Reactions of 1,2,4-Triazines with Nitromethide Ion. A Convenient Method of Preparation of 1,2,4-Triazin-5-ylcarbaldehyde Oximes and their Synthetic Applications [1]

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Dedicated to Professor M. Tišler on the occasion of his 70th birthday

An efficient procedure for the preparation of 1,2,4-triazin-5-ylcarbaldehyde oximes **2a-f** from 1,2,4-triazines **1a-f** and nitromethide ion is described. The oximes **2c-d** were converted into corresponding 5-cyano-1,2,4-triazines **6c-d**. The latter compounds react easily with various nucleophiles to afford 5-substituted 1,2,4-triazines **7a-i** and with 1-pyrrolidino-1-cyclohexene to form cyano derivative of 5,6,7,8-tetrahydroisoquinoline **9**.

Direct introduction of substituents into the 1,2,4-triazine ring has been thoroughly studied during last decade and several new methods involving nucleophilic displacement of hydrogen such as oxidative amination [2], vicarious nucleophilic substitution [3], arylation with organometalic compounds [4] and nucleophilic acylation with alkyl nitronate anions [5] have been elaborated. The latter reaction has shown considerable synthetic utility and allows a highly efficient entry into alkyl 5-(1,2,4-triazinyl) ketones which may serve as intermediates to a variety of other heterocyclic systems possessing interesting pharmacological activity [6]. In this paper we show that regioselective reaction can be extended to direct introduction of protected formyl substituent into 1,2,4-triazine ring using nitromethide ion generated from nitromethane and potassium hydroxide (Scheme 1) [7].

Scheme 1
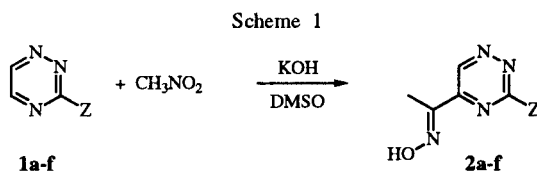
Treatment of 1,2,4-triazine **1a** with nitromethane in the presence of powdered potassium hydroxide in dry dimethyl sulfoxide at room temperature for one hour afforded of 1,2,4-triazin-5-ylcarbaldehyde oxime **2a** in good isolated yield (79%). Under these conditions other possible regioisomers were not formed. The stereochemistry of such obtained oxime **2a** was assigned from the nmr δ value of hydroxyimino group as well as by NOE difference spectroscopy [8] to have the *E* configuration.

As with the unsubstituted 1,2,4-triazine **1a**, 3-methyl-1,2,4-triazine **1b** and 3-phenyl-1,2,4-triazine **1c** react efficiently with nitromethide ion giving exclusively 5-substitution products.

Similar behaviour was observed with 1,2,4-triazines **1d-e** which contain nucleofugal groups at C-3. Both compounds gave 1,2,4-triazin-5-ylcarbaldehyde oximes **2d** and **2e** under the conditions employed with **1a-c**. The moderate yield of **2e** may be explained by a competitive dimerization process leading to 3,3'-bis(methylthio)-5,5'-bi-1,2,4-triazine **3** (15%), thus partly consuming the starting 3-methylthio-1,2,4-triazine **1e**. Interestingly, under the applied reaction conditions no substitution of the nucleofugal groups takes place although it is well known, that alkyl 3-(1,2,4-triazinyl) sulfides easily undergo *ipso* substitution of alkyltio group with nucleophilic agents [9]. Finely, we have examined the reaction of 3-(*N*,*N*-dimethylamino)-1,2,4-triazine **1f** with nitromethide ion. As could be expected the reaction with less electrophilic **1f** proceeds more slowly (7 hours) (and in lower yield) than the remaining triazines **1a-e** (Table 1).

1,2,4-Triazines which are blocked at the most active 5-position, *i.e.* 5-phenyl- and 3,5-diphenyl-1,2,4-triazines are practically unreactive on substitution with nitromethide ion. With 5-phenyl-1,2,4-triazine **4** only a few percent of 3-nitromethyl-5-phenyl-1,2,4-triazine **5** was obtained in addition to unconsumed **4**.

