Synthesis of 5-(1-Naphthylmethyl)-4-aryl-*s*-triazol-3-thiols/ylthioglycolic Acids as Possible Antiinflammatory Agents

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Several 5-(1-naphthylmethyl)-4-aryl-*s*-triazol-3-thiols/ylthioglycolic acids were synthesized as possible antiinflammatory agents. The interpretation of infrared, nuclear magnetic resonance, and mass spectra is discussed for chemical characterization of these compounds.

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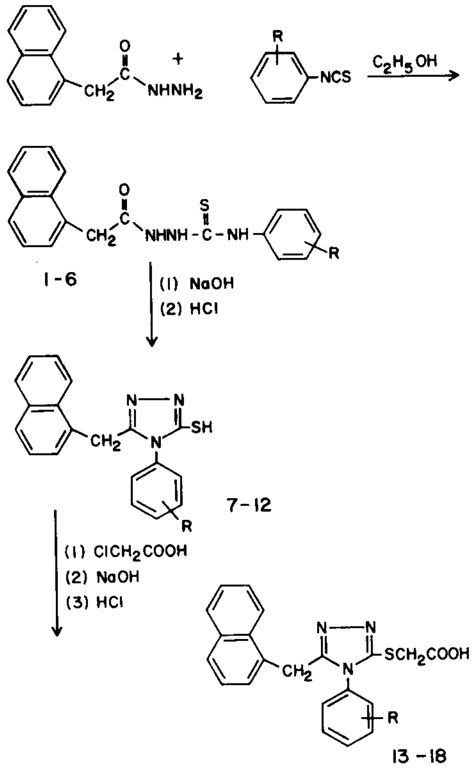
Various substituted-*s*-triazoles have recently received significant importance because of their diverse pharmacological properties. These included analgesic, antiasthmatic, diuretic, antihypertensive, anticholinergic, and antiinflammatory properties (1-5). Several derivatives of naphthylacetic acid have also been found to possess antiinflammatory activity (6,7). Earlier studies have also reported antiinflammatory activity of a series of naphthylthiosemicarbazides and their corresponding oxadiazoles (8,9). On the basis of these observations and in continuation to our earlier studies (10), we wish to report the synthesis of some 5-(1-naphthylmethyl)-4-aryl-*s*-triazol-3-thiols and their corresponding thioglycolic acids. These compounds were synthesized by following the steps outlined in Scheme I.

The reaction of 1-naphthylacethydrazide with appropriate arylisothiocyanates resulted in the formation of 1-(1-naphthylacetyl)-4-aryl thiosemicarbazides (**1-6**). The cyclization of the various substituted thiosemicarbazides (**1-6**) in the presence of aqueous 2*N* sodium hydroxide solution gave the corresponding 5-(1-naphthylmethyl-4-aryl-*s*-triazol-3-thiols (**7-12**). Finally, the reaction of **1-6** with monochloroacetic acid in the presence of aqueous sodium hydroxide solution yielded 5-(1-naphthylmethyl)-4-aryl-*s*-triazol-3-ylthioglycolic acids (**13-18**).



Scheme I

Table I

Physical Constants of 1-(1-Naphthylacetyl)-4-aryl Thiosemicarbazides

Compound No.	R	M.p. °C	Yield %	Molecular Formula	Analysis % Calculated C	H	N	Found C	H	N
1	4-F	186	98	$C_{19}H_{16}FN_3OS$	64.58	4.53	11.89	64.29	4.31	11.90
2	2,4-Cl_2	185	93	$C_{19}H_{15}Cl_2N_3OS$	56.43	3.71	10.40	56.34	3.68	10.30
3	3,4-Cl_2	194	97	$C_{19}H_{15}Cl_2N_3OS$	56.43	3.71	10.40	56.06	3.92	10.08
4	2-CH_3-4-Cl	158	94	$C_{20}H_{18}ClN_3OS$	62.58	4.69	10.95	62.30	4.67	10.93
5	1-naphthyl	204	96	$C_{23}H_{19}N_3OS$	71.69	4.93	10.91	71.43	4.71	11.16
6	2-naphthyl	175	98	$C_{23}H_{19}N_3OS$	71.69	4.93	10.91	71.96	4.98	11.02

