Turkish Journal of Chemistry

Volume 20 | Number 4 Article 5

1-1-1996

Synthesis of 2,4-Dihydro-4-(2-phenylethyl)-5-(isomeric pyridyl)-3H-1,2,4-triazole-3-thiones and Their Derivatives.

Rashid IQBAL

Khosrow ZAMANI

Nasim H. RAMA

Tr. J. of Chemistry
20 (1996) , 295 – 301.

Synthesis of 2,4-Dihydro-4-(2-phenylethyl)-5-(isomeric pyridyl)-3H-1,2,4-triazole-3-thiones and Their Derivatives.

Rashid IQBAL, Khosrow ZAMANI and Nasim H. RAMA
Department of Chemistry, Quaid-i-Azam University,
Islamabad-PAKISTAN

Received 1.3.1996

Intramolecular cyclization of the three isomeric 1,4-disubstituted thiosemicarbazides 3(a-c) in aqueous sodium hydroxide was attempted to obtain 2,4-dihydro-4-(2-phenylethyl)-5-(isomeric pyridyl)- 3H-1,2,4-triazole-3-thiones 4(a-c). Each of the three isolated triazoles was separately treated with benzyl chloride and with chloroacetic acid to furnish the corresponding benzylthio 5(a-c) and carboxymethylthio derivatives 6(a-c), respectively

Introduction

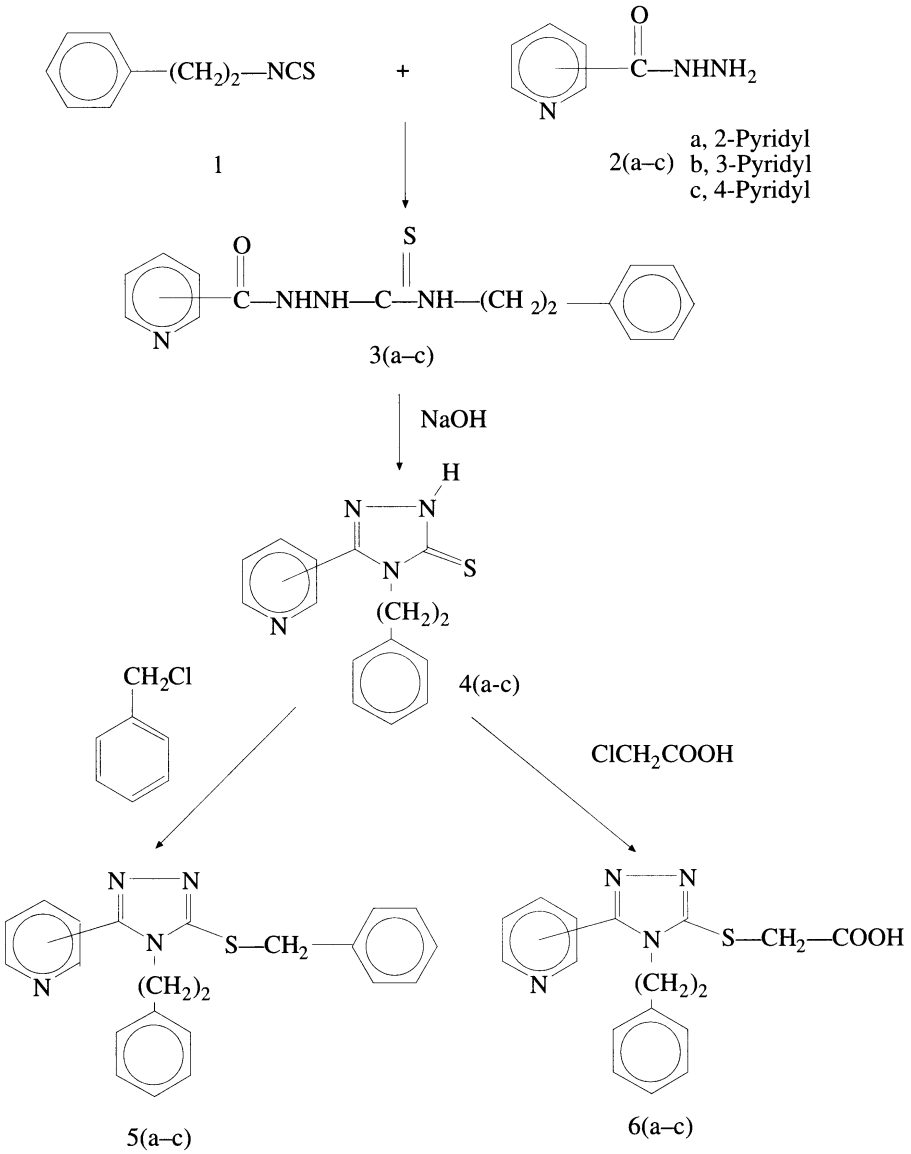
4,5-Disubstituted 2,4-dihydro-3H-1,2,4-triazole-3-thiones and their derivatives have gained a lot of interest in the last decade due to their biological, industrial and agricultural importance. These compounds exhibit diuretic[1,2], antibacterial[3–5], hypoglycemic[6,7], and anti-tubercular[3,8] inhibitors of corrosion of copper, brass, aluminum and steel in a marine environment[9], inhibit fog formation in photographic emulsions[10] are anti-fungal[11,12], plant growth accelerator / inhibitors[13], and herbicides[14]. Keeping in view the potential pharmacological importance of these compounds, it was planned to synthesize new 2,4-dihydro-4-(2-phenylethyl)-5-(isomeric pyridyl)-3H-1,2,4-triazole-3-thiones 4(a-c), thier benzylthio 5(a-c), and carboymethylthio derivatives 6(a-c) (Scheme 1).

