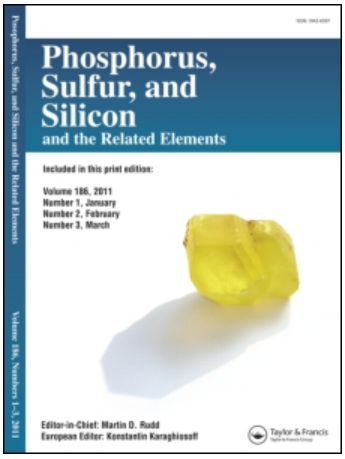

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Reactions of [(4-cyano-3-methylsulfanyl-1-phenyl)pyrazol-5-yl]iminomethylenyl Ethyl Ether with Compounds Containing Amino Group and the Bioactivity of Products

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REACTIONS OF [(4-CYANO-3-METHYLSULFANYL-1-PHENYL)PYRAZOL-5-YL]IMINOMETHYLENYL ETHYL ETHER WITH COMPOUNDS CONTAINING AMINO GROUP AND THE BIOACTIVITY OF PRODUCTS

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The study on reaction of (1-phenyl-3-methylthio-4-cyanopyrazol-5-yl)-iminomethylene ethyl ether with compounds containing amino group was discussed in order to understand its reactivity. Some structures of compounds were verified by x-ray crystallographic study. The results of the bioassay showed that some of these compounds showed good fungicidal activities.

Keywords: Fungicidal activities; iminomethylene ethyl ether; N-(substituted)pyrazolyl methanimidamine; pyrazolo[3,4-d]pyrimidine; x-ray crystallography

INTRODUCTION

N-(substituted)phenyl methanimidamines were widely used as agrochemicals,[1] such as chlorodimeform,[2] amitraz.[3] In recent years, heterocycles is a very important consideration in a study on new pharmaceuticals and agrochemicals.[4] Many new agrochemicals containing pyrazole ring have been synthesised, such as fripronil.[5] Our earlier efforts were made to synthesize N-(substituted)pyrazolyl methanimidamines, the bioassay results showed that this kind of compounds exhibited good fungicidal activities.[6] In order to understand the reactivities of the intermediate, N-[(4-cyano-3-methylsulfanyl-1-phenyl)pyrazol-5-yl]methylenyl ethyl ether (**I**), and to broaden

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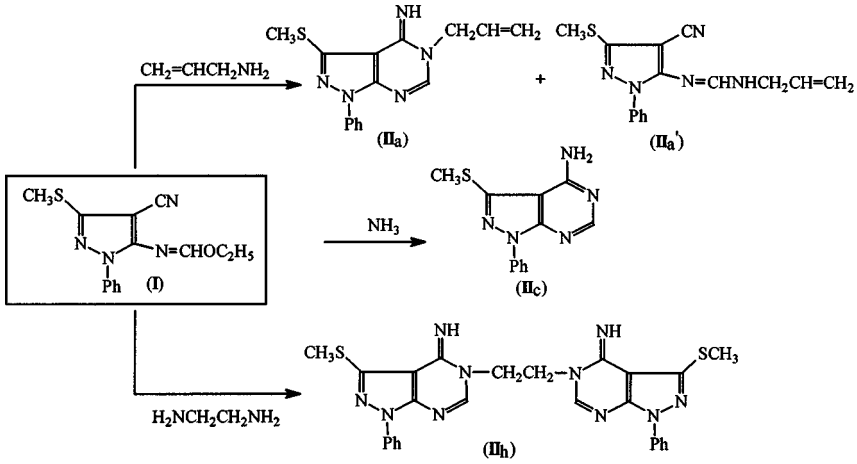
the usage of this kind of compounds, reactions of the intermediate N-pyrzolymethanimidate with compounds containing amino group were studied. And the biological activities of some products were investigated.

DISCUSSION AND RESULTS

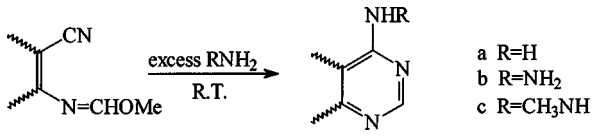
1. Reaction of I with Compound Containing Active Amino Group

In the reaction of **I** with allylamine, a pyrazolo[3,4-d]pyrimidine product $\mathbf{II_a}$ was observed. At the beginning of this reaction, only product $\mathbf{II_a'}$ produced. If the reaction time delays, $\mathbf{II_a'}$ became less and the main product is $\mathbf{II_a}$. But in the same condition when intermediate reacted with ammonium and ethyldiamine, only fused cyclic products were observed (Scheme 1).



