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Syntheses of Some New 4-Amino-5-(N-methyl-arylsulfonamido)methyl-1,2,4-triazole-3-thiones and Their Derivatives

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ABSTRACT

The cyclization of 4-amino-5-(N-methyl-arylsulfonamido)methyl-1,2,4-triazole-3-thiones **II**, *synthesized by the Reid and Heindel approach, with α-chloroacetophenone yields 7H-6-aryl-3-(N-methyl-arylsulfonamido)methyl-s-triazolo[3,4-b][1,3,4]-thiazines* **III**. *Novel compounds* **II** *also react with benzyl chloride to afford 4-amino-3-benzylthio-5-(N-methyl-arylsulfonamido)methyl-1,2,4-triazole* **IV**.© *1996 John Wiley & Sons, Inc.*

INTRODUCTION

4-Amino-5-aryl-1,2,4-triazole-3-thiones and their derivatives have been found to exhibit a wide range of biological activities [1–6]. In continuation of our interest in the synthesis and herbicidal activity of sulfonylureas and heterocyclic sulfonamides [7–9], we wish to describe here the synthesis of some new 4-amino-5-(N-methyl-arylsulfonamido)methyl-1,2,4-triazole-3-thiones **II** and the reactions of each **II** with benzyl chloride and α-chloroacetophenone (Scheme 1). The structural optimization and the biological activities of these compounds will be the subject of our further work.

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RESULTS AND DISCUSSION

A group of six new 4-amino-5-(N-methyl-arylsulfonamido)methyl-1,2,4-triazole-3-thiones **II** were prepared by hydrazinolysis of the corresponding potassium dithiocarbazates **I** with excess hydrazine hydrate following the method of Reid and Heindel [10]. The structures of compounds **II** were confirmed from elemental analyses (Table 1) and spectral data (Table 2). Thus, their NMR spectra showed a singlet at δ 4.56–5.52 (2H, NH_2) and a singlet at 13.44–13.80 (1H, SH, or HNCS) reflecting the thiol-thione tautomeric forms [5,10,11]. Their IR spectra showed stretching band in the regions 3230–3280 cm^{-1} and 1624–1631 cm^{-1} attributable to NH_2 and C=N, respectively. The strong stretching band in the 1335–1362 cm^{-1} and 1151–1160 cm^{-1} indicates the presence of asymmetric and symmetric forms of $-SO_2-$.

Reaction with α-Chloroacetophenone

Treatment of the triazoles **II** with α-chloroacetophenone in refluxing absolute ethanol followed by neutralization with sodium bicarbonate afforded 7H-6-aryl-3-(N-methyl-arylsulfonamido)melthyl-s-triazolo[3,4-b][1,3,4]thiadiazines **III**. The analytical (Table 3) and spectra data (Table 4) were in accordance with the structures assigned. The IR spectra of compounds **III** were devoid of the characteristic stretching frequencies of the NH_2 and C=O groups. The NMR spectra showed a singlet at δ 4.52–4.86 (2H, CH_2) and lacked the signals for both SH and NH_2 protons. These data indicated that cyclization

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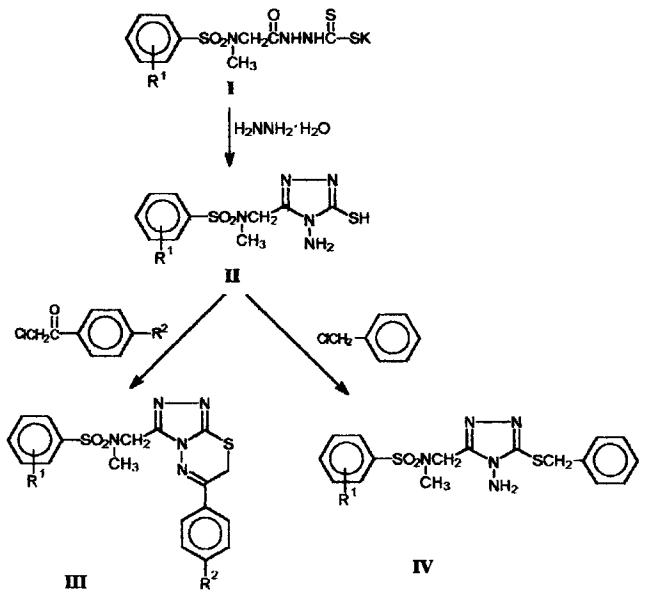

R^1=H, 2-CH_3, 4-CH_3, 2-Cl, 3-Cl, 4-Cl; R^2=H, Cl.

SCHEME 1

of triazoles II with α-chloroacetone involving both functional groups had taken place.

