Synthesis and Antibacterial Activities of 4-Amino-3-(1-aryl-5-methyl-1,2,3-triazol-4-yl)-5-mercapto-1,2,4-triazoles/2-Amino-5-(1-aryl-5-methyl-1,2,3-triazol-4-yl)-1,3,4-thiadiazoles and Their Derivatives

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Treatment of 4-amino-3-(1-aryl-5-methyl-1,2,3-triazol-4-yl)-5-mercapto-1,2,4-triazoles/2-amino-5-(1-aryl-5-methyl-1,2,3-triazol-4-yl)-1,3,4-thiadiazoles with benzaldehyde, acetone and ω-bromoacetophenone was tested and compared. The title compounds Schiff bases, amides, imidazolo[2,1-*b*]-1,3,4-thiadiazoles and 7*H*-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazines have been confirmed by elemental analyses, ^{1}H NMR, IR and MS spectra. All the compounds have also been screened for their antibacterial activities against *B. subtilis*, *S. aureus* and *E. coli*.

Keywords Schiff base, amide, imidazolo[2,1-*b*]-1,3,4-thiadiazole, 7*H*-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazine

Introduction

Schiff bases, amides, imidazolo[2,1-*b*]-1,3,4-thiadiazoles, and 7*H*-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazines containing heterocycles have been attracting much attention as potential antifungal agents.[1-5] 1,2,3-triazole,[6-7] mercapto-1,2,4-triazole,[8] 1,3,4-thiadiazole[9-10] and their related compounds have been found useful in medicine, agriculture and industry. 1,2,3-Triazole and their bezo derivatives constitute a class of compounds which have been attracting considerable attention in industry and agriculture primarily due to their significant biological activities. To our knowledge, not much has been mentioned in the synthesis of 4-amino-3-(1-aryl-5-methyl-1,2,3-triazol-4-yl)-5-mercapto-1,2,4-triazoles (**1**) and 2-amino-5-(1-aryl-5-methyl-1,2,3-triazol-4-yl)-1,3,4-thiadiazoles (**2**). In order to study the structure-activity relationship, we designed some new fused heterocyclic compounds combining two or more active structured units in one molecule as medicinal and biologically active compounds, such as 3-aryl-6-heterocyclic-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazoles and 7*H*-6-aryl-3-heterocyclic-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazines.[11-13] As a part of our interest in this area, we report the reactions of compounds **1** and **2** with benzaldehyde, acetone and ω-bromoacetophenone. Such heterocyclic groups were incorporated into Schiff base, acetic amide and imidazolo[2,1-*b*]-1,3,4-thiadiazole for the first time (Scheme 1).

Experimental

The melting points were taken on an X-4 microscopic melting point apparatus and were uncorrected. IR spectra were recorded on a 5-DX spectrometer in KBr disc. ^{1}H NMR spectra were obtained on a Bruker AC-80 instrument (DMSO-d_6 or CH_3COCH_3-d_6) with TMS as

