insecticidal prominence. The measured log P values for the positional isomers, **2** and **3a**, were 0.79 and 0.98 at 25°C, respectively, which indicates that the 6-chloro-5-fluoro derivative (**2**) is apparently more hydrophilic than the isomer (**3a**). The attributed better systemic property of compound **2** probably contributes significantly to its higher insecticidal activity against the two sucking insects tested. A future study will identify the factors attributing to insecticidal difference between the positional isomers with a help of QSAR using a variety of substituents on the pyridine ring.

Acknowledgements

We thank Dr. Keiichiro Nishimura for his suggestions for improving the manuscript, and the Central Research Institute of Ishihara Sangyo Kaisha, LTD for the insecticidal tests.

References

1) S. Kagabu, Y. Murase, R. Imai, N. Ito and K. Nishimura: *Pest Manag. Sci*. **63**, 75–83 (2007).
2) K. Nishimura, K. Kiriyama and S. Kagabu: *J. Pestic Sci*. **31**, 110–115 (2006).
3) S. Kagabu: *Rev. Toxicol*. **1**, 75–129 (1997).
4) T. J. Kress, L. L. Moore and S. M. Costantino: *J. Org. Chem*. **41**, 93–96 (1976).
5) K. S. Gudmundsson, J. M. Hinkley, M. S. Brieger, J. C. Drach and L. B. Townsend: *Synth. Commun*. **27**, 861–870 (1997).
6) S. Kagabu, R. Ishihara, Y. Hieda, K. Nishimura and Y. Naruse: *J. Agric. Food Chem*. **55**, 812–818 (2007).
7) A. Okazawa, M. Akamatsu, A. Ohoka, H. Nishiwaki, W.-J. Cho, Y. Nakagawa, K. Nishimura and T. Ueno: *Pestic. Sci*. **54**, 134–144 (1998).
8) A. Nakayama and M. Sukekawa: *Pestic. Sci*. **52**, 104–110 (1998).
9) S. Kagabu, K. Moriya, K. Shibuya, Y. Hattori, S. Tsuboi and K. Shiokawa: *Biosci. Biotechnol. Biochem*. **56**, 362–363 (1992).