SCHEME 1

Although the dimroth rearrangement occured in reaction of methanimidate with ammonia, hydrazine at room temperature (Scheme 2),[7,8] we did not find any 4-(substituted)amino-pyrazolo[3,4-d]pyrimidine product, but 4-imino-pyrazolo[3,4-d]pyrimidines.

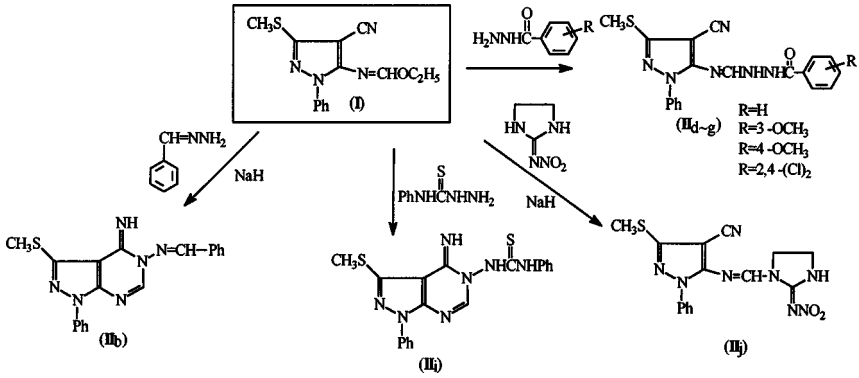


SCHEME 2

2. Reaction of I with Compound Containing Inactive Amino Group

When N-[(4-cyano-3-methylsulfanyl-1-phenyl)pyrazol-5-yl]methylenyl ethyl ether **I** reacted with (substituted)benzoyl hydrazine and phenyl thiosemicarbazide, the more reactive time was needed. The use of lewis acid, such as BF_3Et_2O, can shorten the reaction time. **I** reacted with phenyl thiosemicarbazide to give 4-imino-pyrazolo[3,4-d]pyrimidine product $\mathbf{II_I}$, but with benzoyl hydrazine to give compounds $\mathbf{II_{d\sim g}}$.

At room temperature, **I** can not react with benzenylhydrazone and 2-nitroiminoimidazolidine without any catalyst. The poor yield of the products with the catalysis of BF_3Et_2O may due to most of intermediate **I** decomposing into pyrazol-5-ylamine and N-(pyrazol-5-yl)formamide.[6] If NaH was added, the reaction occurred to give products in good yield, although pyrazol-5-ylamine was still observed.



SCHEME 3

3. Spectrum of the Products

The ^{1}H NMR data indicated that the proton of group N=CH in methanimidamine $\mathbf{II_a}$ showed double peak and the protons of group N=CH in pyrazolo[3,4-d]pyrimidines showed single peaks. Another evidence for the difference of the methanimidamine $\mathbf{II_a}'$ and pyrazolo[3,4-d]pyrimidine $\mathbf{II_a}$ is the C≡N stretching absorption band near 2200 cm^{-1}(s).

4. X-ray Crystallography Study of Compound II_i

In order to comfirm the structure further more, the 4-imino-pyrazolo[3,4-d]pyrimidine products $\mathbf{II_a}$,[9] $\mathbf{II_I}$ were characterized by x-ray diffraction. The perspective view of compound $\mathbf{II_i}$ is showed in

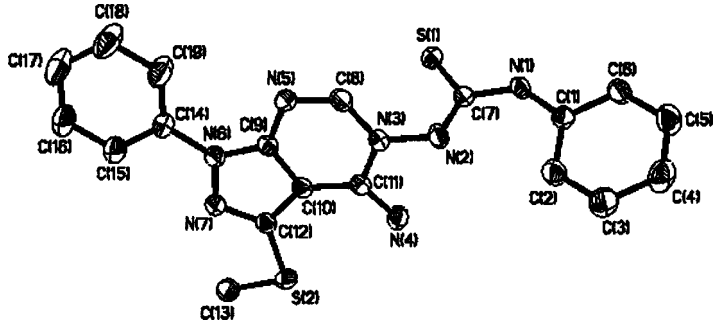


FIGURE 1 Perspective view of the compound $\mathbf{II_i}$ and the atomic labelling scheme.