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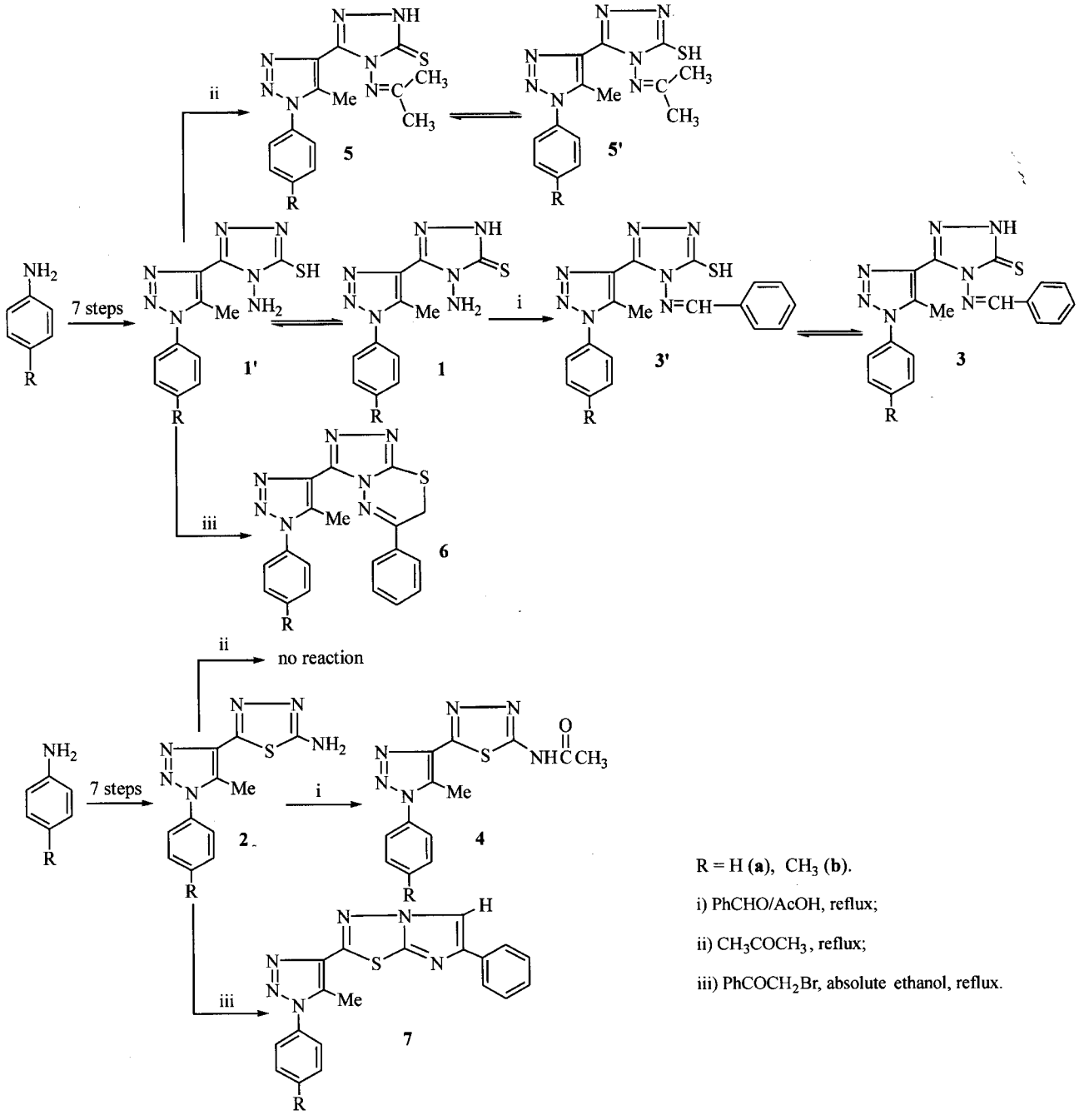
Scheme 1 Reaction procedure for the formation of products **3**—**7** from **1** or **2**.



R = H (**a**), CH_3 (**b**).

i) PhCHO/AcOH, reflux;

ii) CH_3COCH_3, reflux;

iii) $PhCOCH_2Br$, absolute ethanol, reflux.

internal standard. Mass spectra were performed in a ZAB-HS (EI) spectrometer. Elemental analyses were taken on an Elementar Vario EL apparatus.

Preparation of 4-*amino*-3-(1-*aryl*-5-*methyl*-1,2,3-*triazol*-4-*yl*)-5-*mercapto*-1, 2, 4-*triazoles* (**1**) *and* 2-*amino*-5-(1-*aryl*-5-*methyl*-1, 2, 3-*triazol*-4-*yl*)-1, 3, 4-*thiadiazole* (**2**)

A series of *s*-triazoles **1** and 1,3,4-thiadiazoles **2** bearing 1-aryl-5-methyl-1,2,3-triazol-4-yl as substrates were prepared using aniline/*p*-toluiline according to literature methods.[11,14-16] *s*-Triazole **1a** and 1,3,4-thiadiazoles **2** have not been prepared before.

1a Colorless needle, m.p. 176—178 ℃; ^{1}H NMR δ: 14.06 (s, 1H, NH*), 7.66 (s, 5H, Ph—H), 5.92 (s, 2H, NH_2*), 2.45 (s, 3H, CH_3) (*: exchangeable with D_2O); IR (KBr) ν: 3289, 3139, 2940, 1632, 1592, 1484, 1270, 944 cm^{-1}; MS *m/z* (%): 273 (M^+, 35); Anal. calcd for $C_{11}H_{11}N_7S$: C 48.34, H 4.06, N 35.87; found C 48.10, H 4.18, N 35.55.

1b Colorless plate, m.p. 185—187 ℃ (lit[15] 189—190 ℃); ^{1}H NMR δ: 14.02 (s, 1H, NH*), 7.51—7.49 (m, 4H, ArH), 5.91 (s, 2H, NH_2*), 2.47 (s, 3H, CH_3), 2.43 (s, 3H, CH_3); IR (KBr) ν: 3301, 2947, 1601, 1493, 1271, 973 cm^{-1}.

