The Synthesis of 1-[(Substituted)pyrazol-5-yl]-iminomethyl-2-nitroiminoimidazolidine and its Derivatives

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In this article 1-[(substituted)pyrazol-5-yl]iminomethyl-2-nitroimino imidazolidines (**II**) and their derivatives were synthesized. All the compounds were verified by elemental analysis, ^{1}H NMR and IR . In the reaction of **II** with halides, two different results were observed.

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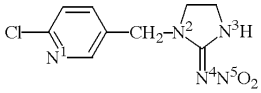
Introduction.

2-Nitroiminoimidazolidinyl is a part of the structure of a new class of insecticide neonicotinoids. Neonicotinoids [1,2] are a novel and distinct class of insecticides. They combine selective activity against insects with a favorable safety profile. Neonicotinoids act as agonists of the nicotinic acetylcholine receptor (nAChR) [3,4]. According to the model



IMI

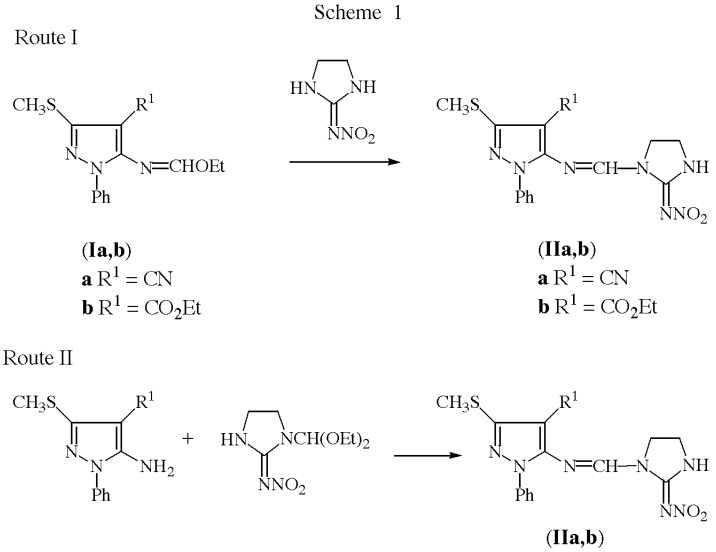
proposed by Yamamoto *et al.* [5], the distance between N1 and N2 of imidacloprid (**IMI)** is the major factor for the activity. By retaining the 2-nitroiminoimidazolidine part in **IMI**, our efforts were made to design and synthesize novel compounds, 1-[(substituted)pyrazol-5-yl]iminomethyl-2-nitroiminoimidazolidine (**II**) and their derivatives, in order to find lead compounds with high bioactivities.

Results and Discussion.

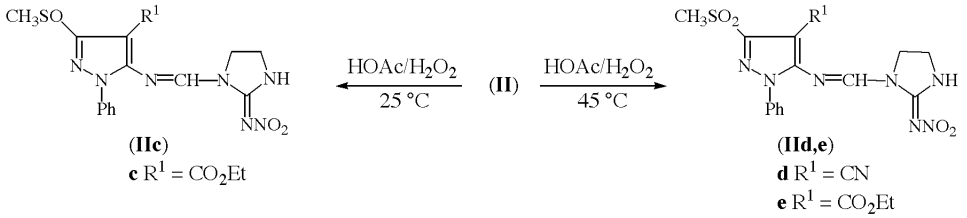
Synthesis of compounds $\mathbf{II}_{a,b}$.

Our studies began with 5-amino-4-cyano(or ethoxycarbonyl)-3-methylthio-1-phenyl- pyrazole. There are two routes to the synthesis of $\mathbf{II}_{a,b}$ [6]. In route (I), reaction of the 5-aminopyrazole with triethyl orthoformate, provided the reqired [4-cyano(or ethoxycarbonyl)-3-methylthio-1-phenylpyrazol-5-yl]-iminomethyl ethyl ether (**I**) (Scheme 1). The reaction of the imidate **I** with an equivalent of 2-nitroiminoimidazolidine provided $\mathbf{II}_{a,b}$ by the catalysis of BF_3•Et_2O in low yield. Excellent yields of $\mathbf{II}_{a,b}$ (83-89%) were obtained in the presence of sodium hydride. In the media of Lewis acid and hard base, the imidate **I** can changed into 5-aminopyrazole. In the route (**II**), low yields of $\mathbf{II}_{a,b}$ were obtained by reaction of the corresponding 5-aminopyrazole with 1-diethoxymethyl-2-nitroiminoimidazolidine in the presence of Lewis acid or high temperature.

