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Regioselective Synthesis of 1,2,4-Triazol-3(2H)-ones and their 3(2H)-Thiones: Kinetic Studies and Selective Pyrolytic Deprotection

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ABSTRACT: *Selective pyrolytic deprotection of 2-ethyl and 2-cyanoethyl-4-arylidenimino-1,2,4-triazol-3(2H)-ones and their 3(2H)-thiones was studied by flash vacuum pyrolysis. This study is useful in regioselective synthesis of 2- and 4-substituted 1,2,4-triazoles of potential biological applications. The kinetic results and product analysis lend support to a reaction pathway involving a six-membered transition state.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:50–55, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10086

INTRODUCTION

Electrophilic substitutions of asymmetric heterocyclic urea and thiourea derivatives (represented here by 1,2,4-triazol-3(2H)-ones and their 3-thione derivatives) are known to give mixtures of different regioisomeric products [1]. This usually leads to tedious separation and identifications. We have recently demonstrated the potential synthetic utility of thermally labile N-ylidenimino moiety as a protecting group for one of the heterocylic urea and thiourea nitrogens leading to the regioselective substitution of the other nitrogen. Our kinetic studies proved that these N-ylidenimino groups are thermally eliminated via a cyclic six-membered transition state as nitriles (Scheme 1) [2,3]. Application of this technique led to a high regioselective synthesis of the biologically interesting 2-glucosyl-1,2,4-triazole-3(2H)-thiones (**2b**) (R = tetraacetyl-β-D-glucosyl) (Scheme 1) [4], related to the broad spectrum antiviral Ribavirin [5].

In the present investigation, we envisaged the possible utility of 2-ethyl or 2-(2-cyanoethyl)-1,2,4-triazol-3(4H)-ones and their thiones **1a,b** ($R = C_2H_5$, CH_2CH_2CN respectively) as potential starting material for the protection of N-2 in these triazoles, hoping it to assist in regioselective substitution at other nitrogen sites in the ring. It is shown in Scheme 2 that achieving this goal, depends on the conversion of **1a,b** (R = H) into the corresponding 4-arylidinimino-2-ethyl-1,2,4-triazol-3(2H)-ones **1a** ($R = C_2H_5$) and 4-arylidinimino-2-β-cyanoethyl-1,2,4-triazol-3(2H)-ones (**1a**, $R = CH_2CH_2CN$) and their thiones **1b** ($R = C_2H_5$, CH_2CH_2CN). Compounds **1a,b** are expected to undergo thermal elimination of arylnitriles and ethylene or cyanoethylene via a thermally allowed six-memebered transition state. Successful selective thermal removal of these protecting groups (i.e., ArCN and $RCH{=}CH_2$), which is anticipated to proceed at different temperatures, will allow the regioselective synthesis of each of **2a,b** ($R = C_2H_5$, CH_2CH_2CN respectively). The latter can then be subjected to electrophilic nitrogen

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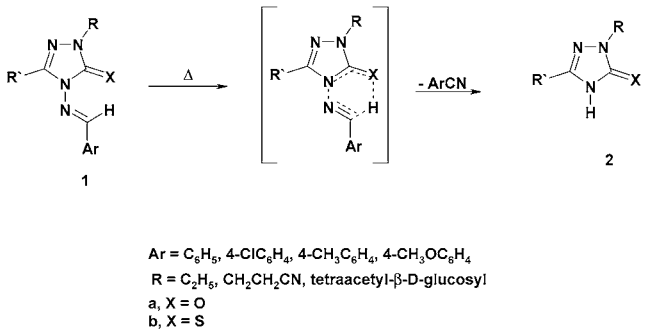