2a Colorless plate, m.p. 255—257 ℃; ^{1}H NMR δ: 7.60 (s, 5H, PhH), 5.93 (s, 2H, NH_2), 2.55 (s, 3H, CH_3); IR (KBr) ν: 3219, 3066, 2973, 1653, 1598, 1501, 1457, 974 cm^{-1}; MS *m/z* (%): 258 (M^+, 36); 229 (30), 156 (100), 77 (75); Anal. calcd for $C_{11}H_{10}N_6S$: C 51.15, H 3.90, N 32.54; found C 49.91, H 4.10, N 32.36.

2b Colorless plate, m.p. 262—264 ℃; ^{1}H NMR δ: 7.50—7.61 (m, 4H, ArH), 5,93 (s, 2H, NH_2), 2.56 (s, 3H, CH_3), 2.42 (s, 3H, CH_3); IR ν: 3260, 3087, 2948, 1622, 1512, 975 cm^{-1}; MS *m/z* (%): 272 (M^+, 44), 244 (100), 169 (90), 91 (76); Anal. calcd for $C_{12}H_{12}N_6S$: C 52.93, H 4.44, N 30.86; found C 52.69, H 4.56, N 30.52.

Preparation of 3-(1-*aryl*-5-*methyl*-1, 2, 3-*triazol*-4-*yl*)-4-*phenylideneamino*-5-*mercapto*-*s*-*triazoles* (**3**) *and* 2-(1-*aryl*-5-*methyl*-1,2,3-*triazol*-4-*yl*)-5-*acetamido*-1,3,4-*thiadiazoles* (**4**)

1/2 (1 mmol) was dissolved in hot acetic acid (30 mL) and the equimolecular benzaldehyde was added. The mixture was refluxed and monitored by TLC until the substrates disappeared. After removal of the excess acetic acid *in vacuo*, water (20 mL) was added to the residue. The resulting solid was filtered, washed with water, and finally recrystallized from EtOH to give **3/4**.

Preparation of 3-(1-*aryl*-5-*methyl*-1, 2, 3-*triazol*-4-*yl*)-4-*dimethylideneamino*-5-*mercapto*-*s*-*triazoles* (**5**)

The substrate **1/2** (1 mmol) was dissolved in hot acetone and refluxed for 8 h. As the reaction was over, excess of acetone was distilled off. On cooling, needle crystal was separated out.

Preparation of condensed heterocycles 7*H*-3-(1-*aryl*-5-*methyl*-1,2,3-*triazol*-4-*yl*)-6-*phenyl*-*s*-*triazolo*[3,4-*b*]1,3,4-*thiadiazines* (**6**) *and* 2-(1-*aryl*-5-*methyl*-1,2,3-*triazol*-4-*yl*)-6-*phenyl*-*imidazolo*[2,1-*b*]-1,3,4-*thiadiazoles* (**7**)

A mixture of compound **1/2** (1 mmol) and ω-bromoacetophenone (1 mmol) in absolute ethanol was refluxed over an oil bath. The solution was concentrated and the resulting solid was filtered, washed with water and recrystallized from ethanol to give **6** and **7**.

Results and discussion

In general, the rate-determining step of the formation of a Schiff base proceeds by the nucleophilic attack of an amine to the carbonyl carbon of the aldehyde function. For this reason, it would be expected that compounds **1** would be much reactiver than **2** because the amine radical was connected with heterocycle by nitrogen in **1** but carbon in **2** on account of the alpha effect. That is to say, α-N has lone pair electron that enlarges the electron cloud density of NH_2 connecting with it. So the NH_2 of compounds **1** has higher basic capacity than that of compounds **2** and shows better nucleophilic reactivity. Our experiments exhibited this propose was well grounded. For example, it was difficult to synthesize Schiff base if **2** were treated with benzaldehyde in usually solvent such as ethanol catalyzed by H_2SO_4, *p*-toluene sulfonic acid or acetic acid. Boiling **2** and benzaldehyde in acetic acid yielded *N*-heterocyclylacetic amides **4**, just not Schiff base. The Schiff bases **3** could be obtained by treatment of **1** according to El-Emam reported.[17]

The reaction of compounds **1** or **2** with acetone also showed the different reactivity. Schiff bases **5** were separated from the reaction of **1** with acetone, but no reaction was occurred for **2**.