The oximes of 5-formyl-1,2,4-triazines prepared in this way can be readily converted into the corresponding 5-cyano-1,2,4-triazines. It is well known that the cyano substituent at the 5-position of the 1,2,4-triazine ring is an efficient leaving group in reactions with nucleophiles [10,11]. A disadvantage of this route to functionalized 1,2,4-triazines however is the fact that some of the required 5-cyano-1,2,4-triazines are not readily obtained and must often be prepared by multistep synthesis [12]. We thus attempted to synthesize two representatives of this class, *i.e.* 5-cyano-3-phenyl-1,2,4-triazine **6c** and 5-cyano-3-isopropylthio-1,2,4-triazine **6d** from 1,2,4-triazin-5-ylcarbaldehyde oximes **2c** and **2d**.

Table I

1,2,4-Triazin-5-ylcarbaldehyde Oximes **2a-f**

2	Z	Yield % [a]	Mp °C	Formula	Analyses % Calcd./Found			¹H NMR δ ppm [c]
					C	H	N	
a	H	79	138-139	C₄H₄N₄O (124.13)	38.70 38.93	3.24 2.99	45.15 44.76	[d]
b	CH₃	91	139-140	C₅H₆N₄OxH₂O (156.15)	38.45 38.62	5.16 4.97	35.88 35 73	[d]
c	Ph	78	172-173 [b]	C₁₀H₈N₄O (200.20)	60.00 59.84	4.03 3.73	27.99 28.25	[d]
d	SCH(CH₃)₂	74	115-116 [b]	C₇H₁₀N₄SO (198.25)	42.41 42.41	5.08 4.99	28.26 28.46	[d]
e	SCH₃	40	157-158	C₅H₆N₄SO (170.19)	35.29 35.21	3.55 3.61	32.92 33.19	[d]
f	N(CH₃)₂	41	200-201	C₆H₉N₅O (167.17)	43.11 43.16	5.43 5.42	[e]	2.97 (s 6H), 8.50 (s, 1H), 8.95 (s, 1H), 12.55 (s, 1H)

[a] Non optimized yields. [b] Recrystalized from an ethanol - water mixture. [c] In DMSO. [d] For nmr δ - value *see* reference 8. [e] Large number of nitrogens in compound **2f** led to variability in the microanalytical data of nitrogen atom.

We were unable to convert aldoxime **2c** to its nitrile **6c** by standard methods (phosphorus pentoxide, triethyl phosphate) however, dehydration of **2c** using phenyl isocyanate in boiling benzene with a catalytic amounts of triethylamine proceeded smoothly to provide the crystalline 5-cyano-3-phenyl-1,2,4-triazine **6c** almost quantitatively. Compound **6c** was identified by means of elemental analysis, nmr and mass spectroscopy data (see experimental section). In the ir spectra of **6c** there is no absorbtion band characteristic for the cyano group [13]. Similarly, treatment of **2d** under the conditions employed with **2c** gave 5-cyano-3-isopropylthio-1,2,4-triazine **6d** as a yellow oil in good yield.

We have found that both cyano compounds react easily with ammonia, amines, potassium hydroxide, sodium ethoxide and some carbon nucleophiles under mild conditions to provide the 5-substituted-1,2,4-triazines **7a-i** (Scheme 2).

Scheme 2

6c-d   + Nu ⟶   **7a-i**

↓ NH₂OH

7j
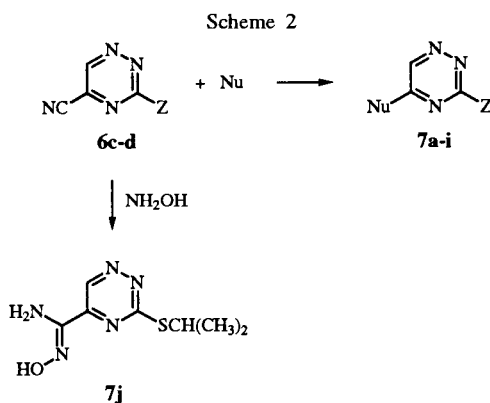
The choice of nitrogen nucleophiles used in this study is not large but it shows that ammonia generally afford higher yields than secondary amines as would be expected on steric

considerations. Also 5-cyano-3-isopropylthio-1,2,4-triazine **6b** was found to undergo nucleophilic displacement of the cyano group exclusively: we did not observe any competitive attack of nucleophile on C-3 carbon bearing the isopropylthio group. Also, substitution of the cyano group took place in the reaction of **6b** with the carbanion derived from chloromethyl phenyl sulfone. This is the case that substitution of cyano group occurs faster than the vicarious nucleophilic substitution of hydrogen at the 6-position of the triazine ring: only traces of the vicarious nucleophilic substitution product could be detected by nmr in the crude precipitate. On the other hand no substitution of the cyano group was observed in the reaction of **6d** with hydroxylamine hydrochloride in a 1:1 mixture of dioxane-water in the presence of potassium carbonate: 3-isopropylthio-1,2,4-triazin-5-ylcarboxamide oxime **7j** was obtained which resulted from addition of the nucleophile to the cyano group.