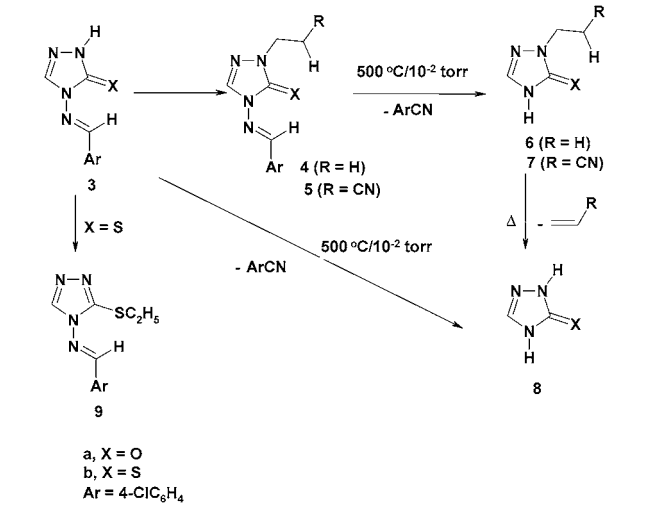
SCHEME 1 Thermal elimination of 4-arylideneimino-2-cyanoethyl-1,2,4-triazol-3(2H)-ones and their thione analogues.

substitution to give, probably, the 4-substituted derivatives, which could then be pyrolyzed to give the corresponding deprotected regioisomers. Application of this procedure is now under investigation as a straightforward route to the 4-glycosyl derivatives of potential biological interest [6].

RESULTS AND DISCUSSION

Kinetics

The kinetic data of the gas-phase elimination reactions of the compounds under study are given in Table 1. Each rate constant represents an average of three runs conducted at the same temperature which are in agreement to within ±2% rate spread. Each elimination process is followed up to 90–95% reaction. Arrhenius parameters were obtained using the results of Table 1. The Arrhenius plots were strictly linear over the 90–95% reaction coverage. Arrhenius log A(s^{-1}), the energy of activation E_a(kJ mol^{-1}), and the first-order rate constants k(s^{-1}) of the elimination reactions at 500 K are given in Table 2.



SCHEME 2 Selective pyrolytic deprotection of 2-ethyl and 2-cyanoethyl-4-arylidenimino-1,2,4-triazol-3(2H)-ones and their thione analogues.

Synthesis, Flash Vacuum Pyrolysis, and Product Analysis

In the present investigation, we started with the synthesis of 4-chlorobenzylidenimino-1,2,4-triazol-3(2H)-one (**3a**) and its thione **3b**. Ethylation of **3a** in ethanolic sodium ethoxide with ethyl iodide gave the corresponding 2-ethyl derivative **4a**. Similar treatment of the 3-thioxo derivative **3b** did not give the corresponding 2-ethyl derivative **4b** but gave the 3-ethylthio derivative **9**. On the other hand, cyanoethylation of the triazolones and their corresponding thiones gave the corresponding, required 2-(2-cyanoethyl) derivatives **5a,b** respectively.

We investigated the application of flash vacuum pyrolysis (FVP) at different temperatures to study the selective removal of each of the protecting groups at N-2 and N-4 as a function of temperature. It is shown in Scheme 2 that FVP of **3a** at 500°C and 10^{-2} Torr gave an almost quantitative yield of *p*-chlorobenzonitrile and 1,2,4-triazol-3(2H)-one (**8a**). Similarly, FVP of **3b** gave *p*-chlorobenzonitrile and 1,2,4-triazole-3(2H)-thione (**8b**) and FVP of **4a** and **5a,b** at 500°C and 10^{-2} Torr gave *p*-chlorobenzonitrile together with 2-ethyl-1,2,4-triazol-3(2H)-one (**6a**), and *p*-chlorobenzonitrile together with 2-β-cyanoethyl-1,2,4-triazoles (**7a,b**), respectively. In the latter case, a minor quantity of acrylonitrile was detected. On the other hand, FVP of **4a** at 800°C and 10^{-2} Torr gave *p*-chlorobenzonitrile together with 2-ethyl-1,2,4-triazol-3(2H)-one (**6a**), as the major product and the triazole **8a** as a minor product (ca 8%). Under the latter conditions, each of **5a,b** gave mainly *p*-chlorobenzonitrile and acrylonitrile as the major products (Scheme 2), together with a minor amount of the expected corresponding triazoles **8a,b**. It is clear that, at such a high temperature, the triazole ring is not stable and fragments as reported for the FVP of some other triazole derivatives [7]. The intermediate formation of **6a** and **7a,b** in the pyrolysis of **4a** and **5a,b** at 800°C to give **8a,b** was confirmed by FVP of each of **6a** and **7a,b** at 800°K and 10^{-2} Torr (cf Table 3). Although heating many glucosyl derivatives **1b** (R = tetra-O-acetyl-β-D-glucosyl) at 180–220°C gave quantitative yields of the corresponding glucosyl derivative **2b** (R = tetraacetyl-β-D-glucosyl) and arylnitrile [4], application of FVP on (**1b**) (R = H, Ar = *p*-chlorophenyl) proceeded only above 500°C and gave *p*-chlorobenzonitrile and acetic acid as