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Table II

Physical Constants of 5-(1-Naphthylmethyl)-4-aryl-*s*-triazol-3-thiols

Compound No.	R	M.p. °C	Yield %	Solvent of Crystallization	Molecular Formula	Analysis % Calculated			Found		
						C	H	N	C	H	N
7	4-F	215	83	ethanol	$C_{19}H_{14}FN_3S$	68.06	4.18	12.54	67.97	4.16	12.46
8	2,4-Cl_2	231.4	96	ethanol	$C_{19}H_{13}Cl_2N_3S$	59.07	3.37	10.88	59.16	3.37	10.78
9	3,4-Cl_2	281 dec.,	92	xylene	$C_{19}H_{13}Cl_2N_3S$	59.67	3.37	10.88	59.25	3.10	10.62
10	2-CH_3-4-Cl	213	97	methanol	$C_{20}H_{16}ClN_3S$	65.66	4.38	11.49	65.59	4.38	11.42
11	1-naphthyl	252 dec.,	92	acetic acid	$C_{23}H_{17}N_3S$	75.20	4.63	11.44	75.32	4.69	11.31
12	2-naphthyl	245.8	100	xylene	$C_{23}H_{17}N_3S$	75.20	4.63	11.44	75.03	4.70	11.41

Table III

Physical Constants of 5-(1-Naphthylmethyl)-4-aryl-*s*-triazol-3-ylthioglycolic Acids

Compound No.	R	M.p. °C	Yield %	Solvent of Crystallization	Molecular Formula	Analysis % Calculated			Found		
						C	H	N	C	H	N
13	4-F	173.4	68	ethanol	$C_{21}H_{16}FN_3O_2S$	64.12	4.07	10.69	64.13	4.16	10.12
14	2,4-Cl_2	197.6	83	toluene	$C_{21}H_{15}Cl_2N_3O_2S$	56.76	3.38	9.46	56.91	3.36	9.40
15	3,4-Cl_2	174.4	90	ethanol	$C_{21}H_{15}Cl_2N_3O_2S$	56.76	3.38	9.46	56.64	3.37	9.39
16	2-CH_3-4-Cl	229.9	87	ethylacetate	$C_{22}H_{18}ClN_3O_2S$	62.34	4.50	9.92	62.15	4.21	9.86
17	1-naphthyl	211.6	90	ethanol	$C_{25}H_{19}N_3O_2S$	70.59	4.47	9.88	70.50	4.49	9.78
18	2-naphthyl	143.4	94	toluene	$C_{25}H_{19}N_3O_2S$	70.59	4.47	9.88	70.58	4.45	9.85

Table IV

Spectral Analyses of 1-(1-Naphthylacetyl)-4-arylthiosemicarbazides (**1-6**)

Compound No.	Infrared Spectra (cm^{-1}) NH	C=O	C=S	R (CH_3)	Nuclear Magnetic Resonance Spectra (δ) -CH_2-	Aromatic Protons	-NHCSNH-	-CONH-
1	3200	1600	1350	---	4.00 (s)	7.00-8.20 (m)	9.66 (bs)	10.26 (bs)
2	3260	1670	1350	---	4.03 (s)	7.33-8.26 (m)	9.33 (bs)	10.23 (bs)
3	3280	1670	1360	---	4.00 (s)	7.33-8.20 (m)	9.80 (bs)	10.33 (bs)
4	3100	1680	1350	2.13 (s)	4.00 (s)	7.10-8.26 (m)	9.33 (bs)	10.23 (bs)
5	3140	1700	1370	---	4.06 (s)	7.16-8.30 (m)	9.90 (bs)	10.36 (bs)
6	3120	1650	1340	---	4.06 (s)	7.20-8.26 (m)	9.86 (bs)	10.33 (bs)

Table V

Spectral Analyses of 5-(1-Naphthylmethyl)-4-aryl-*s*-triazol-3-thiols (**7-12**)

