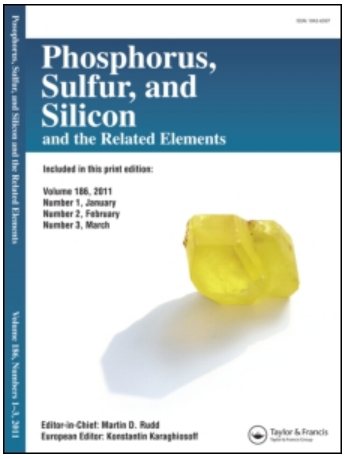

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SYNTHESIS AND STRUCTURE OF 4-PHENYL-1,3,4,4H-THIADIAZIN-5(6H)-ONE

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SYNTHESIS AND STRUCTURE OF 4-PHENYL-1,3,4,4H-THIADIAZIN-5(6H)-ONE

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4-Phenyl-1,3,4,4H-thiadiazin-5(6H)-one **2** was synthesized by the reaction of methyl carboxylatomethyl-*N*-anilinothioformimidate **1** with triethylamine in methanol and the structure of **2** was determined by X-ray analysis. The mechanism of formation of **2** is discussed.

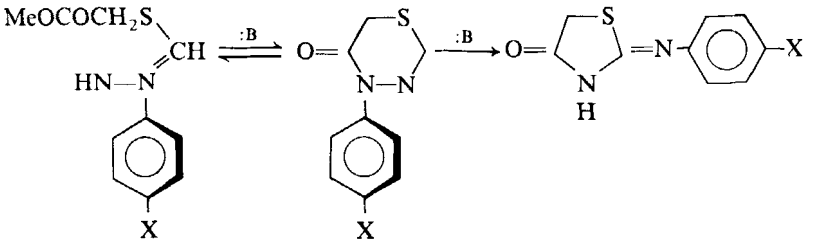
INTRODUCTION

The chemistry of thiazole and thiadiazole analogs has been a subject of increasing interest in recent years because of their use in pharmacological and synthetic applications,[1-4] but few papers have appeared on the chemistry of thiadiazinone except for the synthesis of 4-phenyl-1,3,4,4H-thiadiazin-5(6H)-one **2** from the reaction of methyl carboxylatomethyl-*N*-anilinothioformimidate **1** with sodium methoxide.[5] However, the authors have now found that the compound thus obtained by Sato *et al.* is not the thiadiazinone **2** but 2-phenylimino-1,3-thiazolidin-4-one and that **2** can be synthesized by the reaction of **1** with a weak base such as triethylamine in methanol. The present paper deals with the mechanistic pathway to and X-ray analysis of **2**.

RESULTS AND DISCUSSION

Reaction of Thioformimidate 1 with Bases

Sato and coworkers reported that a compound of mp 181°C (**A**) obtained by the reaction of **1a** with CH_3ONa in CH_3OH was the thiadiazinone.[5] We reinvestigated the reaction with the use of triethylamine instead of CH_3ONa and obtained a compound of mp 77–8°C (**B**). Compound **A** was not formed under these conditions. The compound **B** thus obtained has been found to give **A** by reaction with CH_3ONa in CH_3OH. The structural investigation of **A** by ^{1}H-NMR and IR-spectra revealed that **A** is 2-phenylimino-1,2-thiazolidin-4-one **3** which had already been synthesized by the reaction of 1-phenyl-2-thiourea and chloroacetic acid.[6] The X-ray analysis of **B** revealed that **B** is 4-phenyl-1,3,4,4H-thiadiazin-5(6H)-one **2**. Thus, it can be assumed that the reaction of **1** with CH_3ONa first gives the thiadiazinone **2** which is then converted to **3** by the action of a base although the rearrangement mechanism is not yet clear.[7]



