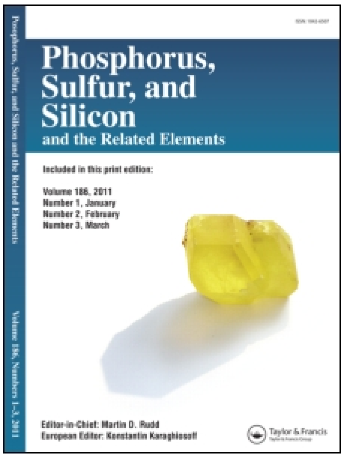

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME HETEROCYCLIC S-TRIAZOLE DERIVATIVES

Abdu E. Abdel-raham[a]; Ibrahim M. A. Awad[a]; Etify A. Bakhite[a]
[a] Chemistry Department, Faculty of Science, Assiut University, Assiut, Egypt

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Communication

SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME HETEROCYCLIC s-TRIAZOLE DERIVATIVES

ABDU E. ABDEL-RAHAM, IBRAHIM M. A. AWAD† and ETIFY A. BAKHITE
Chemistry Department, Faculty of Science, Assiut University, Assiut, Egypt

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3-Aryloxymethyl-4-phenyl-5-mercapto-s-triazoles (**1a–c**) were condensed, in the presence of a basic catalyst, with various alkyl/aralkyl halides affording different new thioethers **2a–i**, **3a–c**, **4a–l** and **5a–c** respectively.

Treatement of **5a–c** with hydrazine hydrate gave pyrazole derivatives **6a–c**. On the other hand, **1a–c** condensed with different amines in the presence of formalin forming the corresponding Mannich bases **7a–d**, **8a–f** and **9a–c** respectively in good yields. The structural configurations of synthesized compounds were confirmed by elemental and spectroscopic analysis. Biological activity of some representative compounds were screened in vitro against several strains of bacteria.

Key words: Alkylation; Mannich reactions; thioethers; pyrazoles; piperazines and benzotriazoles.

It has been reported that; S-substituted thiotriazoles exhibit broad spectrum biological effects: as tuberculotherapeutic,[1–3] as fungicidal[4,5] and as bactericidal[6,7] agents; Mannich bases and their derivatives possess favourable pharmacological properties.[8] Within these respects, we undertook the synthesis of other new S-substituted thiotriazoles and Mannich bases containing s-triazole nucleus.

RESULTS AND DISCUSSION

3-Aryloxymethyl-4-phenyl-5-mercapto-s-triazoles (**1a–c**) were prepared according to the method of Sen Gupta.[9] These compounds were reacted with alkyl (aralkyl) halides and *N*-chloromethyl benzotriazole by refluxing in alcoholic sodium hydroxide solution gave 5-alkyl(aralkyl)thio- and 5-(benzotriazol-1-ylmethyl)thio-s-triazole derivatives (**2a–i** and **3a–c**) respectively.

Similarly, the reaction of triazoles **1a–c** with p-substituted phenacyl bromides by refluxing in ethanol and neutralized with aqueous ammonia afforded 3-aryloxymethyl-4-phenyl-5-(p-substituted phenacyl)thio-s-triazoles (**4a–1**) in good yields.

Also, triazoles **1a–c** were easily reacted with equimolecular amount of 3-chloro-2,4-pentanedione in refluxing methanol to give the corresponding

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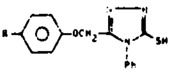
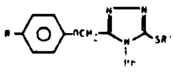
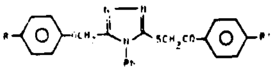
† Author to whom correspondence should be addressed.



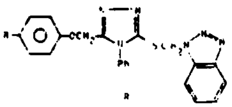
	R
Ia	H
b	CH_3
c	Cl



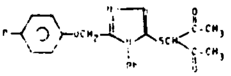
	R	R'
IIa	H	CH_3
b	H	C_2H_5
c	H	CH_2Ph
d	CH_3	CH_3
e	CH_3	CH_2CH_3
f	CH_3	CH_2Ph
g	Cl	CH_3
h	Cl	C_2H_5
i	Cl	CH_2Ph



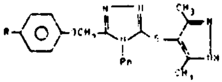
	R	R'
IVa	H	H
b	H	CH_3
c	H	Cl
d	H	Br
e	CH_3	H
f	CH_3	CH_3
g	CH_3	Cl
h	CH_3	Br
i	Cl	H
j	Cl	CH_3
k	Cl	Cl
l	Cl	Br