Reaction with Benzyl Chloride

It has been reported that the reactions of 4-amino-5-aryl-1,2,4-triazole-3-thiones with methyl bromoacetate and acid chlorides afforded S- and N-substituted products, respectively [5]. Thus, the NMR spectra of the compounds obtained by treating 4-amino-5-(N-methyl-arylsulfonamido)methyl-1,2,4-triazole-3-thiones II with benzyl chloride, revealed a singlet at δ 4.26–4.60 for CH_2 protons and were devoid of the signals for SH protons, indicating that substitution on SH had taken place. Tables 3 and 4 list the analytical and spectral data of compounds III and IV.

EXPERIMENTAL

Instruments

All melting points were determined on a micromelting-point apparatus and are uncorrected. Elemental analysis data were obtained by use of a Yanaco CHN Corder MR-3 apparatus. Infrared spectra were recorded with a Shimadzo-IR 435 infrared spectrophotometer. ^{1}H-NMR spectra were recorded on either a JEOL-FX-90Q (90 MHz) or a Bruker AC-P200 (200 MHz) spectrometer using tetramethylsilane (TMS) as an internal standard.

4-Amino-5-(N-methyl-arylsulfonamido)methyl-1,2,4-triazole-3-thiones II

Following the procedure of Reid and Heindel [10], a mixture of each potassium dithiocarbazate I (0.04 mol), hydrazine hydrate (85%, 0.08 mol), and 14 mL of water was refluxed for 2.5 hours. The color of each reaction mixture changed to green slowly. After a rapid filtration and dilution with 20 mL of water, each reaction mixture was acidified with concentrated hydrochloric acid. The white precipitate that had formed in each case was filtered off, washed three times with 80 mL of cold water, and crystallized from ethanol (Table 1).

7H-6-Aryl-3-(N-methyl-arylsulfonamido)methyl-s-triazolo[3,4-b][1,3,4]-thiadiazines III

α-Chloroacetophenone or α,4-dichloroacetophenone (0.003 mol) was added portionwise to a stirred so-

TABLE 1 Physical Constants and Analytical Data of 4-Amino-5-(N-methyl-arylsulfonamido)methyl-1,2,4-triazole-3-thiones II

		Yield mp (°C)			Analysis (Calcd./Found) %		
Compd.	R^1	(%)		Formula	C	H	N
II_1	H	66	156.4–157.8	$C_{10}H_{13}N_5O_2S_2$	40.12 40.23	4.38 4.18	23.39 23.02
II_2	2-CH_3	68	118.0–120.0	$C_{11}H_{15}N_5O_2S_2$	42.16 42.05	4.82 5.02	22.35 22.55
II_3	4-CH_3	84	165.0–167.0	$C_{11}H_{15}N_5O_2S_2$	42.16 42.15	4.82 4.84	22.35 22.42
II_4	2-Cl	76	138.5–140.5	$C_{10}H_{12}ClN_5O_2S_2$	36.09 36.30	3.63 3.62	21.04 21.03
II_5	3-Cl	65	183.0–185.0	$C_{10}H_{12}ClN_5O_2S_2$	36.09 36.26	3.63 3.32	21.04 21.22
II_6	4-Cl	78	195.2–196.4	$C_{10}H_{12}ClN_5O_2S_2$	36.09 36.27	3.63 3.58	21.04 21.19

TABLE 2 Spectral Data of 4-Amino-5-(N-methyl-arylsulfonamido)methyl-1,2,4-triazole-3-thiones **II**

		γ (Potassium bromide) cm^{-1}				
Compd.	R^1	*N–H*	*C=N*	$-SO_2$-(as)	$-SO_2$-(s)	δ (DMSO-d_6) ppm
II_1	H	3280	1624	1335	1151	2.80 (s, 3H, CH_3), 4.36 (s, 2H, CH_2), 4.96 (s, 2H, NH_2), 7.5–8.0 (m, 5H, Ph–H), 13.68 (s, 1H, SH)
II_2	2-CH_3	3235	1624	1340	1156	2.44 (s, 3H, Ph–CH_3), 2.80 (s, 3H, CH_3), 4.54 (s, 2H, CH_2), 5.44 (s, 2H, NH_2), 7.4–8.0 (m, 4H, Ph–H), 13.80 (s, 1H, SH)
II_3	4-CH_3	3269	1625	1362	1158	2.48 (s, 3H, Ph–CH_3), 2.80 (s, 3H, CH_3), 4.32 (s, 2H, CH_2), 4.56 (s, 2H, NH_2), 7.44 (d, 2H, J = 7.2 Hz, Ph–H), 7.76 (d, 2H, Ph–H), 13.44 (s, 1H, SH)
II_4	2-Cl	3230	1631	1350	1162	2.96 (s, 3H, CH_3), 4.64 (s, 2H, CH_2), 5.12 (s, 2H, NH_2), 7.4–8.3 (m, 4H, Ph–H), 13.76 (s, 1H, SH)
II_5	3-Cl	3268	1612	1345	1160	2.82 (s, 3H, CH_3), 4.40 (s, 2H, CH_2), 5.52 (s, 2H, NH_2), 7.6–7.8 (m, 4H, Ph–H), 13.62 (s, 1H, SH)
II_6	4-Cl	3270	1627	1362	1160	2.84 (s, 3H, CH_3), 4.40 (s, 2H, CH_2), 4.88 (s, 2H, NH_2), 7.6–8.0 (m, 4H, Ph–H), 13.72 (s, 1H, SH)