Experimental

Melting points were determined using a Gallenkamp digital melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elemer 1320 spectrophotometer using KBr disc. UV spectra were obtained using a Lambda 5 Perkin Elemer UV/Vis spectrophotometer using EtOH as solvent. ^{1}H-NMR spectra were recorded on a Bruker 250 MHz instrument.

Preparation of 2-phenylethyl isothiocyanate 1

A mixture of 2-phenylethyl amine (0.5 mol, 62.9 ml), carbon disulphide (0.78 mol, 74.8 ml) and methanol (95%, 90 ml) was cooled to about 10°. Ammonia (33%, 0.63 mol) was added dropwise to the reaction mixture with continuous stirring. Heavy crystals of the dithiocarbamate separated out. The mixture was allowed to stand overnight. The solid was then filtered, washed with diethylether (150 ml) and dissolved in 800 ml cold water. An aqueous solution of lead nitrate (0.5 mol, 174 g) was slowly added to the solution of dithiocarbamate. The mixture was then steam distilled to yield 2-phenylethyl isothiocyanate as a bright yellow oil, which was received in a conical flask containing 1ml of dilute sulfuric acid (2N). The steam distillate was then subjected to separation of organic phase from the aqueous phase. The aqueous phase was then extracted with diethylether (2 × 30 ml). The organic layer was separated, combined, dried over anhydrous sodium sulfate, filtered and subjected to removal of solvent. The isothiocyanate left behind was combined with the major portion obtained above. The infrared (neat) of the isolated 2-phenylethyl isothiocyanate indicated a prominent characteristic absorption band at 2050 cm^{-1} attributable to N=C=S group.



(Scheme 1)

Preparation of thiosemicarbazide derivatives 3(a-c).

Corresponding isomeric pyridinecarboxylic acid hydrazide 2(a-c) (0.013 mol, 3.99 g) was disolved in 50% aqueous ethanol. Each isomer required a different volume of aqueous ethanol. 2-Phenylethyl isothiocyanate 1 (0.013 mol, 2.2 g) was separately dissolved in 120 ml of 50% aqueous ethanol. The two ethanolic solutions were mixed together by pouring solution I into solution II. The mixture thus obtained was refluxed on a hot water bath for a time period mentioned in Table 1. Formation of compound 3c did not require any reflux, and the crude product precipitated as soon as the two solution were mixed. After the reflux time was over, as determined by TLC- monitoring, the reaction mixture was cooled to room temperature, which allowed precipitation of the crude product. In each case the crude product was filtered off and recrystallized from water-ethanol (30:70).