The potential of 5-cyano-1,2,4-triazines for synthesis of more elaborate ring systems is illustrated by reaction of **6d** with cyclohexanone derived enamine. It was well established that 1,2,4-triazines bearing electron withdrawing substituents undergo [4+2] cycloaddition reactions with electron-rich dienophiles (LUMO diene-controlled Diels-Alder reaction with inverse electron demand) [15]. Thus treatment of the cyano compound **6d** with a two molar excess of 1-pyrrolidino-1-cyclohexene in boiling dioxane furnished addition product **8** obtained *via* nitrogen extrusion from the initially formed highly strained cycloadduct (Scheme 3).

The ¹H nmr spectra of the product have shown that two isomeric hexahydroisoquinolines (compounds **8a,b**) are formed in this transformation [16]. Attempted separation of these stereoisomers failed, owing to their very similar

Table II
5-Substituted 1,2,4-Triazines 7a-i

7	Z	Nu	Yield % [a]	Mp °C	Formula	Analyses Calcd./Found			^{1}H NMR δ ppm
						C	H	N	
a	Ph	-NH$_2$	90	252-253 [b] (ethanol-chloroform)					
b	SCH(CH$_3$)$_2$	-NH$_2$	91	156-157 (ethanol-chloroform)	C$_6$H$_{10}$N$_4$S (170.23)	42.33 42.30	5.92 6.11	32.90 32.90	(DMSO-d$_6$): 1.5 (d, 6H, J = 6 Hz), 3.82 (m, 1H, J = 6Hz), 7.65 (bs, 2H), 8.35 (s, 1H)
c	SCH(CH$_3$)$_2$	⬡N-	61	35-36 (hexane)	C$_{11}$H$_{18}$N$_4$S (238.32)	55.42 55.46	7.60 7.62	23.50 23.58	(CDCl$_3$): 1.40-4.0 (m, 17H), 8.72 (s, 1H)
d	SCH(CH$_3$)$_2$	O⬡N-	74	74-75 (hexane)	C$_{10}$H$_{16}$N$_4$SO (240.34)	49.98 49.99	6.70 6.72	23.31 23.37	(CDCl$_3$): 1.4 (d, 6H, J = 5.8 Hz), 3.30-4.50 (m, 9H), 8.4 (s, 1H)
e	Ph	-OH	90	244-246 [c] (ethanol)					
f	SCH(CH$_3$)$_2$	-OC$_2$H$_5$	70	liquid	C$_8$H$_{13}$N$_3$SO (199.23)	48.22 48.00	6.57 6.83	21.08 21.54	(CDCl$_3$): 1.1-1.7 (m, 9H), 4.15 (m, 1H), 4.60 (q, 2H), 8.50 (s, 1H)
g	SCH(CH$_3$)$_2$	-CH(CN)(CO$_2$Et)	75	204-205 (ethanol-water)	C$_{11}$H$_{14}$N$_4$SO$_2$ (266.34)	49.62 49.45	5.29 5.22	21.04 20.95	(DMSO-d$_6$): 1.15-1.60 (m, 9H), 3.9-4.4 (m, 3H), 9.1 (s, 1H)
h	Ph	-CH$_2$NO$_2$	83	104-105 (ethanol-water)	C$_{10}$H$_8$N$_4$O$_2$•H$_2$O (234.17)	51.29 51.33	4.30 4.09	23.92 23.94	(DMSO-d$_6$): 6.05 (s, 2H), 7.7-8.2 (m, 2H), 9.8 (s, 1H)
i	Ph	-CH(Cl)(SO$_2$Ph)	68	145-146 (ethanol-water)	C$_{16}$H$_{12}$N$_3$SO$_2$Cl (345.75)	55.57 55.65	3.49 3.57		(CDCl$_3$): 6.30 (s, 1H), 7.40-8.80, (m, 10H), 9.70 (s, 1H) [d]

[a] Non optimized yields. [b] Reference [2], mp 252-253°C. [c] Reference [14], mp 244-245°C, [d] The ^{1}H nmr spectra of the crude precipitate showed a low intensity signal at δ = 4.95 ppm. The signal can be attributed to CH$_2$ group being present in the vicarious nucleophilic substitution product at C-6.