TABLE 3 Physical Constants and Analytical Data of Compounds **III** and **IV**

						Analysis (Calcd./Found) %		
Compd.	R^1	R^2	*Yield (%)*	*mp (°C)*	*Formula*	*C*	*H*	*N*
III_1	H	H	99	173.5–175.0	$C_{18}H_{17}N_5O_2S_2$	54.12 54.35	4.92 4.45	17.53 17.60
III_2	H	Cl	99	194.0–195.5	$C_{18}H_{16}ClN_5O_2S_2$	49.82 50.00	3.72 3.80	16.14 16.10
III_3	2-CH_3	H	89	163.0–165.0	$C_{19}H_{19}N_5O_2S_2$	55.19 55.52	4.63 4.96	16.94 16.85
III_4	4-CH_3	H	73	198.0–200.0	$C_{19}H_{19}N_5O_2S_2$	55.19 55.35	4.63 4.61	16.94 17.20
III_5	4-CH_3	Cl	82	184.0–186.0	$C_{19}H_{18}ClN_5O_2S_2$	50.94 51.03	4.50 4.11	15.63 15.75
III_6	2-Cl	H	92	177.0–178.4	$C_{18}H_{16}ClN_5O_2S_2$	49.82 50.31	3.72 3.66	16.14 16.04
III_7	3-Cl	Cl	72	199.5–200.5	$C_{18}H_{15}Cl_2N_5O_2S_2$	46.16 46.26	3.23 3.11	14.95 14.94
III_8	4-Cl	H	76	175.5–176.5	$C_{18}H_{16}ClN_5O_2S_2$	49.94 49.88	3.72 3.77	16.18 16.02
III_9	4-Cl	Cl	95	200.0–201.6	$C_{18}H_{15}Cl_2N_5O_2S_2$	46.16 46.33	3.23 3.23	14.95 14.94
IV_1	2-CH_3	H	66	126.0–127.5	$C_{18}H_{21}N_5O_2S_2$	53.58 53.57	5.24 5.37	17.36 17.35
IV_2	4-CH_3	H	74	160.0–161.5	$C_{18}H_{21}N_5O_2S_2$	53.58 53.54	5.24 5.27	17.36 17.19
IV_3	2-Cl	H	86	123.0–123.5	$C_{17}H_{18}ClN_5O_2S_2$	48.16 48.13	4.28 4.33	16.52 16.30
IV_4	3-Cl	H	88	142.0–143.2	$C_{17}H_{18}ClN_5O_2S_2$	48.16 48.27	4.28 4.19	16.52 16.26
IV_5	4-Cl	H	81	142.0–143.0	$C_{17}H_{18}ClN_5O_2S_2$	48.16 48.38	4.28 4.38	16.52 16.48