Scheme 1



Scheme 2



(**IIc**)
c $R^1 = CO_2Et$

(**IId,e**)
d $R^1 = CN$
e $R^1 = CO_2Et$

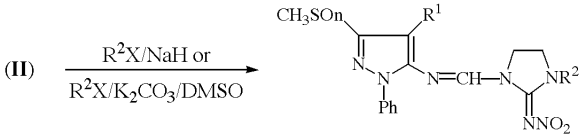
Synthesis of Compounds $\mathbf{II}_{c\text{-}e}$.

The treatment of $\mathbf{II}_b$ with hydrogenperoxide and acetic acid under different condition provided 3-methylsulfinyl $\mathbf{II}_c$, or 3-methylsulfonyl $\mathbf{II}_e$ (Scheme 2) [7,8,9].

Synthesis of compounds **III** and **IV.**

When $\mathbf{II}_{a,b}$ were reacted with iodomethane in the presence of sodium hydride at room temperature, $\mathbf{III}_{a,c}$ were obtained respectively. In the same condition, the treatment of $\mathbf{II}_{a,b}$ with bromoalkane did not provide the corresponding **III**, and if the reaction temperature is higher than 40 °C, the products are 5-aminopyrazole and 2-nitroiminoimidazolidine. $\mathbf{III}_{b,d\text{-}f}$ can be obtained in the presence of K_2CO_3 at 60-70 °C in DMSO (Scheme 3).

Scheme 3



(**IIIa-f**)

a n = 0, $R^1 = CN$, $R^2 = CH_3$
b n = 0, $R^1 = CN$, $R^2 = CH_2CH_2CH_3$
c n = 0, $R^1 = CO_2Et$, $R^2 = CH_3$
d n = 0, $R^1 = CO_2Et$, $R^2 = CH_2CH_2CH_3$
e n = 0, $R^1 = CO_2Et$, $R^2 = (CH_2)_3CH_3$
f n = 2, $R^1 = CO_2Et$, $R^2 = (CH_2)_3CH_3$

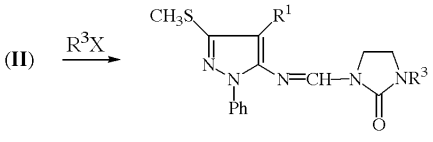
Table 1

Physical Data and Elemental Analysis of Compounds **II**,**III**,**IV**

Compound	Yield %	mp. C°	Elemental Analysis (Calc. %) C	H	N
$\mathbf{II}_a$	89	246-248	48.65(48.64)	4.14(3.81)	29.91(30.25)
$\mathbf{II}_b$	84	230-231	48.91(49.00)	4.59(4.58)	23.49(23.21)
$\mathbf{II}_c$	74	248-249	46.94(47.11)	4.61(4.42)	22.36(22.62)
$\mathbf{II}_d$	65	273-276	44.76(44.71)	3.29(3.51)	27.62(27.84)
$\mathbf{II}_e$	67	240-241	45.28(45.43)	4.31(4.26)	21.62(21.83)
$\mathbf{III}_a$	60	201-203	49.78(49.99)	4.20(4.20)	29.05(29.15)
$\mathbf{III}_b$	30	163-165	52.41(52.41)	4.81(4.89)	27.32(27.17)
$\mathbf{III}_c$	68	226-227	50.05(50.11)	5.28(4.91)	22.64(22.72)
$\mathbf{III}_d$	22	173-174	52.12(52.28)	5.34(5.48)	21.29(21.34)
$\mathbf{III}_e$	56	128-129	53.52(53.26)	5.64(5.75)	20.82(20.70)
$\mathbf{III}_f$	48	159-160	48.71(48.87)	5.10(5.13)	19.55(19.95)
$\mathbf{IV}_a$	31	148-149	63.53(63.44)	4.88(4.84)	20.31(20.18)
$\mathbf{IV}_b$	40	178-179	54.15(54.26)	4.60(4.55)	21.11(21.09)
$\mathbf{IV}_c$	34	154-157	61.91(62.18)	5.66(5.46)	15.30(15.11)
$\mathbf{IV}_d$	22	124-126	54.68(54.89)	4.93(5.18)	15.06(15.24)
$\mathbf{IV}_e$	63	154-156	54.05(53.92)	4.93(5.20)	15.96(15.72)
$\mathbf{IV}_f$	68	194-196	55.32(55.36)	4.51(4.65)	16.83(16.84)

Otherwise, the treatment of $\mathbf{II}_a$ with benzyl chloride did not provide the corresponding product **III** in the presence of K_2CO_3 at 60-70 °C in DMSO. The product obtained was 3-benzyl-1-(4-cyano-3-methylthio-1-phenylpyrazol-5-yl)iminomethylimidazolidin-2-one ($\mathbf{IV}_a$) (Scheme 4). The same phenomena were observed in the reaction of $\mathbf{II}_b$ with ethyl bromoacetate, ethyl chloroformate and 2-chloro-5-chloromethylpyridine.