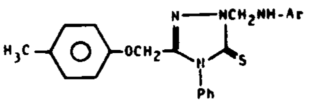
	R
IIIa	H
b	CH_3
c	Cl



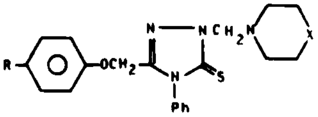
	R
Va	H
b	CH_3
c	Cl



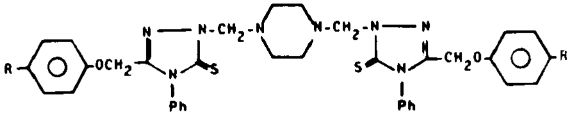
	R
VIa	H
b	CH_3
c	Cl



VIIa	$p\text{-}CH_3C_6H_4$
b	$p\text{-}ClC_6H_4$
c	$p\text{-}NO_2C_6H_4$
d	2-pyridyl



	R	X
VIIIa	H	CH_2
b	H	O
c	CH_3	CH_2
d	CH_3	O
e	Cl	CH_2
f	Cl	O



	R
IXa	H
b	CH_3
c	Cl

TABLE I

Physical and analytical data of **1a–b**, **2a–i**, **3a–c**, **4a–l**, **5a–c**, **6a–c**, **7a–d**, **8a–f** and **9a–c**

Compd. no.	M.P. °C	Yield %	Molecular formula	Analytical data Calcd./Found (%)				
				C	H	N	S	Cl
1a	155–6	90	$C_{15}H_{13}N_3OS$	63.59	4.62	14.83	11.31	—
				63.67	4.50	14.94	11.30	—
1b	184	95	$C_{16}H_{15}N_3OS$	64.63	5.08	14.13	10.78	—
				64.57	5.08	14.13	10.58	—
1c	212	93	$C_{15}H_{12}N_3OSCl$	56.69	3.81	13.22	10.09	11.16
				56.65	3.78	13.11	10.00	11.20
2a	91	74	$C_{16}H_{15}N_3OS$	64.63	5.08	14.13	10.78	—
				64.73	5.12	14.08	10.60	—
2b	66	75	$C_{17}H_{17}N_3OS$	65.57	5.50	13.49	10.30	—
				65.69	5.52	13.57	10.42	—
2c	82	78	$C_{22}H_{19}N_3OS$	70.75	5.13	11.25	8.58	—
				70.66	5.18	11.39	8.50	—
2d	91	82	$C_{17}H_{17}N_3OS$	65.57	5.50	13.49	10.30	—
				65.25	5.59	13.52	10.10	—
2e	100	83	$C_{18}H_{19}N_3OS$	66.43	5.88	12.91	9.85	—
				66.23	5.79	13.00	9.85	—
2f	116	79	$C_{23}H_{21}N_3OS$	71.29	5.46	10.84	8.27	—
				71.22	5.56	10.61	8.10	—
2g	125	77	$C_{16}H_{14}N_3OSCl$	57.92	4.25	12.66	9.66	10.68
				58.00	4.33	12.70	9.52	10.70
2h	82	80	$C_{17}H_{16}N_3OSCl$	59.04	4.66	12.15	9.27	10.25
				58.88	4.45	10.30	9.66	10.11
2i	100	90	$C_{22}H_{18}N_3OSCl$	64.78	4.45	10.30	7.86	8.69
				64.90	4.40	10.31	7.65	8.60
3a	127	78	$C_{22}H_{18}N_6OS$	63.75	4.38	20.27	7.73	—
				63.68	4.39	20.07	7.58	—
3b	120	80	$C_{23}H_{20}N_6OS$	64.47	4.70	19.61	7.48	—
				64.87	4.82	19.45	7.31	—
3c	114–5	75	$C_{22}H_{17}N_6OSCl$	58.86	3.82	18.72	7.14	7.90
				58.65	3.81	18.66	7.02	7.59
4a	80	80	$C_{23}H_{19}N_3O_2S$	68.81	4.77	10.47	7.99	—
				68.54	4.90	10.37	8.22	—
4b	122	90	$C_{24}H_{21}N_3O_2S$	69.38	5.09	10.11	7.72	—
				69.50	5.14	9.90	7.86	—
4c	155	90	$C_{23}H_{18}N_3O_2SCl$	63.37	4.16	9.64	7.35	8.13
				63.50	4.18	9.80	7.12	8.00
4d	157	95	$C_{23}H_{18}N_3O_2SBr$	57.50	3.78	8.75	6.67	16.63
				57.22	3.90	8.55	6.81	16.60
4e	110–112	78	$C_{24}H_{21}N_3O_2S$	69.38	5.09	10.11	7.72	—
				69.29	5.05	10.31	7.80	—
4f	145	92	$C_{25}H_{23}N_3O_2S$	69.91	5.40	9.78	7.46	—
				70.02	5.55	9.63	7.50	—
4g	157	90	$C_{24}H_{20}N_3O_2SCl$	64.07	4.48	9.34	7.13	7.88
				64.16	4.46	9.21	7.11	7.76
4h	175	93	$C_{24}H_{20}N_3O_2SBr$	58.29	4.08	8.50	6.48	16.16
				58.15	4.12	8.86	6.28	16.35
4i	165	82	$C_{23}H_{18}N_3O_2SCl$	63.37	4.16	9.64	7.35	8.13
				63.53	4.14	9.80	7.41	8.17
4j	163	91	$C_{24}H_{20}N_3O_2SCl$	64.07	4.48	9.34	7.13	7.88
				64.01	4.53	9.38	7.00	8.00
4k	184	90	$C_{23}H_{17}N_3O_2SCl$	58.73	3.64	8.93	6.82	15.07
				58.78	3.63	8.81	6.66	15.23
4l	180	85	$C_{23}H_{17}N_3O_2SBrCl$	53.66	3.33	8.16	6.23	—
				53.67	3.42	8.14	6.40	—