TABLE 1 Kinetic Data for Pyrolysis of Compounds **1b** (R = tetraacetyl-β-D-glucosyl), **4a, 5a**, and **5b**

Compound	*T (K)*	*10^4 k(s^{-1})*	*Log A (s^{-1})*	*E_a (kJ mol^{-1})*	***k_{500} (s^{-1})***
1b	462.7	1.16	16.55 ± 0.23	181.50 ± 2.16	3.94×10^{-3}
	470.4	2.50			
	479.8	6.35			
	488.9	15.35			
	497.7	31.25			
4a	554.6	0.62	13.95 ± 0.30	192.78 ± 3.37	6.56×10^{-7}
	578.8	3.77			
	588.4	7.02			
	598.5	13.14			
5a	561.7	1.91	13.74 ± 0.32	187.80 ± 3.60	1.33×10^{-6}
	571.8	3.83			
	582.3	8.27			
	592.4	14.47			
	602.35	29.38			
5b	449.1	0.51	14.32 ± 0.62	160.43 ± 5.60	3.62×10^{-3}
	457.7	1.01			
	467.6	2.31			
	477.8	5.82			
	487.6	11.94			
	497.3	34.41			

the major products besides other decomposition products. Temperatures, products, and yields of FVP of **1b, 3a,b, 4a, 5a,b, 6a**, and **7a,b** are shown Table 3.

The present investigation demonstrates that 4-arylideneimino-2-ethyl-1,2,4-tiazol-3(2H)-one (**4a**) and the 2-cyanoethyl derivatives **5a,b** can be pyrolyzed in a controlled manner to selectively deprotect the N-4 followed by N-2 positions. Application of this technique is useful in regioselective synthesis of 2- and 4-substituted 1,2,4-triazoles of potential biological applications. One such application has already been used for the highly regioselective synthesis of the biologically interesting 2-glucosyl-1,2,4-triazole-3(2H)-thiones (**2b**) (R = tetraacetyl-β-D-glucosyl) (Scheme 1) [4], related to the broad spectrum antiviral Ribavirin [5]. Other labile protecting groups and their application in the regioselective synthesis of different substituted nitrogen heterocycles containing cyclic asymmetric urea and thiourea moiety are now under further investigation.

TABLE 2 Arrhenius Parameters and Rate Coefficients $k(s^{-1})$ at 500 K for Pyrolysis of Substrates **1b** (R = tetraacetyl-β-D-glucosyl), **4a, 5a**, and **b**

Compound	*Log A (s^{-1})*	*E_a (kJ mol^{-1})*	*k_{500} (s^{-1})*
1b	16.55 ± 0.23	181.50 ± 2.16	3.94×10^{-3}
4a	13.95 ± 0.30	192.78 ± 3.37	6.56×10^{-7}
5a	13.74 ± 0.32	187.80 ± 3.60	1.33×10^{-6}
5b	14.32 ± 0.62	160.43 ± 5.60	3.62×10^{-3}

Reaction Pathway and Molecular Reactivity

The results of Table 2 together with the products of the elimination reactions of the substrates **4a, 5a,b** and **1b** (R = tetraacetyl-β-D-glucosyl) allow the following conclusions and comparisons to be made:

1. Elimination of 4-chlorobenzonitrile from the substrates under study is suggested to proceed by a reaction pathway involving a 6-centre transition state (Scheme 3).
2. 4-Chlorobenzylidenimino-2-ethyl-1,2,4-triazol-3(2H)-one (**4a**) eliminates at almost the same rate as its cyano analog **5a**; this is expected, as both undergo thermal elimination reaction via similar transition state.
3. 4-Chlorobenzylidenimino-2-β-cyanoethyl-1,2,4-triazole-3(2H)-thione (**5b**) is 2.6×10^3 more reactive than its oxygen analog **5a**. This large difference in molecular reactivity is ascribed to the greater protophilicity and lability together with the relative thermodynamic stability and the π-bond energy difference of the thio and carbonyl bonds in **5b** and **5a** respectively. The reactivity of **1b** is explained in the same manner.

EXPERIMENTAL

Kinetic Measurements and Product Analysis

Procedures for the kinetic measurements have been detailed in an earlier work [8].

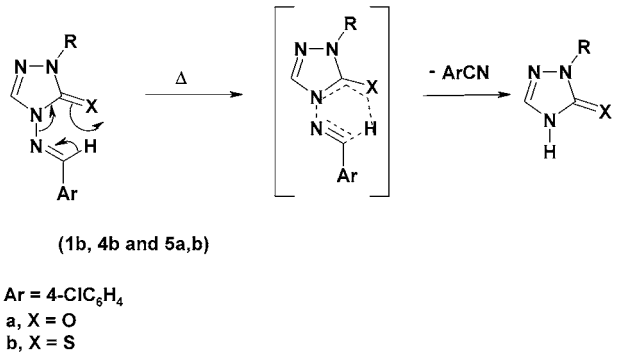
TABLE 3 Temperature, Products, and Yields of FVP of **1b** (R = Tetraacetyl-β-D-glucosyl), **3a, 3b, 4a, 5a,b**

		Products (yield%)		
Substrate	*T (°C)*	*p-Chloro-Benzonitrile*	*Triazole Derivatives*	*Others*
1b	500	(80)	**2b** (55), **8b** (20)	Acetic acid (78)[a]
	800	(25)	**8b** (3)	Acetic acid (88)[a]
3a	500	(65)	**8a** (25)	
	700	(60)	**8a** (5)	
3b	500	(100)	**8b** (40)	
4a	500	(100)	**6a** (65), **8a** (1)	
	800	(50)	**6a** (40), **8a** (8)	
5a	500	(95)	**7a** (30), **8a** (10)	
	800	(22)	**7a** (15), **8a** (2)	Acrylonitrile (39)
5b	500	(100)	**7b** (60), **8b** (2)	
	800	(50)	**7b** (5), **8b** (5)	Acrylonitrile (52)
6b	800		**6a** (60), **8a** (2)	
7a	800		**8a** (4)	Acrylonitrile (43)
7b	800		**8b** (8)	Acrylonitrile (40)

[a] Each **1b** molecule contains 4-acetate unites.

Flash Vacuum Pyrolysis

The sample was volatilized from a tube in a Büchi Kugelrohr oven through a 30 × 2.5 cm horizontal fused quartz tube. This was heated externally by a Carbolite Eurotherm tube furnace MTF-12/38A to the temperature indicated in Table 3, the temperature being monitored by a Pt/Pt-13%Rh thermocouple situated at the center of the furnace. The products were collected in a U-shaped trap and cooled in liquid nitrogen. The whole system was maintained at a pressure of 10^{-2} Torr by an Edwards Model E2M5 high capacity rotary oil pump, the pressure being measured by a Pirani gauge situated between the cold trap and the pump. Under these conditions the contact time in the hot zone was estimated to be ≅10 ms. The different zones of the products collected in the U-shaped trap were analyzed by ^{1}H, ^{13}C NMR, IR, and GC-MS. Relative and percent yields were determined from ^{1}H NMR spectrascopy. Melting points are uncorrected. IR spectra were recorded on (KBr) Shimadzu IR-740 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 400 spectrometer And MSspectra on Gc/Ms INCOS XL Finnigan MAT. Microanalysis were performed using LECO CHNS-932.