^{1}H NMR spectra inhibited that there was a double-bonded sulfur (**1**, **3** and **5**) rather than a mercapto group in 5-position (**1'**, **3'** and **5'**). For instance, the H connected with *s*-triazole ring of **1a** showed the ^{1}H NMR singlet at δ 14.09, which indicated that mercapto group existed in thione rather than in thiol form.

The condensation of **1/2** with ω-bromoacetophe-

none was successful. The synthesis and antibacterial evaluation about some analog of 7*H*-3-(1-aryl-5-methyl-1,2,3-triazol-4-yl)-6-phenyl-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazines (**6**) have been described in previous papers.[13-15] 2-(1-Aryl-5-methyl-1,2,3-triazol-4-yl)-6-phenyl-imidazolo[2,1-*b*]-1,3,4-thiadiazoles (**7**) were got for the first time. Absolute ethanol was proved to be the efficient solvent for the formation of products **6**—**7**. These two sorts of active fused heterocycles still are noticed by chemists because of their broad-spectrum biological activities.[18-19]

The structures assigned to the products **3**—**7** are based on elemental analyses, ^{1}H NMR, IR and MS spectra (Tables 1 and 2).

Table 1 Physical properties and elemental analyses of compounds **3**—**7**

Compd.	Yield (%)	m.p. (℃)	Molecular formula	Crystals	Elemental analyses Cacld. (Found, %)		
					C	N	H
3a	88	198—200	$C_{18}H_{15}N_7S$	Yellow needle	59.82 (59.59)	27.13 (27.58)	4.18 (4.13)
3b	90	222—224	$C_{19}H_{17}N_7S$	Yellow needle	60.78 (60.59)	26.11 (26.22)	4.56 (4.56)
4a	76	282—284	$C_{13}H_{12}N_6OS$	Pale yellow needle	51.99 (52.12)	27.98 (27.69)	4.03 (4.10)
4b	79	318—320	$C_{14}H_{14}N_6OS$	Pale yellow needle	53.49 (53.41)	26.73 (26.65)	4.49 (4.64)
5a	85	247—248	$C_{14}H_{15}N_7S$	Colorless needle	53.66 (53.77)	31.29 (31.31)	4.82 (5.10)
5b	88	251—253	$C_{15}H_{17}N_7S$	Colorless needle	55.03 (55.12)	29.95 (29.99)	5.23 (5.26)
6a	82	214—216	$C_{19}H_{15}N_7S$	Colorless granule	61.11 (59.98)	26.26 (26.09)	4.05 (4.13)
6b[a]	41	236—238	$C_{20}H_{19}N_7S$	Pale yellow granule	62.02 (62.00)	25.32 (25.30)	4.39 (4.42)
7a	80	244—245	$C_{19}H_{14}N_6S$	Colorless plate	63.67 (63.65)	23.45 (23.16)	3.94 (3.64)
7b	83	249—251	$C_{20}H_{16}N_6S$	Colorless needle	64.50 (64.38)	22.56 (22.52)	4.33 (4.39)

[a]The compound has been reported in literature[15].

Table 2 IR, Mass and ^{1}H NMR spectral data of compounds **3**—**7**

Compd.	IR (KBr) ν (cm^{-1})	MS *m/z* (%)	^{1}H NMR
3a	3138, 2950, 1595, 1493, 1432, 1365, 1272, 966	361 (M^+, 14), 273 (19), 258 (27), 229 (100), 156 (46), 103 (40), 77 (80)	14.71 (s, 1H, NH), 9.92 (s, 1H, =CH), 7.84 (s, 2H, ArH), 7.60 (s, 8H, ArH), 2.54 (s, 3H, CH_3)
3b	3088, 2925, 1600, 1494, 1422, 1368, 1278, 974	375 (M^+, 16), 272 (12), 244 (41), 243 (100), 229 (25), 169 (38), 103 (21), 91 (26)	14.36 (s, 1H, NH), 9.63 (s, 1H, =CH), 7.97—7.85 (m, 2H, ArH), 7.62—7.47 (m, 7H, ArH), 2.45 (s, 3H, CH_3), 2.42 (s, 3H, CH_3)
4a	3169, 2909, 1700, 1570, 1502, 1369, 1316, 973	300 (M^+, 20), 272 (26), 230 (100), 156 (26), 130 (16), 77 (47), 43 (62)	12.69 (s, 1H, NH), 7.68 (s, 5H, Ph—H), 2.65 (s, 3H, CH_3), 2.42 (s, 3H, CH_3)
4b	3167, 2919, 1701, 1570, 1516, 1368, 1317, 974	314 (M^+, 15), 286 (8), 286 (46), 244 (67), 170 (34), 91 (49), 65 (29), 43 (100)	12.68 (s, 1H, NH), 7.54 (d, J = 2.8 Hz, 4H, ArH), 2.63 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 2.23 (s, 3H, CH_3)
5a	3105, 2937, 1634, 1595, 1498, 1378, 1297, 975	314 (M^+, 19), 313 (M^+, 100), 272 (76), 229 (34), 156 (45), 77 (62), 56 (37), 42 (5)	13.91 (s, 1H, N—H), 7.68 (s, 5H, Ph—H), 2.56 (s, 3H, CH_3), 2.30 (s, 3H, *cis*-CH_3), 2.07 (s, 3H, *trans*-CH_3)