Compound No.	Infrared Spectra (cm^{-1}) C=C/C=N	C=S	R (CH_3)	Nuclear Magnetic Resonance Spectra (δ) -CH_2-	Aromatic Protons	Mass Spectra m/e (Relative Intensity)
7	1580, 1505, 1410	1310	---	4.34 (s)	6.84-8.16 (m)	167 (100), 141 (53), 127 (19), 109 (15), 95 (51), 59 (12)
8	1580, 1560, 1540 1520, 1495	1325	---	4.31 (s)	6.84-8.16 (m)	167 (76), 161 (5), 141 (51), 127 (26), 59 (18)
9	1580, 1570, 1550 1500, 1420	1305	---	4.19 (s)	6.52-8.16 (m)	386 (5), 167 (100), 161 (79), 141 (100), 127 (50), 95 (7), 59 (8)
10	1600, 1570, 1495, 1455, 1410, 1400	1320	1.46 (s)	4.32 (s)	6.76-8.16 (m)	------
11	1595, 1570, 1495 1410	1330	---	4.19 (s)	6.52-8.16 (m)	367 (6), 167 (66), 141 (100), 127 (100), 95 (6), 59 (10)
12	1600, 1570, 1455, 1410	1320	---	4.38 (s)	6.84-8.16 (m)	367 (26), 366 (90), 167 (54), 141 (94), 127 (64), 95 (5), 59 (6)

Table VI

Spectral Analyses of 5-(1-Naphthylmethyl)-4-aryl-*s*-triazol-3-ylthioglycolic acids (**13-18**)

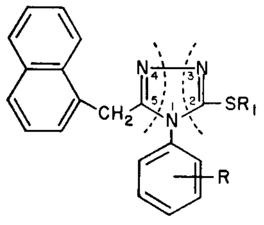
Compound	Infrared Spectra (cm^{-1})			Nuclear Magnetic Resonance Spectra (δ)				Mass Spectra
No.	C=O	C=N/C=C	C-OH	R(CH$_3$)	S-CH$_2$-	-CH$_2$-	Aromatic Protons	m/e (Relative Intensity)
13	1740	1605, 1510	1400	---	3.92 (s)	4.43 (s)	6.68-8.16(m)	393 (60), 392 (93), 167 (100), 141 (100), 127 (31), 116 (18), 109 (66), 95 (37)
14	1730	1580, 1560 1505	1410	---	3.96 (s)	4.46 (s)	6.68-8.32 (m)	444 (49), 443 (46), 167 (100), 161 (37), 159 (41), 141 (100), 127 (43), 116 (28), 91 (26)
15	1750	1600, 1570	1410	---	3.94 (s)	4.48 (s)	6.84-8.16 (m)	444 (75), 443 (100), 167 (100), 166 (67), 160 (33), 141 (100), 127 (57), 116 (28), 91 (14)
16	1725	1600, 1575 1495	1410	1.37 (s)	4.00 (s)	4.42 (s)	6.68-8.32 (m)	423 (69), 378 (46), 167 (100), 141 (100), 127 (41), 91 (33)
17	1730	1690, 1600 1530, 1575	1410	---	4.02 (s)	4.36 (s)	6.84-8.16 (m)	425 (100), 380 (12), 335 (100), 167 (100), 141 (100), 127 (100), 116 (52), 91 (27)
18	1750	1610, 1575 1480	1400	---	4.08 (s)	4.51 (s)	6.68-8.32 (m)	425 (100), 380 (44), 335 (100), 167 (100), 141 (100), 127 (100), 116 (46), 91 (37)

The infrared spectra of **1-6** exhibited N-H stretching absorption bands in the region between 3100-3280 cm^{-1}. The absorption bands due to the C=O group were observed in the range of 1650-1700 cm^{-1} and C=S group weakly absorbed between 1340-1370 cm^{-1}. In the nuclear magnetic resonance spectra, the thiosemicarbazides (**1-6**) exhibited broad singlet between 10.23-10.36 ppm due to the amidic proton (CONH) and 9.33-9.86 ppm due to the thiocarbamidic protons (NHCSNH). Upon addition of deuterium oxide to the sample, the N-H protons readily exchanged with deuterium and consequently the signals due to N-H protons disappeared. The -CH$_2$- group attached to the naphthyl ring appeared as a singlet in the range of 4.00-4.06 ppm. The chemical shifts of the aromatic protons ranged from 7.00-8.30 ppm. The thiosemicarbazides were found to be unstable in the mass spectrometer.