(1b, 4b and 5a,b)

Ar = 4-ClC$_6$H$_4$
a, X = O
b, X = S

SCHEME 3 Cyclic transition state formulation of elimination pathway of 1,2,4-triazol-3(2H)-ones and their thione analogues.

*4-Chlorobenzylidenimino-2-ethyl-1,2,4-triazol-3(2H)-one (**4a**).* Compound **3a** (1.12 g, 5 mmol) was added to a solution of freshly prepared sodium ethoxide (prepared from 0.2 g of Na in 25 ml of absolute ethanol). After the mixture had been stirred at room temperature for 30 min ethyl iodiode (1 ml, 10 mmol) was added and the reaction mixture was heated under reflux for 18 h. After cooling, the precipitated NaI was filtered off and washed with 10 ml of ethanol. The combined filtrate was concentrated in vacuo and the residue was crystallized from ethanol to give pale white flakes. Yield 0.96 g (75%), mp 119–120°C. ^{1}H NMR ($CDCl_3$): δ 1.37 (t, 3H, J = 7.2 Hz, CH_3), 3.90 (q, 2H, J = 7.2 Hz, CH_2), 7.43 (m, 2H, ArH), 7.74 (m, 2H, ArH), 7.76 (s, 1H, CH=N triazol), 9.81 (s, 1H, ArCH=N). ^{13}C NMR ($CDCl_3$) δ 14.1, 41.0, 129.5, 129.6, 132.3, 135.8, 137.9, 149.8, 153.7. Anal Calcd for $C_{11}H_{11}ClN_4O$ (250.7): C, 52.70; H, 4.42; N, 22.35. Found: C, 52.43; H, 4.25; N, 21.99.

*4-Chlorobenzylidenimino-3-ethylthio-1,2,4-triazole (**9**).* Compound **3b** (1.2 g, 5 mmol) was added to a solution of freshly prepared sodium ethoxide (prepared from 0.2 g of Na in 25 ml of absolute ethanol). After stirring at room temperature for 30 min, ethyl iodiode (1 ml, 10 mmol) was added

and the reaction mixture was heated under reflux for 3 h. After cooling, the precipitated NaI was filtered off and washed with 10 ml of ethanol. The combined filtrate was concentrated in vacuo and the residue was crystallized from ethanol to give colorless crystals. Yield 1.1 g (85%), mp 163–5°C. MS: *m/z* 266, 268 (M^+, M + 2). ^{1}H NMR ($CDCl_3$): δ 1.48 (t, 3H, J = 7.4 Hz, CH_3), 3.33 (q, 2H, J = 7.4 Hz, CH_2), 7.48 (m, 2H, ArH), 7.83 (m, 2H, ArH), 8.58 (s, 1H, CH=N triazole), 8.72 (s, 1H, ArCH=N). ^{13}C NMR ($CDCl_3$): δ 14.8, 26.1, 129.4, 129.7, 130.3, 136.3, 138.9, 151.2, 154.9. Anal Calcd for $C_{11}H_{11}ClN_4S$ (266.8): C, 49.53; H, 4.16; N, 21.00; S, 12.02. Found: C, 49.70; H, 4.12; N, 20.97; S, 11.73.