Figure 1 and packing diagram of this compound in a unit cell is shown in Figure 2. Selected bond distances and angles with their estimated standard deviations are listed in Table I.

In this compounds, the C(11)=N(4) bond distance is 1.312 Å, slightly shorter the normal C=N bond distance (1.33 Å).[10] The plane defined by C(8), C(9), C(10), N(3), N(4), N(5), C(11), N(6), C(12), N(6), and S(2) atoms is coplanar within the average deviation of 0.0404 Å to form a fully delocalized system. The six-member ring of C(8), C(9), N(3), C(10), N(5), and C(11) atoms formed a π_6^7 configuration in which the N(3) atom is sp^2 hydrobrid which results in the formation of the trigonal configurations of the N(3) nitrogen. The sum of the C(8)-N(3)-C(11), C(8)-N(3)-N(2) and C(11)-N(4)-N(2) bond angles is 359.8°. In the unit cell, there is a weak action between S(2) and S(1) $(-x+1, -y+1,$

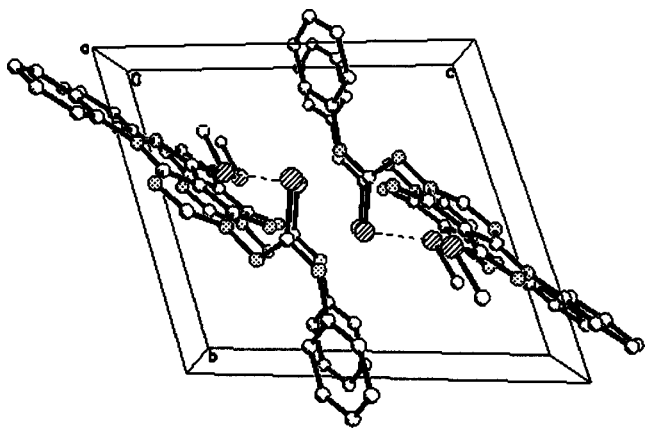


FIGURE 2 Packing diagram of the compound $\mathbf{II_i}$.

TABLE I Selected Bond Lengths [Å] and Angles [°] for Compound $\mathbf{II_i}$

C(1)-N(1)	1.414(4)	N(6)-C(9)	1.355(4)
N(1)-C(7)	1.356(4)	N(6)-N(7)	1.387(3)
S(1)-C(7)	1.716(3)	N(6)-C(14)	1.426(4)
N(2)-C(7)	1.327(4)	N(7)-C(12)	1.311(4)
N(2)-N(3)	1.407(3)	C(8)-N(5)	1.288(4)
S(2)-C(12)	1.736(3)	N(5)-C(9)	1.353(4)
S(2)-C(13)	1.789(3)	C(9)-C(10)	1.384(4)
N(3)-C(8)	1.366(4)	C(10)-C(11)	1.400(4)
N(3)-C(11)	1.368(4)	C(10)-C(12)	1.426(4)
N(4)-C(11)	1.312(4)		
C(2)-C(1)-N(1)	124.9(3)	C(8)-N(5)-C(9)	114.1(3)
C(6)-C(1)-N(1)	116.5(3)	N(5)-C(9)-N(6)	127.4(3)
C(7)-N(1)-C(1)	131.4(3)	N(5)-C(9)-C(10)	124.9(3)
C(7)-N(2)-N(3)	112.1(3)	N(6)-C(9)-C(10)	107.7(3)
C(12)-S(2)-C(13)	99.96(16)	C(9)-C(10)-C(11)	119.0(3)
C(8)-N(3)-C(11)	121.8(3)	C(9)-C(10)-C(12)	105.0(3)
C(8)-N(3)-N(2)	119.3(3)	C(11)-C(10)-C(12)	135.9(3)
C(11)-N(3)-N(2)	118.7(3)	N(4)-C(11)-N(3)	118.2(3)
C(9)-N(6)-N(7)	110.0(2)	N(4)-C(11)-C(10)	127.4(3)
C(9)-N(6)-C(14)	131.0(3)	N(3)-C(11)-C(10)	114.4(3)
N(7)-N(6)-C(14)	119.0(2)	N(7)-C(12)-C(10)	110.5(3)
C(12)-N(7)-N(6)	106.8(2)	N(7)-C(12)-S(2)	124.6(2)
N(2)-C(7)-N(1)	115.9(3)	C(10)-C(12)-S(2)	124.9(2)
N(2)-C(7)-S(1)	126.9(2)	C(19)-C(14)-N(6)	121.8(3)
N(1)-C(7)-S(1)	117.2(2)	C(15)-C(14)-N(6)	118.7(3)
N(5)-C(8)-N(3)	125.7(3)		