1 **2** **3**

a: X = H
b: X = CH_3

X-ray Analysis

The structure of **B** was determined by the X-ray method to be thiadiazinone **2**. The ORTEP drawing (Figure 1) shows that the C(2)—O(1) group is almost coplanar with the S(1)—C(1)—N(1)—N(2) plane. The C(2)—N(2) and N(1)—N(2) distances are 1.38 and 1.40 Å, respectively, which are nearly equal to the corresponding single C—N (1.38 Å) and N—N (1.41 Å) distances, respectively. The N(1)—C(1) distance (1.27 Å) is a little longer than the localized double bond (1.23 Å) and the C(1)—S(1) distance (1.75 Å) is shorter than the usual single bond (1.81 Å).[8-9] Furthermore, the S(1)—C(2) distance (2.74 Å) is much shorter than the Van der Waals radii (3.0 Å) of each atom. These observations indicate that the π-electron delocalization takes place through the N(1)—C(1)—S(1)—C(2) plane involving a through-space interaction between S(1) and C(2) atoms.

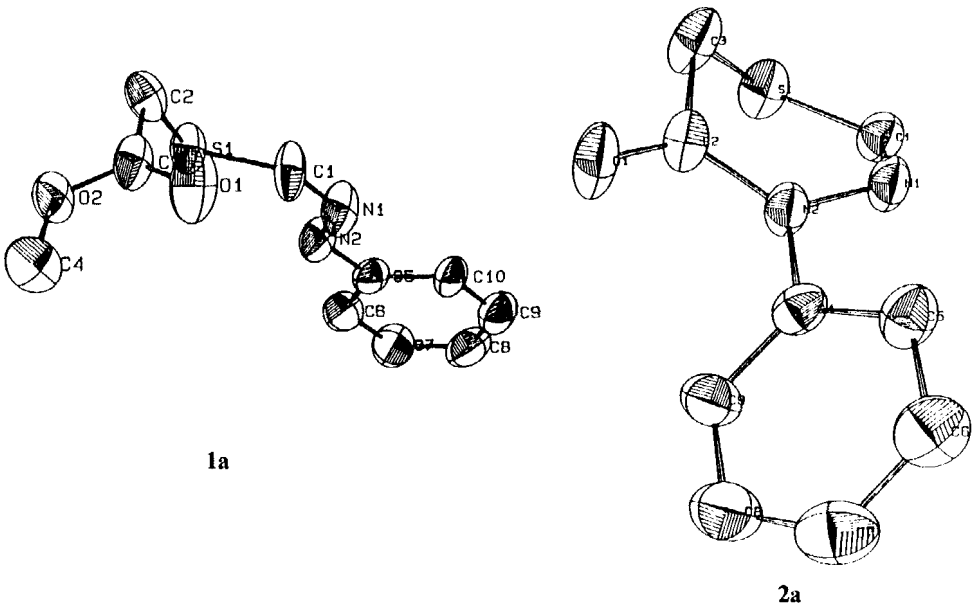
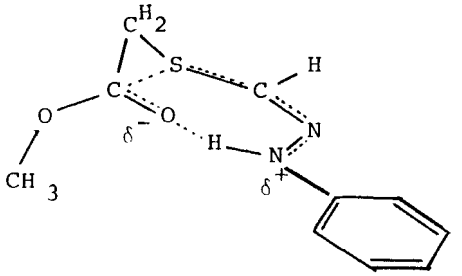
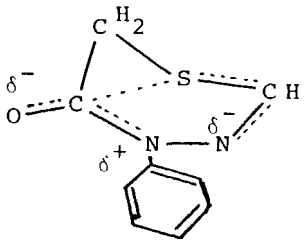


FIGURE 1 ORTEP drawing of compounds **1a** and **2a**.