*4-Chlorobenzylidenimino-2-*β*-cyanoethyl-1,2,4-triazol-3(2H)- one (***5a***).* A solution of **3a** (1.12 g, 5 mmol) in aqueous pyridine (50%, 10 ml) and acrylonitrile (0.4 ml, 5.7 mmol) was heated under reflux for 18 h. After cooling, the mixture was poured over crushed ice and acidified with conc. HCl (5 ml). The precipitate was collected, dried, and recrystallized from ethanol as colorless needles. Yield 0.9 g (65%), mp 134–136°C. MS: *m/z* 275, 277 (M^+, M + 2). IR: 3421, 3211, 3125, 2249, 1707, 1561, 822 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.88 (t, 2H, J = 6.9 Hz, CH_2CN), 4.16 (t, 2H, J = 6.8 Hz, CH_2N), 7.45 (m, 2H, ArH), 7.74 (m, 2H, ArH), 7.81 (s, 1H, CH=N triazole), 9.76 (s, 1H, ArCH=N). ^{13}C NMR ($CDCl_3$) δ 17.3, 41.1, 116.6, 129.2, 129.3, 131.6, 136.5, 137.8, 149.3, 154.1. Anal Calcd for $C_{12}H_{10}ClN_5O$ (275.7): C, 52.28; H, 3.66; N, 25.40. Found: C, 51.90; H, 3.48; N, 24.99.

*4-Chlorobenzylidenimino-2-*β*-cyanoethyl-1,2,4-triazol-3(2H)-thione (***5b***).* A solution of **3b** (1.2 g, 5 mmol) in aqueous pyridine (50%, 10 ml) and acrylonitrile (0.4 ml, 5.7 mmol) was heated under reflux for 18 h. After cooling, the mixture was poured over crushed ice and acidified with conc. HCl (5 ml). The precipitate was collected, dried, and recrystallized from ethanol as pale creamy crystals. Yield 1.1 g (75%), mp 133–135°C. MS: *m/z* 291, 293 (M^+, M + 2). IR: 3434, 3134, 2249, 832, 817, 757 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.00 (t, 2H, J = 6.9 Hz, CH_2CN), 4.54 (t, 2H, J = 6.9 Hz, CH_2N), 7.46 (m, 2H ArH), 7.79 (m, 2H, ArH), 8.08 (s, 1H, CH=N triazole), 10.50 (s, 1H, ArCH=N). ^{13}C NMR ($CDCl_3$): δ 16.3, 44.3, 116.5, 129.4, 129.9, 130.9, 138.8, 139.7, 158.7, 161.4. Anal Calcd for $C_{12}H_{10}ClN_5S$ (291.8): C, 49.45; H, 3.45; N, 24.00; S, 10.99. Found: C, 49.74; H, 3.48, N, 23.89; S, 10.98.

*2-Ethyl-1,2,4-triazol-3(2H)-one 6a and 1,2,4-triazol-3(2H)-one (***8a***).* Compound **6a** was obtained from the FVP of **4a** by column chromatographic separation with silica gel on eluting first with petroleum ether (40–60)/ethyl acetate mixture, starting with 90:10 ratio and gradually increasing the ethyl acetate ratio till 50%. Pure **8a** was then collected by elution with MeOH.

Compound **6a**: mp 101–3°C (lit. [9] 103–104°C). MS: *m/z* = 131 (M^+). IR: 3434, 2825, 1631, 1605, 1384, 1352 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.37 (t, 3H, J = 7.4 Hz, CH_3), 3.88 (q, 2H, J = 7.4 Hz, CH_2), 7.53 (s, 1H, CH=N triazole), 11.60 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 13.9, 40.1, 129.2, 155.0.
Compound **8a**: mp 232–234°C (lit. [10] 232234°C). MS: *m/z* = 85 (M^+). ^{1}H NMR (DMSO-d_6): δ 11.4 (br s, 2H, 2NH), 7.70 (s, 1H, CH). ^{13}C NMR (DMSO-d_6): δ 136.9 (CH), 156.6 (C=O).

*2-*β*-Cyanoethyl-1,2,4-triazol-3(2H)-one (***7a***) and 1,2,4-triazol-3(2H)-one (***8a***).* These compounds were obtained from the FVP of **5a** by column chromatography followed by **8a** exactly as described above. Compound **7a**: mp 127–128°C. MS: *m/z* = 138 (M^+). ^{1}H NMR ($CDCl_3$): δ 2.87 (t, 2H, J = 6.8 Hz, CH_2CN), 4.14 (t, 2H, J = 6.8 Hz, CH_2N), 7.54 (s, 1H, CH=N triazole), 11.85 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 17.5, 40.7, 116.7, 134.9, 155.0. Anal Calcd for $C_5H_6N_4O$ (138.1): C, 43.48; H, 4.38; N, 40.56. Found: C, 43.24; H, 4.53, N, 40.17.