$-z+1$), the distance is 3.436 Å. And weak hydrogen bond N(1)—H(1A)$\cdots$S(1) ($-x+1$, $-y+1$, $-z+1$), N(4)—H(4C)$\cdots$S(1) ($-x+1$, $-y+1$, $-z+1$) exist, the distances are 3.575 Å and 3.332 Å respectively.

5. Biological Activities of Products

The results of bioassay showed that some of the products have good fungicidal activities. Table II was listed fungical activities of some products.

EXPERIMENTAL

All melting points were deterimined 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 $CDCl_3$ and $(CD_3)_2SO$ resolutions on FX-90Q and AC-P200 spectrometer, and chemical shifts were expressed in δ units using TMS as internal reference.

TABLE II Inhibition Rates of Some Products (%)

Compds.	P. zeae[a]	A. solani[a]	R. solani[a]	Palo[b]
II_a	23.5	50.0	30.0	/
II_a'	44.7	58.3	68.9	90.5
II_c	64.3	31.6	38.5	/
II_d	29.4	62.5	25.0	/
II_g	22.6	/	/	/

[a]In vitro at the concentration of 50 μg/ml.
[b]In vivo at the concentration of 500 μg/ml.

General Procedure for the Preparation of Compounds $II_{a,c,h,d\sim g,l}$[6]

To a solution of ethyl N-[1-Phenyl-4-cyano)pyrazol-5-yl]formimidate (0.96 g, 4 mmol) in anhydrous acetonitrile (15 ml) was added phenylthiosemicarbazide(0.67 g, 4 mmol) at room temperature. When compounds **I** disappeared tracing by TLC, the mixture was evaporated. The residue was purified by silica gel column to give the title compound (**II_i**).

General Procedure for the Preparation of Compounds $II_{b,j}$

To a solution of 2-nitroiminoimidazolidine (0.52 g, 4 mmol) in anhydrous acetonitrile (15 ml), 80% sodium hydride (0.18 g, 6 mmol) was added. After stirring one-half hour, a solution of ethyl N-[1-Phenyl-4-cyano)pyrazol-5-yl]formimidate (0.96 g, 4 mmol) in anhydrous acetonitrile (10 ml) was added. When compounds **I** disappeared tracing

TABLE III Physical Data and Elemental Analysis of Compounds **II**

			Elementary analysis: found (calcd.)		
Compd.	Yield (%)	m.p. (°C)	C	H	N
II_a	61.5	92–94	60.83(60.58)	4.86(5.08)	23.27(23.55)
II_a'	28.9	92–94	60.38(60.58)	5.00(5.08)	23.41(23.55)
II_b	66.4	218–220	60.67(60.62)	4.15(4.28)	22.26(22.32)
II_c	89.8	180–181	55.89(56.01)	4.13(4.31)	27.00(27.22)
II_d	74.4	140–142	60.60(60.62)	4.08(4.28)	22.34(22.32)
II_e	54.8	186–187	59.11(59.10)	4.21(4.46)	20.39(20.68)
II_f	45.9	148–150	59.36(59.10)	4.40(4.46)	20.57(20.68)
II_g	58.4	221–223	51.25(51.25)	3.15(3.17)	18.77(18.87)
II_h	57.3	258–260	57.77(57.76)	4.25(4.47)	25.63(25.91)
II_I	56.5	136–137	55.96(56.00)	4.22(4.20)	23.78(24.00)
II_j	89.3	246–248	48.65(48.64)	4.14(3.81)	29.91(30.25)