TABLE I (*Continued*)

Compd. no.	M.P. °C	Yield %	Molecular formula	Analytical data Calcd./Found (%) C	H	N	S	Cl
5a	160	94	$C_{20}H_{19}N_3O_3S$	62.98	5.02	11.02	8.41	—
				62.87	5.00	11.19	8.67	—
5b	163	90	$C_{21}H_{21}N_3O_3S$	63.78	5.35	10.63	8.11	—
				63.75	5.31	10.62	8.04	—
5c	159	92	$C_{20}H_{18}N_3O_3SCl$	57.76	4.36	10.10	7.71	8.52
				57.96	4.33	10.01	7.66	8.80
6a	173	80	$C_{20}H_{19}ON_5S$	63.64	5.07	18.55	8.49	—
				63.70	5.04	18.90	8.42	—
6b	158–160	85	$C_{21}H_{21}ON_5S$	64.43	5.41	17.89	8.19	—
				64.33	5.29	17.79	8.32	—
6c	164	84	$C_{20}H_{18}ON_5SCl$	58.32	4.40	17.00	7.78	8.61
				58.16	4.46	17.08	7.50	8.80

5-(2′,4′-diketopentan-3′-yl)thio-s-triazole derivatives (**5a–c**), which underwent further reaction with hydrazine hydrate to furnish the promising products of 3-aryloxymethyl-4-phenyl-5-(3′,5′-dimethylpyrazol-4′-yl)thio-s-triazoles (**6a–c**) in excellent yields.

On the other hand, the reaction of compounds **1a–c** with aromatic/heterocyclic amines in presence of formalin gave the corresponding Mannich bases **7a–d**.

Furthermore, the 3-aryloxymethyl-4-phenyl-1-(*N*-piperidino/morpholino methyl)-5-thiono-s-triazoles (**8a–f**) were obtained from the reaction of **1a–c** with piperidine/morpholine in the presence of formalin. Finally, the interaction of triazoles **1a–c** with piperazine in the presence of formalin solution led to the formation of 1,4-bis-(3′-arloxymethyl-4′-phenyl-5′-thiono-s-triazol-l′-ylmethyl)-piprazines (**9a–c**).

The structure of the synthesized compounds were confirmed on the basis of their elemental analysis (Table I), IR spectra (Table II) and ^{1}H NMR spectra (Table III).