$\nu_{C=O}$ 1710cm^{-1}
$\nu_{C=N}$ 1585cm^{-1}
ν_{NH} 3310cm^{-1}
(sharp and weak)

1a



$\nu_{C=O}$ 1650cm^{-1}
$\nu_{C=N}$ 1650cm^{-1}

2a

FIGURE 2

The X-ray analysis of **1** has also been carried out (Figure 1). The N(1)—N(2) distance (1.28 Å) and the S(1)—C(1) distance (1.69 Å) are much shorter than the single-bond length (1.41 Å) and (1.81 Å), respectively; the C(1)—N(1) distance (1.33 Å) is longer than the delocalized double bond (1.23 Å); and the S(1)—C(3) distance (2.93 Å) is shorter than the Van der Waals radii (3.0 Å) of each atom. Furthermore, the O(1)—N(2) distance is only 2.72 Å and a sharp and weak NH stretching frequency appears at 3310 cm^{-1} in the IR spectra. These observations indicate that the π-electrons of the thioformimidate group are delocalized through the seven-membered ring formed on the N(2)—N(1)—C(1)—S(1)—C(3)—O(1) plane involving the hydrogen-bonding interaction between N(2)H and O(1) and the through-space interaction between S(1) and C(3) atoms as shown in Figure 2.

Reaction Pathway

Several experiments have been conducted to elucidate the mechanism of formation of **2** from **1**. The reaction of either **1** or **2** with Et_3N in methanol was found to give a 1 : 2 mixture of **1** and **2** as determined by HPLC and ^{1}H-NMR spectral analysis, indicating that the formate **1** is in an equilibrium with **2**. Without Et_3N no reaction of either **1** or **2** occurs. Kinetic studies by UV spectroscopy (Table I, II) indicate that the reaction is of first order and that the rate equation is not a function of CH_3OH or Et_3N concentrations. The H—D exchange rates of **1**, **2** and other analogs were determined in CD_3OD in the presence of Et_3N by means of NMR spectroscopy (Table III). The half-life τ of **1** is nearly 0 and that of **2** is also very small. These features suggest that neither the aminolysis of **1** nor the alcoholysis of **2** proceeds in a conventional way, since the usual aminolysis of ester proceeds via general base catalysis, or without a base, and the alcoholysis of amide occurs under strongly acidic conditions or proceeds via the B_{AC} mechanism under basic conditions.[10–13] The authors wish to postulate a ketene as one of the most likely intermediates. Truce *et al.*[14] reported that the alcoholysis of carboxylic acid halides in the presence of

TABLE I

Initial reaction rate of **1a**[a]

Concentration mol · l^{-1}	Reaction Rate mol · l^{-1} · sec^{-1}
[I] = 1×10^{-1} [:B] = 1×10^{-1}	1.0×10^{-4}
[I] = 0.5×10^{-1} [:B] = 1×10^{-1}	0.42×10^{-4}
[I] = 1×10^{-1} [:B] = 2×10^{-1}	1.1×10^{-4}

[a]The reaction rates were determined by measuring appearance of **2a** at 240 nm and disappearance of **1a** at 285 nm in the presence of triethylamine (:B) in methanol at 45°C.

TABLE II

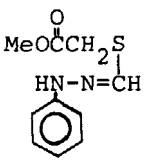
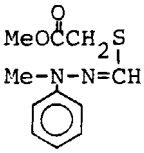
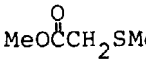
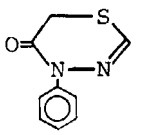
Rate and equilibrium constants for the reversible reaction [a]

	$k_1 + k_{-1}$	k_1	k_{-1}	k_1/k_{-1}[b]
1a	4.75	1.43	3.14	0.45
1b	3.52	1.53	1.99	0.77