TABLE 4 Spectral Data of Compounds **III** and **IV**

Compd.	R^1	R^2	γ (Potassium bromide) cm^{-1} N–H	C=N	$-SO_2$-(as)	$-SO_2$-(s)	δ ($CDCl_3$)
III_1	H	H		1600	1353	1162	2.81 (s, 3H, CH_3), 3.96 (s, 2H, CH_2), 4.59 (s, 2H, CH_2), 7.4–8.0 (m, 10H, Ph–H)
III_2	H	Cl		1585	1345	1153	2.76 (s, 3H, CH_3), 4.20 (s, 2H, CH_2), 4.52 (s, 2H, CH_2), 7.4–8.1 (m, 9H, Ph–H)
III_3	2-CH_3	H		1593	1330	1156	2.39 (s, 3H, Ph–CH_3), 2.78(s, 3H, CH_3), 3.92 (s, 2H, CH_2), 4.57 (s, 2H, CH_2), 7.2–7.7 (m, 9H, Ph–H)
III_4	4-CH_3	H		1593	1250	1158	2.39 (s, 3H, Ph–CH_3), 2.78 (s, 3H, CH_3), 3.97 (s, 2H, CH_2), 4.57 (s, 2H, CH_2), 7.5–8.0 (m, 5H, Ph–H), 7.25 (d, 2H, J = 8.2 Hz, Ph–H), 7.66 (d, 2H, Ph–H)
III_5	4-CH_3	Cl		1588	1349	1157	2.41 (s, 3H, Ph–CH_3), 2.75 (s, 3H, CH_3), 3.95 (s, 2H, CH_2), 4.54 (s, 2H, CH_2), 7.29 (d, 2H, J = 8.2 Hz, Ph–H), 7.66 (d, 2H, Ph–H), 7.47 (d, 2H, J = 8.7 Hz, Ph–H), 7.96 (d, 2H, Ph–H)
III_6	2-Cl	H		1570	1324	1156	2.91 (s, 3H, CH_3), 3.95 (s, 2H, CH_2), 4.86 (s, 2H, CH_2), 7.4–8.0 (m, 9H, Ph–H)
III_7	3-Cl	Cl		1588	1351	1164	2.87 (s, 3H, CH_3), 3.99 (s, 2H, CH_2), 4.60 (s, 2H, CH_2), 7.4–8.0 (m, 8H, Ph–H)
III_8	4-Cl	H		1580	1350	1161	2.84 (s, 3H, CH_3), 3.97 (s, 2H, CH_2), 4.62 (s, 2H, CH_2), 7.41 (d, 2H, J = 8.6 Hz, Ph–H), 7.72 (d, 2H, Ph–H), 7.5–8.0 (m, 5H, Ph–H)
III_9	4-Cl	Cl		1582	1350	1159	2.80 (s, 3H, CH_3), 3.96 (s, 2H, CH_2), 4.59 (s, 2H, CH_2), 7.46 (d, 2H, J = 8.6 Hz, Ph–H), 7.72 (d 2H, Ph–H), 7.49 (d, 2H, J = 8.8 Hz, Ph–H), 7.93 (d, 2H, Ph–H)
IV_1	2-CH_3	H	3228	1595	1336	1154	2.41 (s, 3H, Ph–CH_3), 2.65 (s, 3H, CH_3), (s, 2H, CH_2), 4.46 (s, 2H, CH_2), 4.67 (s, 2H, NH_2), 7.2–7.8 (m, 9H, Ph–H)
IV_2	4-CH_3	H	3280	1594	1340	1152	2.42 (s, 3H, Ph–CH_3), 2.67 (s, 3H, CH_3), 4.26 (s, 2H, CH_2), 4.33 (s, 2H, CH_2), 4.63 (s, 2H, NH_2), 7.2–7.3 (m, 5H, Ph–H), 7.31 (d, 2H, J = 8.4 Hz, Ph–H), 7.63 (d, 2H, Ph–H)
IV_3	2-Cl	H	3260	1621	1335	1159	2.78 (s, 3H, CH_3), 4.32 (s, 2H, CH_2), 4.60 (s, 2H, CH_2), 4.60 (s, 2H, NH_2), 7.2–8.0 (m, 9H, Ph–H)
IV_4	3-Cl	H	3268	1626	1336	1157	2.76 (s, 3H, CH_3), 4.35 (s, 2H, CH_2), 4.40 (s, 2H, CH_2), 5.81 (s, 2H, NH_2), 7.2–7.8 (m, 9H, Ph–H)
IV_5	4-Cl	H	3260	1632	1334	1153	2.68 (s, 3H, CH_3), 4.28 (s, 2H, CH_2), 4.35 (s, 2H, CH_2), 4.70 (s, 2H, NH_2), 7.2–7.8 (m, 9H, Ph–H)

lution of each triazole **II** (0.003 mol) in 15 mL of absolute ethanol. Each mixture was then refluxed for 6 hours, cooled to room temperature, and neutralized with aqueous sodium bicarbonate solution. The solid product obtained in each case was crystallized from ethanol (Table 3).

4-Amino-3-benzylthio-5-(N-methyl-arylsulfonamido)methyl-1,2,4-triazoles **IV**

Benzyl chloride (0.002 mol) dissolved in 20 mL of absolute ethanol was mixed with each triazole **II** (0.002 mol) and heated for 8 hours, and each mixture was cooled to room temperature. Neutralization with sodium bicarbonate in each case gave a precipitate that was filtered off, washed with 20 mL of cold water, and crystallized from the ethanol–water mixture (Table 3).

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