Preparation of 2,4-dihydro-4-(2-phenylethyl)-5-(isomeric pyridyl)-3H-1,2,4-triazole-3-thiones 4(a-c).

The corresponding thiosemicarbazide 3(a-c) (0.01 mol, 3.0 g) was dissolved in (50-80 ml) NaOH(4N). The reaction mixture was refluxed for 7.5-8.5 hours and then cooled to room temperature and filtered. The filtrate was acidified with HCl (4N) to pH 4. In each case a solid precipitated, which was washed with cold water and recrystallized from 50% aq. ethanol.

Preparation of 3-benzylthio-4-(2-phenylethyl)-5-(isomeric pyridyl)-1,2,4-triazoles 5(a-c).

A solution of 4(a-c) (0.005 mol, 1.4 g) in ethanolic alkali (0.2 g NaOH in 15 ml aq.ethanol) was mixed with benzyl chloride (0.005 mol; 0.63 g) reflexed for 1.5-2.0 hours. On the cooling of the reaction mixture, a crode precipitate was obtained which was recrys-tallized from water-ethanol (20: 80).

Preparation of 3-carboxymethylthio-4-(2-phenylethyl)-5-(isomeric pyridyl)-1,2,4-triazoles 6(a-c).

Compound 4(a-c) (0.005 mol; 1.4 g) was dissolved in 10 ml 1.6N aq. sodium hydroxide solution and mixed with chloroacetic acid (0.005 mol; 0.47 g, dissolved in 10 ml water). The mixture was refluxed for 2.0-2.5 hours. After the reflux time was over, the reaction mixture was cooled, filtered and acidified with 1N HCl to pH 3-4. The reaction mixture was then cooled in an ice bath, which resulted in precipitation of the crude product. This was filtered and recrystallized from water-ethanol (20:80).

Results and Discussion

Isomeric pyridinecarboxylic acid hydrazides 2(a-c) were prepared by the treatment of the corresponding pyridinecarboxylic acids with hydrazine hydrate following the reported procedure[15]. The acid hydrazides 2(a-c), when reacted with 2-phenylethyl isothiocyanate 1, yielded 4-(2-phenylethyl)- 1-(isomeric pyridoyl) thiosemicarbazides 3(a-c) in excellent yield. The isomeric substituted thiosemicarbazides 3(a-c), when subjected to react with 4N sodium hydroxide, underwent intramolecular dehydrative cyclization to furnish the corresponding isomeric 1,2,4-triazole-3-thiones 4(a-c). Compounds 4(a-c), when treated separately with benzyl chloride and chloroacetic acid, yielded benzylthio 5(a-c) and carboxymethylthio derivatives 6(a-c)

of 4(a-c), respectively. The reaction time, percentage yield and the observed melting points of the final products and the intermediate compounds are tabulated in Table 1. The purity of all isolated compounds was established by TLC in two different solvent systems using silica plates. The R_f-values thus determined are listed in Table 2. This Table also shows the agreement of calculated and found percentages of C,H,N and S in the isolated compounds. The infrared spectra (KBr;disc) and ultraviolet spectra (ethanol solution) of all the isolated compounds were recorded and the important data are listed in Table 3.

Table 1. Reaction time and physical data

Isolated compound	Reflux time (h)	Yield (%)	M.p.$_{obs.}$ (c)	Recrystallization solvent (water:ethanol)
3a	5.5	94.5	173.0	30:70
3b	8.5	84.3	171.2	30:70
3c	*	89.7	222.5	30:70
4a	7.5	87.3	176.4	20:80
4b	8.5	78.2	157.3	50:50
4c	7.5	86.7	171.5	50:50
5a	1.5	70.3	134.5	50:50
5b	2.0	45.7	112.5	50:50
5c	1.5	72.6	181.2	50:50
6a	2.0	77.5	197.5	20:80
6b	2.5	45.4	126.4	20:80
6c	2.0	71.2	228.5	20:80

*In this case reflux was not required and the crude triazole separated just after mixing the reagents.