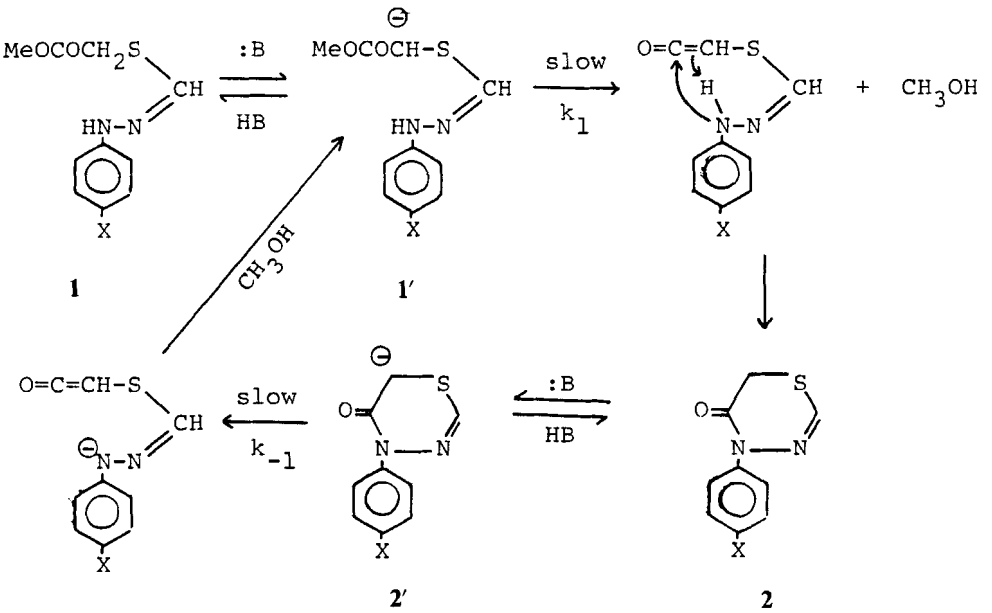
[a]In methanol at 45°C.
[b]$K = k_1/k_{-1}$.

TABLE III

H—D and CH_3O—CD_3O exchange rates in CD_3OD—$N(Et)_3$ system at 35°C[a]

Compounds		Rate τ (min) —CH_2—	Rate τ (min) —OCH_3
	**1a**	0	5
		35	150
		900	1400
	**2a**	30	—

[a][S] = 1 (mol/l), [$N(Et)_3$] = 1 (mol/l).



SCHEME 1

Et_3N proceeds largely by an elimination-addition process involving a ketene intermediate. α-Carbethoxy-β-phenylisovaleoyl chloride was known to give (α, α-dimethylbenzyl)carbethoxyketene in excellent yield by treatment with triethylamine.[15] Thus, the conversion of **1** to **2** is initiated by proton abstraction from the methylene group of **1** with a base to yield the rather stable deprotonated species (**1′**) which can then cleave slowly to the transient ketene intermediate in the following way (Scheme 1). The reaction of **2** to give **1** is similarly initiated by proton abstraction to give the anion (**2′**), followed by the formation of the ketene intermediate. Presumably, the addition of a nucleophile to the ketene is very fast. The stability of the deprotonated species **1′** and **2′** is apparently assisted by electron-accepting delocalization on the adjacent C=O and S groups. The π-electron delocalization as described in the X-ray section may also partly contribute to the stabilization of the deprotonated anions. The cleavage of the anions **1′** and **2′** to the ketene intermediate requires a rather pronounced conformational change from the stabilized resonance forms of **1** and **2** shown in Figure 2.

This leads to ketene formation as the rate determining step. Substituent effects on the rate constants, k_1 and k_{-1} in Table II, can be nicely explained by the ketene-intermediate mechanism.

EXPERIMENTAL

General Data. Melting points were obtained on a Yanaco hot-stage apparatus and are uncorrected. The ^{1}H-NMR spectra were recorded on a JEOL FX-200 NMR spectrometer at 200 MHz with TMS as an internal standard. Infrared spectra were run on a JASCO IR-Al spectrometer with the samples in potassium bromide pellets. Mass spectral data were obtained on a Shimadzu KLB-9000 GC-MS spectrometer. Absorption spectra were recorded on a Hitachi 124 spectrometer equipped with a

thermostat at 45 ± 0.1°C. High pressure liquid chromatography (HPLC) was run on a Yanaco L-2000 unit using a pre-packed column of Yanaco GEL-5510 (4 mm × 250 mm). Thin-layer chromatography and column chromatography were carried out using pre-coated Kieselgel 60-F254 sheets and Kieselgel 60 (240–400 mesh), respectively.