Scheme 4



(**IVa-f**)

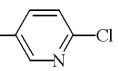
a $R^1 = CN$, $R^3 = CH_2Ph$
b $R^1 = CN$, $R^3 = CO_2Et$
c $R^1 = CO_2Et$, $R^3 = CH_2Ph$
d $R^1 = CO_2Et$, $R^3 = CO_2Et$
e $R^1 = CO_2Et$, $R^3 = CH_2CO_2Et$
f $R^1 = CO_2Et$, $R^3 =$ 

Table 2

The ^{1}H NMR Data of Compounds **II**,**III**,**IV**

Compound	^{1}H NMR(DMSO-d_6), δ (ppm)
II$_a$	2.56 (s, 3H, CH_3S), 3.66-3.84 (m, 4H, NCH_2CH_2N), 7.32-7.82 (m, 5H, Ph), 8.72 (s, 1H, N=CH)
II$_b$	1.28 (t, 3H, CH_3CH_2O), 2.48 (s, 3H, CH_3S), 3.72-3.96 (m, 4H, NCH_2CH_2N), 4.16 (q, 2H, OCH_2CH_3), 7.24-7.80 (m, 5H, Ph), 8.60 (s, 1H, N=CH)
II$_c$	1.30 (t, 3H, CH_3CH_2), 3.48 (s, 3H, CH_3SO), 3.80-3.98 (m, 4H, NCH_2CH_2N), 4.15 (q, 2H, OCH_2CH_3,), 7.34-7.76 (m, 5H, Ph), 8.72 (s, 1H, N=CH)
II$_d$	3.44 (s, 3H, CH_3SO_2), 3.80-3.96 (m, 4H, NCH_2CH_2N), 7.44-7.80 (m, 5H, Ph), 9.02 (s, 1H, N=CH)
II$_e$	1.32 (t, 3H, CH_3CH_2), 3.52 (s, 3H, CH_3SO_2), 3.84-3.96 (m, 4H, NCH_2CH_2N), 4.28 (q, 2H, OCH_2CH_3), 7.44-7.84 (m, 5H, Ph), 8.92 (s, 1H, N=CH)
III$_a$	2.62 (s, 3H, CH_3S), 3.06 (s, 3H, N-CH_3), 3.98-4.12 (m, 4H, NCH_2CH_2N), 7.40-7.80 (m, 5H, Ph), 8.96 (S, 1H, N=CH)
III$_b$	0.99 (t, 3H, CH_3CH_2), 1.58-1.90 (m, 2H, $CH_3CH_2CH_2$), 2.64 (s, 3H, CH_3S), 3.38 (t, 2H, N-CH_2CH_2), 3.80-4.20 (m, 4H, NCH_2CH_2N), 7.40-7.70 (m, 5H, Ph), 8.84 (s, 1H, N=CH)
III$_c$	1.22 (t, 3H, CH_3CH_2O), 2.46 (s, 3H, CH_3S), 2.96 (s, 3H, CH_3N), 3.92-4.00 (m, 4H, NCH_2CH_2N), 4.15 (q, 2H, OCH_2CH_3), 7.34-7.76 (m, 5H, Ph), 8.72 (s, 1H, N=CH)
III$_d$	0.99 (t, 3H, CH_3CH_2), 1.38 (t, 3H, CH_3CH_2O), 1.60-1.92 (m, 2H, $CH_3CH_2CH_2$), 2.60 (s, 3H, CH_3S), 3.42 (t, 2H, CH_2N), 3.74-4.18 (m, 4H, NCH_2CH_2N), 4.34 (q, 2H, OCH_2CH_3), 7.40-7.76 (m, 5H, Ph), 8.80 (s, 1H, N=CH)
III$_e$	0.94 (t, 3H, CH_3CH_2), 1.28 (t, 3H, CH_3CH_2O), 1.44-1.76 (m, 4H, $CH_3CH_2CH_2CH_2$), 2.54 (s, 3H, CH_3S), 3.32-3.48 (t, 2H, $C_3H_7CH_2N$), 3.96-4.10 (m, 4H, NCH_2CH_2N), 4.24 (q, 2H, OCH_2CH_3), 7.44-7.80 (m, 5H, Ph), 8.76 (s, 1H, N=CH)
III$_f$	0.92 (t, 3H, CH_3CH_2), 1.32 (t, 3H, CH_3CH_2O), 1.60-1.86 (m, 2H, $CH_3CH_2CH_2$), 3.38 (s, 3H, CH_3SO_2), 3.38 (t, 2H, CH_2N), 4.04-4.16 (m, 4H, NCH_2CH_2N), 4.28 (q, 2H, OCH_2CH_3), 7.42-7.76 (m, 5H, Ph), 8.76 (s, 1H, N=CH)
IV$_a$	2.64(s, 3H, CH_3S), 3.36-3.94 (m, 4H, NCH_2CH_2N), 4.52 (s, 2H, CH_2-Ph), 7.56-7.78 (m, 5H, Ph), 8.98 (s, 1H, N=CH)
IV$_b$	1.32 (m, 3H, CH_3CH_2), 2.64 (s, 3H, CH_3S), 3.88-4.04 (m, 4H, NCH_2CH_2N), 4.36 (q, 2H, CH_2CH_3), 7.42-7.78 (m, 5H, Ph), 9.00 (s, 1H, N=CH)
IV$_c$	1.34 (t, 3H, CH_3CH_2), 2.58 (s, 3H, CH_3S), 3.32-3.50, 3.76-3.94 (m, 4H, NCH_2CH_2N), 4.30 (q, 2H, OCH_2CH_3), 4.50 (s, 2H, CH_2-Ph), 7.26-7.78 (m, 10H, Ph,), 8.76 (s, 1H, N=CH)
IV$_d$	1.34 (double t, 6H, CH_3CH_2), 2.56 (s, 3H, CH_3S), 3.84-4.02 (m, 4H, NCH_2CH_2N), 4.18-4.50 (m, 4H, CH_2CH_3), 7.36-7.76 (m, 5H, Ph,), 8.86 (s, 1H, N=CH)
IV$_e$	1.32 (m, 6H, CH_3CH_2), 2.60 (s, 3H, CH_3S), 3.68-4.02 (m, 4H, NCH_2CH_2N), 4.12 (s, 2H, CH_2O-), 4.18-4.44 (m, 4H, CH_2CH_3), 7.34-7.82 (m, 5H, Ph,), 8.78 (s, 1H, N=CH)
IV$_f$	1.20 (t, 3H, CH_3CH_2), 2.49 (s, 3H, CH_3S), 3.42-3.51, 3.71-3.80 (m, 4H, NCH_2CH_2N), 4.10 (q, 2H, OCH_2CH_3), 4.50 (s, 2H, CH_2-pyridine), 7.45-7.70 (m, 8H, Ph, pyridine), 8.64 (s, 1H, N=CH)