The biological activity of some representative compounds (**1a**, **1b**, **1c**, **2a**, **3a**, **4a**, **6a**, **6b**, **7a**, **8c** and **9b**) were tested against seven strains of bacteria (Table IV) and it was found that; most of the compounds exhibited effective activity against *Bacillus cereus* and *Micrococcus roseus*. Whereas some of them are active against *Staphylococcus citreus*. The compounds **1c**, **1a**, **8** and **9b** only showed significant activity against *Escherchia coli*. All the compounds are inactive against *Serratia*

TABLE II

Important IR bands of the prepared compounds

Assignment	**2a–i**	**3a–c**	**4a–l**	**5a–c**	**6a–c**	**7a–d**	**8a–f**	**9a–c**
νC=N	1600	1600	1600	1600	1600	1600	1600	1600
νC=O	—	—	1700–1680	—	—	—	—	—
νC=S	—	—	—	—	—	1330	1330	1330
νNH	—	—	—	—	3200	3400—3200	—	—
νC—S—C	1400	1400	1390	1390	1380	—	—	—
νCH ali.	2940	2940	2930	2950	2950	2920	2920	2940

TABLE III

^{1}H-NMR spectra of a representative examples of the prepared compounds (chemical shifts in δppm)

Com-pound	Aromatic protons (m)	—OCH_2— (s)	—NCH_2N— (s)	
2a	6.60–7.35 (10H)	4.85	—	2.55 (s, 3H of SCH_3 group)
2i	6.56–7.30 (14H)	4.85	—	4.30 (s, 2H of SCH_2 group)
3a	6.60–8.00 (14H)	4.95	6.30	
4a	6.70–8.00 (15H)	4.90	—	5.00 (s, 2H of SCH_2CO group)
4g	6.60–8.00 (13H)	4.90	—	5.00 (s, 2H of SCH_2CO group)
5b	6.60–7.50 (10H, 9H aromatic and 1H of SC*H* group)	4.85	—	2.30 (s, 9H of two-$COCH_3$ and on —CH_3 groups)
6b	6.55–7.50 (10H, 9H aromatic and 1H of SCH group)	4.85	—	2.2 (s, 3H of —CH_3 group) 2.10 (s, 6H of two —CH_3) groups attached to pyrazde moiety)
7a	6.50–7.40 (13H)	4.70	5.50*	5.15 (t, 1H of NH group) 2.22 (s, 6H of two —CH_3 groups)
8c	6.50–7.50 (9H)	4.80	5.10	1.30–1.70 $\left(\text{m, 6H of } CH_2<\begin{matrix}CH_2\text{—}\\CH_2\end{matrix}\text{ group}\right)$ 2.70–2.85 $\left(\text{t, 4H of } N<\begin{matrix}CH_2\text{—}\\CH_2\text{—}\end{matrix}\text{ group}\right)$ 2.20 (s, 3H of —Ch_3 group)
8f	6.50–7.30 (9H)	4.70	5.00	3.53–3.67 $\left(\text{t, 4H of } O<\begin{matrix}CH_2\\CH_2\end{matrix}\text{ group}\right)$ 2.70–2.84 $\left(\text{t, 4H of } N<\begin{matrix}CH_2\\CH_2\end{matrix}\text{ group}\right)$
9b	6.60–7.50 (18H)	4.8 (4H)	5.10 (4H)	2.95 (s, 8H of four methylene groups of piperazine moiety) 2.30 (s, 6H of two-CH_3 groups)

* This signal appeared as doublet and after deutration reappeared as singlet.

TABLE IV

Biological screening of the tested compounds (inhibition zones in mm)

Compound no.	Molecular formula	Bacillus cereus	Micro. luteus	Micro. roseus	Staph. citreus	Escher-coli	Serratia rhodnii	Pseud. aeruginosa
1a	$C_{15}H_{13}OS$	30	-ve	50	70	-ve	-ve	-ve
1b	$C_{16}H_{15}N_3OS$	30	-ve	30	70	-ve	-ve	-ve
1c	$C_{15}H_{12}N_3OSCl$	-ve	-ve	-ve	-ve	30	-ve	-ve
2a	$C_{16}H_{15}N_3OS$	40	20	50	-ve	60	-ve	-ve
3a	$C_{22}H_{18}N_6OS$	30	-ve	-ve	-ve	-ve	-ve	-ve
4a	$C_{23}H_{19}N_3O_2S$	30	-ve	70	30	-ve	-ve	-ve
6b	$C_{21}H_{21}ON_5S$	30	30	80	-ve	-ve	-ve	-ve
7a	$C_{24}H_{24}N_4OS$	50	-ve	50	30	-ve	-ve	-ve
8c	$C_{22}H_{26}N_4OS$	10	-ve	30	80	40	-ve	-ve
9b	$C_{38}H_{40}N_8O_2S_2$	10	-ve	20	80	40	-ve	-ve

rhodnii, Pseudomonas aeruginosa and *Micrococcus luteus* except for **2a** and **6b** which showed remarkable activity against *Micrococcus luteus*.