Table 2. Elemental analysis and R_f values of the isolated compounds

Isolated compond	Molecular formula		-% C	H	N	S	R_f-values (solvent system)
3a	$C_{15}H_{16}N_4OS$	Found	59.91	5.35	18.81	10.15	0.58 (Chloroform-Methanol 1:1)
		Calc.	60.00	5.33	18.67	10.67	0.46 (Pet. ether-Acetone 1:2)
3b	$C_{15}H_{16}N_4OS$	Found	59.86	5.30	18.64	10.48	0.63 (Chloroform-Methanol 1:1)
		Calc.	60.00	5.33	18.67	10.67	0.72 (Pet.ether-Acetone 1:2)
3c	$C_{15}H_{16}N_4OS$	Found	60.04	5.29	18.31	10.44	0.77 (Chloroform-Methanol 1:1)
		Calc.	60.00	5.33	18.67	10.67	0.62 (Pet.ether-Acetone 1:2)
4a	$C_{15}H_{14}N_4S$	Found	63.90	4.77	19.91	11.40	0.81 (Chloroform-Methanol 1:1)
		Calc.	63.83	4.96	19.86	11.35	0.68 (Ethyl acetate-Pet.ether 1:5)
4b	$C_{15}H_{14}N_4S$	Found	63.68	4.88	19.90	11.41	0.73 (Chloroform-Methanol 1:1)
		Calc.	63.83	4.96	19.86	11.35	0.71 (Ethyl acetate-Pet.ether 1:5)
4c	$C_{15}H_{14}N_4S$	Found	63.87	4.96	19.71	11.36	0.62 (Chloroform-Methanol 1:1)
		Calc.	63.83	4.96	19.86	11.35	0.54 (Ethyl acetate-Pet. ether 1:5)
5a	$C_{22}H_{20}N_4S$	Found	70.88	5.44	15.00	8.54	0.46 (Chloroform-Methanol 1:1)
		Calc.	70.97	5.38	15.05	8.60	0.31 (Pet.ether-Acetone 1:4)
5c	$C_{22}H_{20}N_4S$	Found	70.91	5.33	15.14	8.55	0.58 (Chloroform-Methanol 1:1)
		Calc.	70.97	5.38	15.05	8.60	0.68 (Pet.ether-Acetone 1:4)
6a	$C_{17}H_{16}N_4O_2S$	Found	60.22	4.68	16.40	9.48	0.57 (Chloroform-Methanol 1:1)
		Calc.	60.00	4.71	16.47	9.41	0.62 (Pet.ether-Acetone 1:3)
6c	$C_{17}H_{16}N_4O_2S$	Found	60.09	4.74	16.41	9.46	0.73 (Chloroform-Methanol 1:1)
		Calc.	60.00	4.71	16.47	9.41	0.41 (Pet.ether-Acetone 1:3)

Table 3. IR and UV spectroscopic data of the isolated compounds

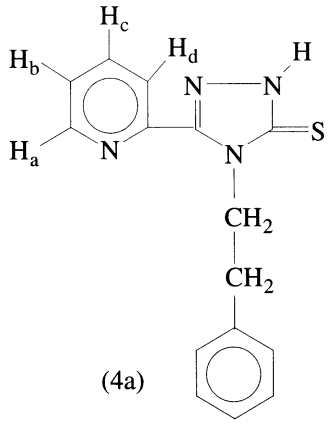
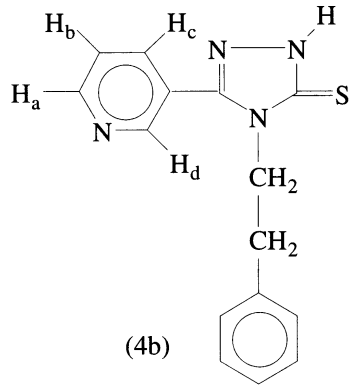
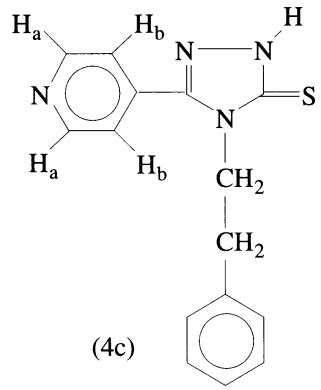
Isolated compound	Characteristic IR absorbance (cm^{-1})	λmax ϵ(max) nm
3a	3300, 3010, 1690, 1600, 1275	207.3 (23408), 246.8 (15112)
3b	3200, 3020, 1685, 1575, 1275	203.1 (26321), 246.8 (14720), 326.4 (4923)
3c	3280, 3005, 1675, 1550, 1250	204.0 (27095), 247.1 (15116), 344.7 (5758)
4a	3310, 3015, 1590, 1275	208.0 (17076), 253.9 (14469), 302.1 (7333)
4b	3500, 3020, 1600, 1285	205.3 (22158), 251.7 (18735)
4c	3280, 3010, 1610, 1295	205.5 (20364), 257.0 (16300), 303.0 (4155)
5a	3030, 1590, 705	281.8 (16895), 213.4 (26482)
5b	3025, 1580, 700	260.2 (11542), 213.6 (27041)
5c	3030, 1610, 705	267.0 (5864), 212.4 (15173)
6a	3035, 2885, 2510, 1720, 1536, 695	284.2 (21055), 212.6 (24585)
6b	3020, 2860, 2500, 1715, 1500, 690	261.5 (19353), 213.8 (31050)
6c	3040, 2920, 2520, 1717, 1580, 705	268.2 (10932), 212.7 (19481)