Contituned

Compd.	IR (KBr) ν (cm^{-1})	MS m/z (%)	^{1}H NMR
5b	3102, 2936, 1633, 1601, 1493, 1375, 1297, 976	328 (M^+, 21), 327 (M^+, 100), 286 (84), 243 (60), 170 (65), 156 (42), 91 (71), 56 (69)	14.15 (s, 1H, NH), 7.50 (d, J = 2.6 Hz, 4H, ArH), 2.45 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 2.26 (s, 3H, *cis*-CH_3), 1.98 (s, 3H, *trans*-CH_3)
6a	3066, 2985, 2359, 1593, 1508, 1372, 1313, 965	373 (M^+,22), 345 (25), 242 (56), 181 (62), 156 (67), 103 (72), 77 (100), 51 (25)	8.03 (q, J = 4.6 Hz, 2H, Ph—H), 7.70—7.56 (m, 8H, PhH), 4.52 (s, 2H, CH_2), 2.54 (s, 3H, CH_3)
6b[a]	3054, 2922, 1601, 1518, 1369, 1262, 966	387 (M^+,10), 359 (24), 256 (26), 228 (14), 170 (41), 169 (80), 91 (100), 77 (89)	7.49—8.05 (m, 5H, Ph—H), 7.43 (s, 4H, ArH), 4.04 (s, 2H, CH_2), 2.68 (s, 3H, CH_3), 2.50 (s, 3H, CH_3).
7a	3108, 3043, 2363, 1596, 1493, 1376, 1274, 962	358 (M^+, 78), 174 (31), 156 (56), 147 (100), 129 (16), 103 (96), 77 (36)	8.79 (s, 1H, =CH), 7.92 (d, J = 7.9 Hz, 2H, Ar—H), 7.69(s, 5H, Ph—H), 7.39 (q, J = 7.4 Hz, 3H, Ar—H), 2.66 (s, 3H,CH_3)
7b	3117, 3046, 1598, 1480, 1375, 1271, 962, 818	372 (M^+, 50), 174 (23), 170 (58), 147 (72), 117 (16), 102 (10), 103 (100), 91 (21)	8.74 (s, 1H, CH), 7.89 (d, J = 6.6 Hz, 2H, ArH), 7.52 (s, 5H, PhH), 7.40 (d, J = 8.2 Hz, 2H, ArH), 2.63 (s, 3H, CH_3), 2.44 (s, 3H,CH_3).

[a]The compound has been reported in literature.[15]

Antibacterial activity

Compounds **1**—**7** were screened for their antibacterial activities against *B. subtilis*, *S. aureus* and *E. coli* employing cup-plate method at the concentration of 100 μg/mL in the nutrient agar media. The number of replication in each case was three. The investigation results are listed in Table 3. The results showed that all compounds were active against *B. subtilis* and *S. aureus*. Except for **1a**, **2a**, **3a**—**b** and **6b**, the other title products displayed an inhibitory effect on *E. coli*. It is worthwhile to notice that compounds **4a**—**b** and **7a**—**b** express significant antibacterial activity. The investigation on the structure-activity relationship shows that thiadiazole ring enhances the antibacterial action of the compounds.

Table 3 Antibacterial activities of compounds **1**—**7**[a]

Compd.	*B. subtilis*	*S. aureus*	*E. coli*
1a	+ +	+	−
1b	+ +	+	+
2a	+	+	−
2b	+	+	+
3a	+	+	−
3b	+	+	−
4a	+ +	+ +	+ +
4b	+ +	+ +	+
5a	+ +	+	+
5b	+ +	+	+
6a	+	+ +	+
6b	+	+	−
7a	+ +	+ +	+ +
7b	+ +	+ +	+

[a]Zone diameter of growth inhibition: < 10 mm (−), 10—13 mm (+) and 14—17 mm (+ +). Diameter of the cup = 8 mm.

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