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were recorded on PYE UNICAM SP 3-100 spectrophotometer using KBr disc technique. The ^{1}H-NMR spectra were recorded by a varian EM-390 90 MHZ NMR spectrometer using $CDCl_3$ as a solvent and TMS as internal standard. Elemental analysis was carried out by elemental analyzer 240°C. The physical and analytical data of the newly synthesized compounds are listed in Table I.

3-Aryloxymethyl-4-phenyl-5-mercapto-s-triazoles (**1a–c**) were prepared according to reported method.[9]

3-Aryloxymethyl-4-phenyl-5-alkyl(aralkyl)thio-s-triazoles (**2a–i**). Compound **1a–c** (0.01 mole) was dissolved in 30 ml of alcoholic KOH solution (4%). To this 0.11 mole of alkyl(aralkyl) halide was added. The reaction mixture was refluxed for 1 hr. Solid compound which formed on cooling was filtered and recrystallized from dil. alcohol to give colourless needles of **2a–i** in 75–90% yield.

3-Aryloxymethyl-4-phenyl-5-(benzotriazol-1′-ylmethyl)thio-5-triazoles (**3a–c**). Compounds **3a–c** were prepared by reaction of **1a–c** and *N*-chloromethyl benzotriazole according to the above procedure in 75–80% yield and crystallized from dil. alcohol.

3-Aryloxymethyl-4-phenyl-5-(p-substituted phenacyl)thio-s-triazoles (**4a–1**). A mixture of **1a–c** (0.01 mole) and p-substituted phenacyl bromide (0.01 mole) in absolute ethanol (50 ml) was refluxed for 4 hrs, cooled and neutralized with aqueous ammonia, the precipitated product was filtered and crystallized from ethanol to give colourless needles of **4a–1** in 78–95% yield.

3-Aryloxymethyl-4-phenyl-5-(2′,4′-diketo-pentan-3′-yl)thio-s-triazoles (**5a–c**). A mixture of **1a–c** (0.01 mole) and 3-chloro-2,4-pentanedione (0.01 mole) in methanol (50 ml) was refluxed for 4 hrs; the reaction mixture was concentrated to a small volume. The crystalline product thus formed after cooling was filtered and recrystallized from ethanol to afford a colourless plates of **5a–c** in 90% yield.

3-Aryloxymethol-4-phenyl-5-(3′,5′-dimethyl-pyrazol-4′-yl)thio-s-triazoles (**6a–c**). To a suspension of **5a–c** (0.01 mole) in methanol (40 ml), hydrazine hydrate (0.01 mole) was added, the mixture was refluxed for 3 hrs, concentrated and diluted with water. The solid thus formed was filtered and recrystallized from dil. alcohol to give white needles of **6a–c** in 80% yield.

3-Aryloxymethyl-4-phenyl-1-(N-aryl/heterocycle aminomethyl)-5-thiono-s-triazoles (**7a–d**). To a mixture of **1b** (0.01 mole) and amine (0.01 mole) in ethanol (50 ml), formalin solution (37%, 1 ml) was added. The contents were stirred for one hour. Then refluxed for a further hour. It was left overnight at room temperature. The product thus formed was filtered off and recrystallized from ethanol to give **6a–d** in 79–90% yield.

3-Aryloxymethyl-4-phenyl-1-(N-piperidino/morpholinomethyl)-5-thiono-s-triazoles (**8a–f**). Compounds **8a–f** were obtained from the reaction of **1a–c** with piperidine (morpholine) and formalin by the same method described above. The products were crystallized from ethanol to give colourless needles of **8a–f** in 80–88% yield.

1,4-Bis(3′-aryloxymethyl-4′-phenyl-5′-thiono-s-triazol-1′-ylmethyl)-piperazines (**9a–c**). The bis compounds were synthesized by the same method of 6a–d using piperazine as amine. The products were recrystallized from ethanol chloroform mixture to give white needles of **9a–c** in 86–90% yield.

Biological screening. The bacteriostatic activity against *Bacillus cereus, Micrococcus luteus, Micrococcus roseus, Staphylococcus citreus, Escherichia coli, Serratia rhodnii* and *Pseudomonas aeruginosa* were tested by usual cup plate agar diffusion technique;[10,11] 10^{-5} M solutions of the selected compounds in DMF were prepared. The dishes were allowed to stand in a refrigerator at 4–8°C for 0.5 h to allow diffusion of the solutions and were then incubated at 28°C for 36 hrs. The inhibition zones were measured with the callipers.

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