The infrared spectra of compounds 3(a-c) (KBr-disc) exhibited a characteristic strong absorption at 1250-1275 cm^{-1} attributable to the C=S of the thiourea residue. The carbonyl absorption in the compounds were observed at 1675-1690 cm^{-1}. Other absorption observed were at 1550- 1600 cm^{-1}($\nu_{C=C}, \nu_{C=N}$) and 3005-3020 cm^{-1} ($\nu_{aromaticC-H}$). The N-H stretching absorptions were found at 3200-3300 cm^{-1}. The UV spectra of compounds 3b and 3c exhibited three maxima, one each in the region of 203.1-204.6 nm,246.8-247.1 nm and 326.4- 344.7 nm. Compound 3a, on the other hand, exhibited two maxima, one at 207. 3 and the other at 246.8 nm. These absorptions may be attributed to $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transition associated with the molecules.

Compounds 4(a-c) were obtained by intramolecular cyclocondensation reaction of 3(a-c). Compound 4b, i.e., 3-pyridyl derivative, was obtained in comparatively low yield (78.2%) even when refluxed for a longer time (8.5h). These results are in accordance with the reported[16] reactivity of 3-pyridyl compounds for other reactions. It has often been observed that the electrons are drawn off to a smaller extent from the 3-position than from the 2- and 4-positions of the pyridine nucleus. A low positive charge on carbonyl carbon in the case of 3-pyridoyl isomer as compared to 2- or 4- pyridoyl isomer does not favour the nucleophilic attack on the carbonyl carbon adjacent to the 3-pyridyl nucleus. ^{1}H-NMR spectral data of the three isolated 1,2,4-triazoles (4a-c) in d^6-dimethylsulfoxide is listed in Table 4. In view of the good agreement of the calculated and found percentages of C,H,N and S, in addition to the ^{1}H-NMR data, the structure of compounds (4a-c) are well established.

In the infrared spectra of compounds 4(a-c) (KBr-disc), lack of absorbance in the region 2590-2550 cm^{-1} indicates that the compounds do not contain any S-H bond. However, they do exhibit absorption inthe region of 3280-3300 cm^{-1} attributable to N-H streching vibration. The presence of N-H and absence of S-H lead to the conclusion that the isolated triazoles 4(a-c) are present in the thione rather than the thiol form. Other strong absorption were observed at 1560-1600 cm^{-1} ($\nu_{C=C}, \nu_{C=N}$) and 3010-3020 cm^{-1} ($\nu_{aromatic\,C-H}$). In the UV spectra of 4a and 4c, three distinct absorption maxima were observed at 203.1-208.0 nm, 253.9-257.6 nm and 303.0- 312.6 nm, while in the case of 4b, only two absorption maxima were observed, at 205.3 nm and 257.1 nm. These absorption bands are assigned to the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transition associated with the molecules.