The infrared spectra of **7-18** showed C=C/C=N absorption bands between 1400-1690 cm^{-1}. The 5-(1-naphthylmethyl)-4-aryl-*s*-triazol-3-thiols (**7-12**) exhibited a characteristic band between 1305-1330 cm^{-1} due to the C=S group because thiols exist in a tautomeric form. The characteristic C=O absorption in substituted thioglycolic acids (**13-18**) was observed in the region of 1725-1750 cm^{-1}. In the nuclear magnetic resonance spectra of **7-18**, the methylene group between the naphthyl moiety and the *s*-triazole nucleus showed a singlet between 4.91-4.51 ppm. The aromatic protons in **7-18** exhibited a multiplet between 6.52-8.32 ppm. The methylene group of thioglycolic acid part in **13-18** appeared as a singlet between 3.92-4.08 ppm.

The mass spectra of all 5-(1-naphthylmethyl)-4-aryl-*s*-triazol-3-thiols (**7-12**) and 5-(1-naphthylmethyl)-4-aryl-*s*-triazol-3-ylthioglycolic acids (**13-18**), except 5-(1-naphthylmethyl)-4-(2-methyl-4-chlorophenyl)-*s*-triazol-3-thiol (**10**), were studied and the molecular ion peak was found to be present in all the compounds except two thiols **1** and **8**. The intensity of the peaks varied from 5-100%. The fragmentation patterns observed for thiols (**7-12**) and thioglycolic acids (**13-18**) were found to be similar (Figure I). The major fragmentation patterns for **7-18** were found to be identical to the earlier studies (10,12).

The cleavage of N$_1$-N$_2$ and N$_4$-C$_5$ bonds gave $C_{10}H_7CH_2CN^+$ ion peak at m/e 167 which was observed in all compounds. This ion lost CN and thus showed $C_{10}H_7CH_2^+$ ion peak at m/e 141. Furthermore, $C_{10}H_7CH_2^+$ ion lost CH$_2$ to give $C_{10}H_7^+$ ion peak at m/e 127. The cleavage of N$_1$-N$_2$ and C$_3$-N$_4$ bonds in 5-(1-naphthylmethyl)-4-aryl-*s*-triazol-3-thiols yielded CNSH$^+$ ion peak at m/e 59 while in 5-(1-naphthylmethyl)-4-aryl-*s*-triazol-3-ylthioglycolic acids, the $CNSCH_2COO^+$ ion peak was observed at m/e 116. Another fragment corresponding to SCH_2COOH^+ ion was observed at m/e 91 in all the thioglycolic acids.



7-12 , R$_1$ =H

13-18 , R$_1$ =CH$_2$COOH

Figure I

EXPERIMENTAL

The melting points of these compounds were taken on a Fisher John's melting point apparatus and are corrected. The infrared spectra were recorded on a Beckman model-33 double beam spectrophotometer as a suspension in nujol in the range of 600-4000 cm^{-1}. The nuclear magnetic resonance spectra were obtained on a Varian Associates A-60 instrument in DMSO-d_6 using tetramethylsilane as an internal standard and the chemical shifts were expressed in δ values. A Dupont model 21-490 spectrometer operating at 70 eV was used to obtain the mass spectra of these compounds.

The various arylisothiocyanates used in the present study were purchased from Transworld Chemicals, Inc., Washington, D.C. and 1-naphthylacethydrazide was obtained from Fluka, AG Chemische Fabrik, Switzerland.

1-(1-Naphthylacetyl)-4-arylthiosemicarbazides (**1-6**).