EXPERIMENTAL

Melting points were determined on Yanco melting point apparatus and are uncorrected. Element analysis was carried out on an MF-3 automatic analyzer. The ^{1}H NMR spectra were recorded in $(CD_3)_2SO$ solution on Jeol FX-90Q and Bruker AC-P200 spectrometers, and chemical shifts were expressed in ppm using TMS as the internal reference.

Procedure for the Preparation of 1-[(4-Cyano(or ethoxycarbonyl)-3-methylthio-1-phenyl)pyrazol-5-yl]iminomethyl-2-nitroiminoimidazolidine **II**$_{a(b)}$.

A solution of [(4-cyano-3-methylthio-1-phenyl)pyrazol-5-yl]iminomethyl ethyl ether (**I**$_a$) (0.96 g, 4 mmol) in anhydrous acetonitrile (15mL), was added into a mixture of 2-nitroiminoimidazolidine (0.52 g, 4 mmol) and 80% sodium hydride (0.18 g, 6 mmol) in anhydrous acetonitrile (15 mL). The mixture was stirred at room temperature for 3 hours, then the solid was isolated by filtation. The solid was washed with water, and purified by silica column chromatography using ethyl acetate/petroleum ether (2:1) as eluent to give compound **II**$_a$.

Procedure for the Preparation of 1-[(4-Ethoxycarbonyl-3-methylsulfinyl-1-phenyl) pyrazol-5-yl]iminomethyl-2-nitroiminoimidazolidine (**II**$_c$).

A suspension of 1-[(4-ethoxycarbonyl-3-methylthio-1-phenyl)pyrazol-5-yl]imino-methyl-2-nitroiminoimidazolidine (**II**$_b$) (0.84 g, 2 mmol) and 30% hydrogenperoxide (3.8 mL) in acetic acid (16.2 mL) was stirred at room temperature for 30 hours. The mixture was diluted with water (50 mL), then the solid was isolated by filtation. The solid was purified by silica column chromatography using ethyl acetate/petroleum ether (1:1) as eluent to give compound **II**$_c$.