General Procedure for the Synthesis of **1** and **2**. A typical experiment was performed as follows:

Methyl carboxylatomethyl-N-anilinothioformimidate **1**. To a mixture of the thioformylphenylhydrazine (10 mmol) and sodium methoxide (10 mmol) in methanol (15 ml) was added dropwise methyl chloroacetate (10 mmol) under nitrogen atmosphere and the mixture was stirred for 3 hr at room temperature (25°C). The reaction mixture was evaporated in a vacuum and then the residue was extracted three times with ether. The ether extract was evaporated in a vacuum to give almost pure **1**.

Product **1a**. colorless needles from ligroin, yield 89%; mp 63–64°C. $C_{10}H_{12}N_2O_2S$, calc: C, 53.55; H, 5.39; N, 12.49. Found: C, 53.59; H, 5.43; N, 12.44. IR (KBr): $\nu_{C=O}$ = 1710 cm^{-1}, $\nu_{C=N}$ = 1585 cm^{-1}, ν_{NH} = 3310 cm^{-1} (sharp monomeric). ^{1}H-NMR ($CDCl_3$): δ = 3.45 (s, 2 H, $-CH_2-$), 3.62 (s, 3 H, $-OCH_3$), 7.01 (s, 5 H, Ph), 7.41 ppm (s, 1 H, —N=CH—).

Product **1b**. colorless needles from ligroin, yield 92%; mp 72–73°C. $C_{11}H_{14}N_2O_2S$, calc: C, 55.44; H, 5.92; N, 11.76. Found: C, 55.49; H, 5.97; N, 11.72. IR (KBr): $\nu_{C=O}$ = 1715 cm^{-1}, $\nu_{C=N}$ = 1580 cm^{-1}, ν_{NH} = 3320 cm^{-1} (sharp monomeric). ^{1}H-NMR ($CDCl_3$): δ = 2.16 (s, 3 H, $-CH_3$), 3.46 (s, 2 H, $-CH_2-$), 3.63 (s, 3 H, $-CH_3$), 6.87 (q, 4 H, Ph), 7.07 ppm (s, 1 H, —N=CH—).

TABLE IV

Experimental data for the X-ray diffraction studies

Parameter	**1a**	**2a**
Formula	$C_{10}H_{12}N_2O_2S_1$	$C_9H_8N_2OS$
Formula weight	224.3	192.2
Crystal system	monoclinic	orthorhombic
Space group	$P_{21/c}$	P_{bca}
a, Å	6.711(1)	17.175(4)
b, Å	15.402(5)	8.741(4)
c, Å	10.753(3)	12.039(2)
α,β,γ, deg	96.91(1)	
V, Å^3	1103.4	1807.4
Z	4	8
D, gcm^{-3}	1.35	1.41

TABLE V

Atomic coordinates for nonhydrogen atoms with their standard deviation in parentheses