Equimolar quantities of 1-naphthylacethydrazide (0.1 mole) and appropriate arylisothiocyanates (0.1 mole) were refluxed in 100 ml. of absolute ethanol for 1 hour. The excess of solvent was removed under reduced pressure. The solid mass thus obtained was washed with ice cold ethanol, dried and recrystallized from ethanol. The physical constants and spectral analyses of these substituted thiosemicarbazides are recorded in Table I and Table IV.

5-(1-Naphthylmethyl)-4-aryl-*s*-triazol-3-thiols (**7-12**).

Following the method reported earlier (11), 0.02 mole of 1-(1-naphthylacetyl)-4-arylthiosemicarbazide was refluxed in 100 ml. of 2*N* aqueous sodium hydroxide solution for 2-3 hours. The reaction mixture was filtered, cooled and acidified to *p*H 2 with 2*N* hydrochloric acid. The precipitate of the crude product was filtered, washed several times with cold water, dried, and recrystallized from suitable solvent. The various 5-(1-naphthylmethyl)-4-aryl-*s*-triazol-3-thiols were characterized by their sharp melting points and elemental and spectral analyses (Table II and V)

5-(1-Naphthylmethyl)-4-aryl-*s*-triazol-3-ylthioglycolic acids (**13-18**).

A mixture of monochloroacetic acid (0.01 mole) and appropriate substituted-*s*-triazol-3-thiols (**7-12**, 0.01 mole) in 50 ml. of aqueous sodium hydroxide (0.02 mole) solution was refluxed for 3 hours. The reaction mixture was filtered while hot and the filtrate after cooling was acidified to *p*H 2 with 2*N* hydrochloric acid. The precipitate was filtered, washed with water, dried and recrystallized from suitable solvents. The various 5-(1-naphthylmethyl)-4-aryl-*s*-triazol-3-ylthioglycolic acids (**13-18**) were characterized by their sharp melting points and elemental and spectral analyses (Table III and VI).

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REFERENCES AND NOTES

(1) M. Yamamoto, S. Morooka, M. Koshiba, S. Inaba and H. Yamamoto, Japanese Patent 76,100,098 (1976); *Chem. Abstr.*, **86**, P121364f (1977).

(2) T. Denzel and H. Hoehm, U. S. Patent, 3,971,801 (1976); *Chem. Abstr.*, **86**, P16675k (1977).

(3) C. Fauran, C. Douzon, G. Raymond and B. Pourias, French Patent Application, 2,269,938 (1975); *Chem. Abstr.*, **84**, P164789z (1976).

(4) F. G. F. Eloy and R. W. Shanahan, U. S. Publ. Patent Application, B,426,439 (1976); *Chem. Abstr.*, **84**, P164787x (1976).

(5) T. George, D. Mehta, R. Tahilramani, J. David and P. Tolwalker, *J Med. Chem.*, **14**, 335 (1971).

(6) J. S. Koltenbrohn, Belgian Patent, 647,400 (1964); *Chem. Abstr.*, **63**, P14787c (1965).

(7) M. W. Whitehouse and R. A. Scherrer, "Antiinflammatory Agents, Chemistry and Pharmacology", Vol. I, Academic Press, New York, N.Y., 1974, pp. 101-104 and references therein.

(8) V. Kishore, S. Kumar, N. K. Narain, S. S. Parmar and V. I. Stenberg, *Pharmacology*, **14**, 390 (1976).

(9) V. Kishore, S. S. Parmar, V. I. Stenberg and S. Kumar, *Res. Commun. Chem. Pathol. Pharmacol.*, **11**, 581 (1975).

(10) P. J. Kothari, V. Kishore, V. I. Stenberg and S. S. Parmar, *J. Heterocyclic Chem.*, **15**, 1101 (1978).

(11) S. S. Parmar, V. K. Rastogi, V. K. Agarwal, J. N. Sinha and A. Chaudhari, *Can. J. Pharm. Sci.*, **9**, 107 (1974).

(12) K. T. Potts, R. Ambruster and E. Houghton, *J. Heterocyclic Chem.*, **8**, 773 (1971).