TABLE IV ^{1}H NMR Data of Compounds **II**

Compd.	^{1}H NMR ($CDCl_3$), δ
II$_a$	2.72(s, 3H, CH_3S), 4.66~4.74(m, 2H, N—CH_2), 5.18~5.40(m, 2H, CH_2=), 5.88~6.30(m, 1H, CH=), 7.30~7.58, 7.96~8.08(m, 5H, Ph-H), 7.78(s, 1H, Pyrimidine-H)
II$_a$′	2.56(s, 3H, CH_3S), 3.94~4.08 (m, 2H, —NCH_2), 4.72(bs, NH), 5.12~5.36 (m, 2H, C=CH_2), 5.68~6.10(m, 1H, C<u>H</u>=CH_2), 7.28~7.50, 7.58~7.84 (m, 5H, Ph-H), 8.36~8.40(d, 1H, N=CH)
II$_b$	2.76(s, 3H, CH_3S), 7.02~7.51(m, 9H, Ph-H), 8.06~8.11(d, 2H, N=CH), 8.46(s, 1H, NH=)
II$_c$	2.74(s, 3H, CH_3—S), 6.04~6.30(broad-s, 2H, N—H), 7.32~7.68, 8.12~8.34 (m, 5H, Ph-H), 8.46(s, 1H, Pyrimidine-H)
II$_d$	δ2.60(s, 3H, CH_3S), δ7.28~8.00(m, 10H, Ph-H), δ8.52(s, 1H, CH=N), δ10.60(broad-s, N—H)
II$_e$	δ2.54(s, 3H, CH_3S), δ3.68(s, 3H, CH_3O), δ7.04~7.92(m, 9H, Ph-H), δ8.54(s, 1H, CH=N), δ10.58(broad-s, N—H)
II$_f$	δ2.58(s, 3H, CH_3S), δ3.84(s, 3H, CH_3O), δ7.00~7.40, 7.80~8.00(m, 9H, Ph-H), δ8.48(s, 1H, CH=N), δ10.56(broad-s, N—H)
II$_g$	δ2.78(s, 3H, CH_3S), δ7.50~8.20(m, 8H, Ph-H), δ8.60(s, 1H, CH=N), δ9.90(broad-s, N—H)
II$_h$	2.56(s, 3H, CH_3—S), 2.68(s, 3H, CH_3—S), 3.64~88(m, 2H, CH_2—N), 4.16~4.32(m, 2H, CH_2—N), 7.30~8.10(m, 12H, Ph-H, Pyrimidine-H)
II$_i$	2.62(s, 3H, CH_3—S), 7.30~7.72(m, 11H, Ph-H, Pyrimidine-H)
II$_j$	δ2.56(s, 3H, CH_3S), δ3.66~3.84(m, 4H, —CH_2CH_2—), δ7.32~7.82(m, 5H, Ph-H), δ8.72(s, 1H, N=CH)

by TLC, the mixture was filtered. The solid was recrystallized from dimethylformide to give compound **II$_j$**.

Physical data and elemental analysis of compounds **II** are listed in Table III. Tables IV and V are ^{1}H NMR date and IR data of compounds **II** respectively.

TABLE V IR Data of Compounds **II**

Compd.	IR, ν/cm^{-1}					
	ν_{N-H}	$\nu_{C\equiv N}$	$\nu_{N=C,\ C=C}$			$\nu_{C=O}$
II$_a$	3296.0	/	1634.8	1592.6	1501.3	/
II$_a$′	3398.5	2200.0	1614.9	1500.0	1466.7	/
II$_b$	3380.5	/	1643.6	1591.5	1510.0	/
II$_c$	3437.5	/	1655.9	1587.8	1501.3	/
II$_d$	3197.0	2214.0	1592.7	1502.3	1468.6	1659.0
II$_e$	3268.5	2203.5	1612.6	1499.3	1479.6	1660.6
II$_f$	3243.0	2211.5	1592.7	1500.9	1450.7	1653.2
II$_g$	3207.0	/	1607.6	1497.8	1451.6	1657.4
II$_h$	3402.0	/	1643.9	1594.4	1502.3	/
II$_i$	3420.5	/	1647.3	1590.5	1497.6	/
II$_j$	3364.5	2214.5	1619.6	1592.4	1497.0	/

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