	1a				**2a**		
Atom	X	Y	Z	Atom	X	Y	Z
S_1	−0.2293(2)	0.2532(1)	0.4205(1)	S_1	0.1536(1)	0.4451(1)	0.1883(1)
O_1	0.2694(9)	0.2938(5)	0.4198(5)	O_1	0.1589(3)	0.0355(5)	0.2947(3)
O_2	0.2016(7)	0.2809(3)	0.2229(4)	N_1	0.1567(3)	0.2244(5)	0.0320(4)
N_1	−0.2897(8)	0.3450(4)	0.6341(5)	N_2	0.1428(3)	0.1180(5)	0.1177(4)
N_2	−0.4677(8)	0.3732(4)	0.5963(5)	C_1	0.1582(4)	0.3671(7)	0.0544(5)
C_1	−0.1782(1)	0.2961(6)	0.5661(6)	C_2	0.1665(4)	0.1371(7)	0.2269(5)
C_2	0.0058(5)	0.1970(5)	0.3749(6)	C_3	0.2071(4)	0.2874(6)	0.2541(5)
C_3	0.1744(1)	0.2608(5)	0.3419(6)	C_4	0.1122(3)	−0.0250(6)	0.0770(5)
C_4	0.3629(3)	0.3402(6)	0.1851(8)	C_5	0.1457(4)	−0.0883(7)	−0.0178(5)
C_5	−0.5926(1)	0.4252(4)	0.6736(6)	C_6	0.1126(4)	−0.2229(7)	−0.0607(6)
C_6	−0.7596(3)	0.4619(5)	0.6238(7)	C_7	0.0495(4)	−0.2918(7)	−0.0079(6)
C_7	−0.8927(5)	0.1545(6)	0.6996(8)	C_8	0.0186(4)	−0.2286(8)	0.0887(6)
C_8	−0.8678(4)	0.5324(5)	0.8218(8)	C_9	0.0494(4)	−0.0923(7)	0.1318(6)
C_9	−0.7000(3)	0.4947(5)	0.0013(7)				
C_{10}	−0.5657(1)	0.4418(5)	0.7979(6)				

TABLE VI

Bond distances (Å) with their standard deviations in parentheses

1a		2a	
S(1)—C(1)	1.69(3)	S(1)—C(1)	1.75(2)
S(1)—C(2)	1.91(4)	S(1)—C(3)	1.83(6)
O(1)—C(3)	1.11(2)	O(1)—C(2)	1.21(2)
O(2)—C(3)	1.35(1)	N(1)—N(2)	1.40(3)
O(2)—C(4)	1.50(3)	N(1)—C(1)	1.27(1)
N(1)—N(2)	1.28(2)	N(2)—C(2)	1.38(2)
N(1)—C(1)	1.33(3)	N(2)—C(4)	1.44(4)
N(2)—C(5)	1.48(3)	C(2)—C(3)	1.52(4)
C(2)—C(3)	1.57(4)	C(4)—C(9)	1.39(4)
C(5)—C(6)	1.31(3)	C(4)—C(5)	1.39(3)
C(5)—C(10)	1.35(1)	C(5)—C(6)	1.40(4)
C(6)—C(7)	1.51(3)	C(6)—C(7)	1.39(4)
C(7)—C(8)	1.33(1)	C(7)—C(8)	1.39(3)
C(8)—C(9)	1.31(3)	C(8)—C(9)	1.40(4)
C(9)—C(10)	1.49(3)		

TABLE VII

Bond Angles (°) with their standard deviation in parentheses

1		2	
S(1)—C(1)—C(2)	109(1)	S(1)—C(1)—C(3)	94(2)
O(2)—C(3)—C(4)	125(1)	N(1)—N(2)—C(1)	119(1)
N(1)—N(2)—C(1)	125(1)	N(2)—C(2)—N(1)	124(1)
N(2)—N(1)—C(5)	124(1)	N(2)—C(2)—C(4)	122(1)
C(1)—S(1)—N(1)	131(1)	N(2)—N(1)—C(4)	112(1)
C(2)—S(1)—C(3)	114(1)	C(1)—N(1)—S(1)	124(1)
C(3)—O(1)—O(2)	118(1)	C(2)—O(1)—N(2)	121(1)
C(3)—O(1)—C(2)	118(1)	C(2)—O(1)—C(3)	122(1)
C(3)—C(2)—O(2)	122(2)	C(2)—N(2)—C(3)	116(2)
C(5)—N(2)—C(6)	121(1)	C(3)—C(2)—S(1)	108(1)
C(5)—N(2)—C(10)	129(1)	C(4)—C(9)—N(2)	119(2)
C(5)—C(6)—C(10)	109(2)	C(4)—C(9)—C(5)	122(2)
C(6)—C(5)—C(7)	122(1)	C(4)—N(2)—C(5)	118(2)
C(7)—C(6)—C(8)	128(1)	C(5)—C(4)—C(6)	117(2)
C(8)—C(7)—C(9)	107(2)	C(6)—C(5)—C(7)	120(2)
C(9)—C(8)—C(10)	125(1)	C(7)—C(6)—C(8)	120(2)
C(10)—C(5)—C(9)	126(1)	C(8)—C(9)—C(7)	120(2)
		C(9)—C(4)—C(8)	118(2)