Table 4. ^{1}H-NMR spectral data of isolated 1,2,4-triazoles (4a-c)

Compounds (4a-c)	Signals	Assignment
 (4a)	3.15, t, 2H	N-CH2
	4.92, t, 2H	Ar-CH2
	7.2-7.4, m, 5H	Ar-H
	7.39, m, 1H	Hb
	7.70, m, 1H	Hc
	7.90, m, 1H	Hd
	8.70, m, 1H	Ha
	12.65, b*, 1H	NH
 (4b)	3.15, t, 2H	N-CH2
	4.37, t, 2H	Ar-CH2
	6.92-7.17, m, 5H	Ar-H
	7.35, m, 1H	Hc
	7.42. m, 1H	Hb
	8.50, m, 1H	Ha
	8.75, m, 1H	Hd
	12.75, b*, 1H	NH
 (4c)	3.15, t, 2H	N-CH2
	4.34, t, 2H	Ar-CH2
	6.95-7.19, m, 5H	Ar-H
	7.23, dd, 2H	Hb
	8.23, dd, 2H	Ha
	12.08, b*, 1H	NH

*b; broad and exchangable

The infrared spectra (KBr-disc) of carboxymethyl derivatives 6(a-c) also lacked C=S stretching vibration frequency in the 1200-1300 cm^{-1} region. However, they exhibited characteristic absorption of a carboxylic acid group; C=O stretching at 1715-1720 cm^{-1} and the bonded O-H vibration at 2500-2520 cm^{-1}. In addition to these absorbences, the infrared spectra of these compounds exhibited absorptions at 3020-3040 ($\nu_{aromatic\,C-H}$), 2860-2920 (ν_{CH2}), 1500-1580 ($\nu_{C=C}, \nu_{C=N}$) and 690-705 (ν_{C-S}).

Acknowledgement

We take this opportunity to thank Professor Dr. F. Effenberger, Institute of Organic Chemistry, University of Stuttgart, for providing laboratory facilities to one of us (RI) when he was on a study visit to Germany. We also acknowledge with thanks the study visit grant from DAAD.

References

1. H.L. Yale and J.J. Piala, **J. Med. Chem., 9**, 42 (1966)
2. M.H. Shah, M.Y. Mhasalkar, M.V. Patki, C.V. Deliwala and U.K. Sheth, **J. Pharm. Sci., 58**, 1398 (1969).
3. M. Kuranari and H. Takeuchi, **Chem. Abstr., 67**, 21918d (1967).
4. H.A. Burch and W.O. Smith, J. **Med. Chem., 9**, 405 (1966).
5. N.A. Abdou and F.M. Amin, Mansoura **J. Phrm. Sci., 6**, 25 (1990).
6. M.Y. Mhasalkar, M.H. Shah, S.T. Nikam, K.G. Anantanarayanan and C.V. Deliwala, **J. Med. Chem., 13**, 672 (1970).
7. M.Y. Mhasalkar, M.H. Shah, S.T. Nikam, K.G. Anantanaryanan, and C.V. Deliwala, **J. Med. Chem., 14**, 260 (1971).
8. I.Mir, M.T. Siddiqui and A. Comrie, **Tetrahedron, 26**, 5235 (1970).
9. A Kotone and T. Hori, **Chem. Abstr., 80**, 62968g (1974).
10. K. Schofield, M.R. Grimmett and B.R.T. Keene, Heteroaromatic Nitrogen Compounds. The Azoles" Cambridge University Press, 1976, P. 34.
11. R.K. Mishra, R.K. Tewari, et. al., **J. Indian Chem. Soc., 68**, 110 (1991).
12. S.P. Suman and S.C. Bahel, **J. Indian Chem. Soc., 56**, 374 (1979).
13. Z. Lixue et.al., **Gaodeng Xuexio Huaxue Xuebao, 11**, 148 (1990).
14. G.S. Gambaryan, **Izv. S. Kh. Nauk., 26**, 40 (1983); **Chem. Abstr., 110**, 2207a (1984).
15. K. Shu, **Med. Prom. S.S.Sr., 11**, 19(1957).
16. L.M. Yoqupolskii, V.S. Mikhailov, G.I. Matyushecheva, **J. Org. Chem. U.S.S.R., 8**, 846 (1972).