Scheme 3
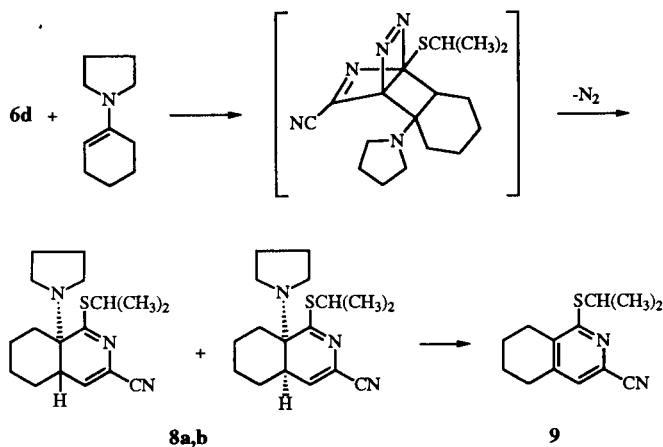
chromatographic behaviour. However, it was found that the mixture can be easily transformed into the tetrahydroisoquinoline 9 by acid-catalyzed elimination of pyrrolidine with acetic acid.

In conclusion, these reactions complement the earlier studies with alkyl nitronate anions and greatly extend the versatility of using readily available cyano derivatives of 1,2,4-triazine for organic synthesis.

EXPERIMENTAL

Melting points were determined on a Buchi melting point apparatus and are uncorrected. The ir spectra were recorded on a Unicam SP-200 instrument. The nmr spectra were recorded in deuteriochloroform or deuteriodimethyl sulfoxide solutions on Varian EM-360L or Bruker AC-80 spectrometers. Mass spectral measurements were carried out with AMD 604 Inectra spectrometer.

The starting materials were prepared according to known procedures: 1,2,4-triazine, 3-methylthio-1,2,4-triazine, 5-phenyl-1,2,4-triazine 1a, 1e and 4 [17], 3-methyl- and 3-pheny-1,2,4-triazines (1b and1c) [18], and 3-(N,N-dimethyl)-1,2,4-triazine 1f [19].

3-Isopropylthio-1,2,4-triazine (1d).

A solution of 5.0 g (0.055 mole) of thiosemicarbazide and 9.35 g (0.055 mole) of 2-iodopropane with 40 ml of absolute ethanol was stirred and refluxed for 5 hours. Ethanol was then evaporated in vacuo. A solution of 7.95 g (0.055 mole) of 40% glyoxal and 4.62 g (0.055 mole) of sodium bicarbonate in 100 ml of water was added to the brown residue. The mixture was stirred at room temperature for 3 hours and an additional 12 hours at 5°. The resulting precipitate was filtered. The filtrate was extracted with chloroform. After evaporation of the solvent from the combined extracts, the remaining oily residue was distilled at 82°/ 0.8 mm to yield 6.47 g (76%) of a yellow oil which crystallized after cooling, mp 23°; ^{1}H nmr (deuteriochloroform): δ 1.55 (d, 6H), 4.07 (m, 1H), 8.37 (d, 1H, J = 2.5 Hz), 8.92 (d, 1H, J = 2.5 Hz).

Anal. Calcd. for $C_6H_9N_3S$ C, 46.43; H, 5.84; N, 27.07. Found: C, 46.36: H, 5.83; N, 27.09.

1,2,4-Triazin-5-ylcarbaldehyde Oximes 2a-f.

To a stirred suspension of powdered potassium hydroxide (4 g) in dry dimethyl sulfoxide (20 ml) a solution of the 1,2,4-triazine 1 (0.01 mole) and nitromethane (0.03 mole) in dimethyl sulfoxide (1-2 ml) was added at once at room temperature. The mixture was stirred at room temperature for 1 hour, then was poured into ice/water (100 ml) and acidified with acetic acid. The products, 2a, 2b, 2e and 2f, were isolated by extraction with ether. The precipitated solids 2e, 2d were collected by filtration and washed with water. The crude products were purified by recrystallization from ethanol-water mixture 2c, 2d, or by chromatography, 2a, 2b, 2e, 2f, using chloroform-acetone (20:1) as the solvent (Table I).

5-Phenyl-3-nitromethyl-1,2,4-triazine (5).