N-Phenyl-1,3,4,4H-thiadiazin-5(6H)-one **2**. A mixture of **1** (10 ml) was stirred for 6 hr at room temperature. Progress of the reaction was monitored by LC on a reversed-phase column using methanol as a solvent. Methanol was then evaporated in a vacuum and the residue was extracted three times with 10 ml portions of ether. To a stirred ether extract was added a hard-acid type of ion-exchange resin (Amberlyst-15: 1 g) and the mixture was stirred at room temperature for 10 min. Then the reaction mixture was filtered and the resins were washed twice with 10 ml portions of ether. The filtrate was evaporated in a vacuum to give **2** in almost pure form.

Product **2a**: colorless needles from ligroin, yield 44%; mp 77–78°C. $C_9H_8N_2OS$, calc: C, 55.25; H, 4.17; N, 14.49. Found: C, 55.28; H, 4.20; N, 14.53. IR (KBr): $\nu_{C=O}$ = 1650 cm^{-1}, $\nu_{C=N}$ = 1650 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 3.77 (s, 2 H, —CH_2—), 7.40 (s, 5 H, Ph), 7.73 ppm (s, 1 H, —N=CH—). MS (70 eV): m/e (relative intensity) = 192 (M^+, 100), 92 (M − 100, 90) 77 ($C_6H_5^+$, 58).

Product **2b**. colorless needles from ligroin, yield 61%; mp 95–97°C. $C_{10}H_{10}N_2OS$, Calc: C, 58.22; H, 4.89; N, 13.58. Found: C, 58.01; H, 4.76; N, 13.51. IR (KBr): $\nu_{C=O}$ = 1668 cm^{-1}, $\nu_{C=N}$ = 1668 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 2.33 (s, 3 H, $-CH_3$), 3.51 (s, 2 H, $-CH_2-$), 7.23 (broad s, 4 H, Ph), 7.68 ppm (s, 1 H, $-N=CH-$). MS (70 eV): m/e (relative intensity) = 206 (M^+, 100), 106 (M − 100, 98), 91 ($CH_3C_6H_4^+$, 61).

X-Ray Analysis of **1** *and* **2**. Single crystals of compounds **1** and **2** were prepared by slow crystallization from hexane. Crystals with dimensions of 0.41 × 0.33 × 0.38 mm for **1** and of 0.48 × 0.43 × 0.40 mm for **2** were used for data collection. All the measurements were performed on a Rigaku AFC-5 diffractometer using graphite-monochromated Mo K_α radiation (λ = 0.7107 Å). The cell parameters were determined by least-squares fitting of 25 reflections in the range of 28° < 2θ < 37°. The intensities of reflections with 2θ values up to 50° were collected by the scan technique (2$\theta \leqq$ 30°) or 2θ scan technique (30° < 2θ < 50°) with a scan rate of 4°/min. The structures were solved by the direct method using a MULTAN 78 program, and were refined by full-matrix least-squares method, minimizing the function $\Sigma_\omega(F_0 - F_0)^2$ with $\omega = \sigma^{-2}$. The last cycles of refinement, which included an isotropic thermal parameters converged the discrepancy factors R (1a: 0.098 for 2001 observed reflections and 2a: 0.077 for 1272 observed reflections), respectively. The crystal data were given in Tables IV–VI.

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