*2-*β*-Cyanoethyl-1,2,4-triazol-3(2H)-thione (***7b***) and 1,2,4-triazole-3(2H)-thione (***8b***).* Compound **7b** was obtained from the FVP of **5b** by column chromatography followed by **8b** as exactly described above.

Compound **7b**: mp 153–154°C. MS: *m/z* = 154 (M^+). IR: 3434, 3124, 2953, 2248, 1552, 1480, 1408, 1285, 1207, 977, 915, 818, 670, 635 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.05 (t, 2H, J = 6.4 Hz, CH_2CN), 4.32 (t, 2H, J = 6.4 Hz, CH_2N), 8.44 (s, 1H, CH=N triazole), 13.70 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 16.7, 43.6, 118.6, 140.1, 165.5. Anal Calcd for $C_5H_6N_4S$ (154.2): C, 38.95; H, 3.92; N, 36.33; S, 20.80. Found: C, 39.34; H, 3.93, N, 36.16; S, 20.57.
Compound **8b**: mp 215–216°C (lit. [11] 215–6°C). MS: *m/z* = 101 (M^+). ^{1}H NMR (CD_3COCD_3): δ 14.4, 3.4 (2br s, 2H, 2NH), 8.56 (s, 1H, CH).

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REFERENCES

[1] Garratt, P. J. In Comprehensive Heterocyclic Chemistry II; Katritzky, A. R.; Rees, C. W.; Scriven, F. V. (Eds.); Pergamon Press: London, 1996; Vol. 4, pp. 137–138 and references cited therein.

[2] Al-Awadi, N. A.; Ibrahim, Y. A.; Kaul, K.; Dib, H. J Phys Org Chem 2001, 14, 521–525.

[3] Al-Awadi, N. A.; Elnagdi, M. H.; Mathew, T.; El-Gamry, I.; Abdel Khalik, M. Int J Chem Kinet 1996, 28, 741–749.

[4] Ibrahim, Y. A.; Abbas, A. A.; Elwahy, H. M. Carbohydrate Lett 1999, 3, 331–338 and references cited therein.

[5] (a) Smith, R. A.; Kirkpatrich, W. (Eds.). Ribavirin, A Broad Spectrum Antiviral Agent; Academic Press: New York, 1980; (b) Sidwell, R. W.; Rivankar, G. R.; Robins, R. K. In Viral Chemotherapy, Vol 2; Sgugar, D. (Ed.); Pergamon Press: New York, 1985; p. 49; (c) Smith, R. A; Night, V.; Smith, J. A. D. (Eds.); Clinical Application of Ribavirin; Academic Press: New York, 1984.

[6] Garratt, P. J. In Comprehensive Heterocyclic Chemistry II; Katritzky, A. R.; Rees, C. W.; Scriven, F. V. (Eds.); Pergamon Press: London, 1996; Vol. 4, pp. 160–163 and references cited therein.

[7] B'Shary, I.; Guimon, C.; Grimaud, M.; Afister-Guillouzo, G. Can J Chem 1988, 66, 2123–2129.

[8] Al-Awadi, N. A.; Kaul K.; El-Dusouqui, O. M. J Phys Org Chem 2000, 13, 499–504.

[9] Kroeger, C. F.; Selditz, P.; Mutscher, M. Chem Ber 1965, 98, 3034–3039.

[10] Kroger, C. F.; Hummel, L.; Mutscher, M.; Beyer, H. Chem Ber 1965, 98, 3025–3033.

[11] Shegal, I. L.; Postovskii, Ya. Metody Poluch Khim Reakt Prep 1966, 14, 116–118.