Compound 5 prepared from 5-phenyl-1,2,4-triazine 4 1.57 g (0.01 mole) and nitromethane 1.83 g (0.03 mole) as described above was purified by column chromatography using chloroform-acetone (10:1) as the solvent to afford 129 mg (6%) of 5, mp82-83°; ir (potassium bromide): 1555, 1354 cm^{-1} (NO$_2$); ^{1}H nmr (deuteriochloroform): δ 6.07 (s, 2H) 7.50-7.80 (m, 3H), 8.20-8.45 (m, 2H), 9.77 (s, 1H); hrms; m/z 216.0646. Calcd. for $C_{10}H_8N_4O_2$: 216. 0647.

5-Cyano-3-phenyl-1,2,4-triazine (6c).

To a solution of 2c (2.0 g, 0.01 mole) and triethylamine (0.1 g, 0.001 mole) in 50 ml of dry benzene, phenyl isocyanate (2.38 g, 0.02 mole) was added under nitrogen at room temperature and the resulting reaction mixture was stirred and refluxed for 2 hours. After that time the precipitate was filtered off. The filtrate was evaporated *in vacuo* and the crude product containing 6c and diphenylurea was purified by column chromatography (silica gel eluent; chloroform) to give 1.7 g (95%) of yellow solid, mp 96-97 °; ^{1}H nmr (deuteriochloroform): δ 7.40-8.01 (m, 3H), 8.52-8.92 (m, 2H), 9.35 (s, 1H); ms: m/z 182 (M$^+$).

Anal. Calcd for $C_{10}H_6N_4$: C, 65.91; H, 3.32; N, 30.75 Found: C, 66.06; H, 3.08; N, 30.69.

5-Cyano-3-isopropylthio-1,2,4-triazine (6d).

Compound 6d prepared from 2d (1.98 g, 0.01 mole), triethylamine (0.1 g, 0.001 mole) and phenyl isocyanate (2.38 g, 0.02 mole) as described above was distilled at 105°/1 mm to yield 1.44 g (80%) of yellow oil; ^{1}H nmr (deuteriochloroform): δ 1.45 (d, 6H, J = 6.25 Hz), 4.05 (m, 1H), 9.10 (s, 1H).

Anal. Calcd for $C_7H_8N_4S$: C, 46.64; H, 4.48; N, 31.09. Found: C, 46.78; H, 4.46; N, 30.99.

5-Amino-3-phenyl-1,2,4-triazine (7a) and 5-Amino-3-isopropyl-thio-1,2,4-triazine (7b).

5-Cyano-3-phenyl-1,2,4-triazine (6c) (1 mmole) or 5 cyano-3-isopropylthio-1,2,4-triazine (6d) (1 mmole) was added to 10 ml of dry liquid ammonia with exclusion of moisture. After the mixture was stirred for 1 hour at -33°, the ammonia was evaporated. Crude solid 7a or 7b was washed with water and then recrystallized from chloroform-ethanol (Table II).

3-Isopropylthio-5-(1-piperidylo)-1,2,4-triazine (7c) and 3-Isopropylthio-5-(4-morpholinylo)-1,2,4-triazine (7d).

To a solution of 0.18 g (1 mmole) of 6d in 3 ml of ethyl ether was added 0.17 g (2 mmoles) of piperidine to prepare 7c or

0.174 g (2 mmoles) of morpholine to prepare 7d. The reaction mixture was stirred at room temperature for 1 hour. The precipitate was filtered. The solvent was evaporated under reduced pressure and the resulting solid, 7c or 7d was recrystallized from a satisfactory solvent (Table II).

3-Phenyl 5-oxo-2,5-dihydro-1,2,4-triazine (7e).

To 5 ml of 0.1 *N* aqueous sodium hydroxide solution was added 0.18 g (1 mmole) of 6c. The resulting mixture was stirred at room temperature for 30 minutes. The mixture was acidified with 1*N* aqueous hydrochloric acid. The precipitate that formed was filtered to give 0.15 g of 7e which was recrystallized from ethanol (Table II).

5-Ethoxy-3-isopropylthio-1,2,4-triazine (7f).

To a solution of sodium ethoxide, 68 mg (1 mmole) in 5 ml of ethanol, was added 180 mg (1 mmole) of 6d. The mixture was stirred at room temperature for 10 minutes. The solvent was evaporated to dryness and the residue was chromatographed on silica gel and eluted with chloroform. Evaporation of the chloroform eluants afforded 139 mg of colourless oil 7f (Table II).

5-(1-Cyano-1-ethoxycarbonylomethyl)-3-isopropylthio-1,2,4-triazine (7g).