Table 3

The IR Data of Compounds **II**, **III**,**IV**

Compound	N-H	CN	C=O	NO_2	
II$_a$	3364.5	2214.5	/	1526.6	1347.4
II$_b$	3354.5	/	1674.1	1526.5	1357.1
II$_c$	3369.5	/	1709.6	1532.9	1341.7
II$_d$	3374.5	2229.5	/	1533.5	1342.2
II$_e$	3369.0	/	1709.1	1533.3	1340.9
III$_a$	/	2213.5	/	1524.0	1354.8
III$_b$	/	2211.5	/	1523.8	1356.4
III$_c$	/	/	1689.7	1522.5	1354.1
III$_d$	/	/	1689.6	1527.6	1357.4
III$_e$	/	/	1686.3	1529.6	1333.0
III$_f$	/	/	1713.5	1519.9	1342.6
IV$_a$	/	2209.5	1732.7	/	
IV$_b$	/	2206.5	1758.8, 1718.1	/	
IV$_c$	/	/	1734.1, 1690.3	/	
IV$_d$	/	/	1744.7, 1732.7, 1677.7/		
IV$_e$	/	/	1738.3, 1690.7	/	
IV$_f$	/	/	1796.6, 1694.7	/	

Procedure for the Preparation of 1-[(4-Ethoxycarbonyl(or cyano)-3-methylsulfonyl- 1-phenyl)pyrazol-5-yl]iminomethyl-2-nitroiminoimidazolidine **II**$_{e(d)}$.

A suspension of 1-[(4-ethoxycarbonyl-3-methylthio-1-phenyl)pyrazol-5-yl]imino-methyl-2-nitroiminoimidazolidine (**II**$_b$) (0.84 g, 2 mmol) and 30% hydrogenperoxide (7.4 mL) in acetic acid (11.7 mL) was stirred at 45-47 °C for 30 hours. The mixture was diluted with water (50 mL), then filtered. The solid was purified by silica column chromatography using ethyl acetate/petroleum ether (1:1) as eluent to give compound **II**$_d$.

General Procedure for the Preparation of 1-[(4-Cyano(or ethoxycarbonyl)-3-methyl-thio-1-phenyl)pyrazol-5-yl]iminomethyl-3-methyl-2-nitroiminoimidazolidine **III**$_{a(c)}$.

To a solution of 1-[(4-cyano-3-methylthio-1-phenyl)pyrazol-5-yl]iminomethyl- 2-nitroiminoimidazolidine (**II**$_a$) (0.74 g, 2 mmol) in anhydrous dimethyl sulfoxide (15 mL), 80% sodium hydride (0.12 g, 4 mmol) was added. After 0.5 hours, iodomethane (0.46 g, 3 mmol) was added. The mixture was stirred at room temperature for 10 hours. Then the mixture was poured into 50 mL ice water. After filtration, the residue was purified by silica column chromatography using ethyl acetate/petroleum ether (1:1) as eluent to give **III**$_a$.

General Procedure for the Preparation of 1-[(1-Phenyl-3-methylthio-4-substituted)pyrazol-5-yl]iminomethyl-3-substituted-2-nitroiminoimidazolidine **III**$_{b,d-f}$.

A suspension of **II**$_a$ (0.74 g, 2 mmol), 1-bromopropane (0.25 g, 2 mmol), anhydrous potassium carbonate (0.45 g, 3 mmol) and anhydrous dimethyl sulfoxide (15 mL), was stirred at 60 °C for 16 hours. Then the mixture was poured into ice water (50 mL), and the solid isolated by filtration. The solid was purified by column chromatography using petroleum ether/ethyl acetate (1:1) as eluent to give **III**$_b$.

General Procedure for the Preparation of 1-[(1-Phenyl-3-methylthio-4-substituted)pyrazol-5-yl]iminomethyl-3-substituted-imidazolidin-2-one **IV**$_{a-f}$.

A suspension of **II**$_a$ (0.74 g, 2 mmol), benzylchloride (0.38 g, 3 mmol), anhydrous potassium carbonate (0.45 g, 3 mmol) and anhydrous dimethyl sulfoxide (15 mL), was stirred at 60 °C for 16 hours. Then the mixture was poured into ice water (50 mL), and the solid isolated by filtration. The solid was purified by column chromatography using petroleum ether/ethyl acetate (1:1) as eluent to give **IV**$_a$.

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