To a solution of 0.226 g (2 mmoles) of ethyl cyanoacetate in 5 ml of dry tetrahydrofuran was added 0.2 g (2 mmoles) of a 48% oil dispersion of sodium hydride in 3 ml of tetrahydrofuran. After being stirred at room temperature for 30 minutes, the resulting mixture was cooled in an ice-water bath and 0.18 g (1 mmole) of 6d was added. The mixture was stirred at 0° for an additional 5 hours. Water was added to form a precipitate which was filtered and recrystallized from ethanol-water to give 0.199 g of 7g (Table 11).

5-Nitromethyl-3-phenyl-1,2,4-triazine (7h) and 3-Phenyl-5-phenylsulfonylchloromethyl-1,2,4-triazine (7i)

To a stirred suspension of powdered potassium hydroxide (0.4 g) in dimethyl sulfoxide (2-3 ml) a solution of 0.18 g (1 mmole) of 6c and 0.122 g (2 mmole) of nitromethane in 1 ml of ethyl ether (to prepare 7h) or 0.18 g (1 mmole) of 6c and 0.2 g (1 mmole) of chloromethyl phenyl sulfone in 1 ml of dimethyl sulfoxide to prepare 7i was added dropwise at 20-25°. The reaction was carried out at room temperature for 1 hour, then the mixture was poured into ice/water and acidified with acetic acid. The resulting precipitate of 7h or 7i was recrystallized from a satisfactory solvent (Table II).

3-Isoprophyltio-1,2,4-triazin-5-yl-carboxamide Oxime (7j).

To a solution of 0.18 g (1 mmole) of 6c in 10 ml of 1:1 mixture of dioxane-water was added 0.136 g (2 mmoles) of hydroxylamine hydrochloride and 0.276 g (2 mmoles) of potassium carbonate. The resulting solution was stirred at room temperature for 3 hours. The precipitate was filtered and recrystallized from ethanol water mixture to give 0.18 g (85%) of 7j, mp 138-139°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.40 (d, 6H), 4.17 (m, 1H), 6.05 (bs, 2H), 9.30 (s, 1H), 11.01 (s, 1H); ir (potassium bromide): 3460, 2320, 1655 cm^{-1}.

Anal. Calcd. for $C_7H_{11}N_5SO$: C, 39.41; H, 5.16; N, 32.82. Found: C, 39.39; H, 5.16; N, 32.98.

3-Cyano-1-isopropylthio-5,6,7,8-tetrahydroisoquinoliine (9).

A solution of 0.18 g (1 mmole) of 6c and 1-pyrrolidino-1-cyclohexene 0.30 g (2 mmoles) in dry 1,4-dioxane (5 ml) was

refluxed for 2 hours under an atmosphere of argon. The volatile components were distilled off under reduced pressure and the residue was chromatographed on silica gel and eluted with chloroform. The evaporation of eluants afforded 3-cyano-1-iso-propylthio-4a,5,6,7,8,8a-hexahydro-8a-(1-pyrrolidino)-isochinoline **8a,b** (65%) as a yellow oil; ^{1}H nmr (deuterio-chloroform): δ 1.30-1.34 (m, 6H), 1.48-1.51 (m, 4H), 1.71-1.77 (m, 6H), 1.98 (m, 1H), 2.50-2.53 (m, 2H), 2.64-2.70 (m, 2H), 2.80-2.93 (m, 2H), 3.84 (m, 1H), 6.22-6.30 (m, 1H; two sets of signals in a ratio 4.5:1); hrms: m/z (M+H) 304.1833. Calcd. for $C_{17}H_{26}N_3S$: 304.1833.

The solution of **8a/8b** mixture 0.152 g (0.5 mmole) in 5 ml of acetic acid was refluxed for 2 hours. The solvent was evaporated *in vacuo*. The oily residue was dissolved in 1 ml of water and extracted with ethyl ether. The solvent was evaporated and the resulting solid was purified by tlc (silica gel/chloroform) to afford 58 mg (50%) of **9**, mp 66-67°; ^{1}H nmr (deuterio-chloroform): δ 1.40 (d, 6H, J = 6.8 Hz), 1.71-1.90 (m, 4H), 2.53 (m, 2H), 2.70 (m, 2H), 4.23 (m, 1H), 7.10 (s, 1H); hrms: m/z = 232.1031 Calcd. for $C_{13}H_{16}N_2S$: 232.1034.

Anal. Calcd. for $C_{13}H_{16}N_2S$: C, 67.20; H, 6.89; N, 12.06. Found: C, 67.37; H, 7.13; N, 11.67.

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