Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 25 Jul 2007.

To cite this article: Shao Ling , Zhou Xin , Zhang Qing , Liu Jian-Bing , Jin Zhong & Fang Jian-Xin (2007): Synthesis, Structure, and Biological Activity of Novel 1H-1,2,4-Triazol-1-yl-thiazole Derivatives, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 37:2, 199-207

To link to this article: http://dx.doi.org/10.1080/00397910601031629

Synthetic Communications®, 37: 199–207, 2007

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910601031629

Synthesis, Structure, and Biological Activity of Novel 1*H*-1,2,4-Triazol-1-yl-thiazole Derivatives

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Abstract: 2-Amino-4-aryl-5-(1*H*-1,2,4-triazol-1-yl)thiazole derivatives were synthesized from the reaction of α-bromo substituted acetophenone and thiourea. The structures were confirmed by elemental analysis, ^{1}H NMR and single crystal X-ray diffraction analysis. Biological evaluation showed that some of them possess antifungal and plant growth regulatory activities.

Keywords: biological activity, structure, synthesis, thiazole, triazole

INTRODUCTION

Thiazole derivatives are reported to exhibit diverse biological activities,[1] such as antituberculous activities, bacteriostatic activities, and fungistaic activities. Furthermore, triazole antifungals are known as potent inhibitors of the cytochrome P450 monooxygensae in the process of fungal biosynthesis of ergosterol, which is an important constitution of fungal cell membrane.[2] These triazole antifungals, such as Sumiseven(S-3307D), propiconazole, and imibenconazole, are applied widely to plant protection.

As a continuation of our studies on triazole derivatives,[3] and in search of novel lead compounds with potential antifungicidal activities; we have sought

Received May 25, 2006
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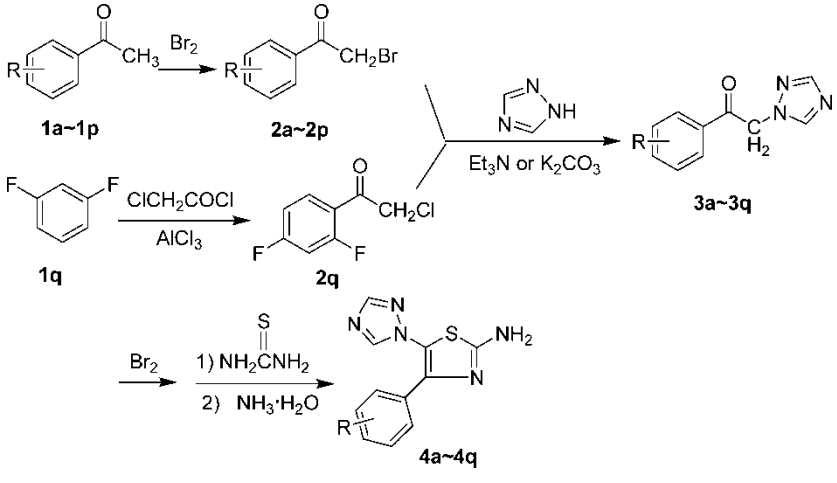
to synthesize such 2-aminothiazole compounds incorporating 1*H*-1,2,4-triazole units. We herein report the synthesis and structure of a series of novel 2-amino-4-aryl-5-(1*H*-1,2,4-triazol-1-yl)-1,3-thiazoles, which have been characterized by spectra data and crystal X-ray diffraction analysis. These compounds were also evaluated for their biological activities including in vitro fungicidal and plant-growth regulatory activities.

RESULTS AND DISCUSSION

Synthesis

Brominating of substituted acetophenone **1a**–**1p** in a conventional manner (bromine/acetic acid) gave α-bromo-substituted acetophenone **2a**–**2p**. Compound **3a** was synthesized by dropping a solution of **2a** in acetone into a mixture of 1*H*-1,2,4-triazole and triethylamine in acetone at 0°C. Compared with **3a**, **3b**–**3p** were obtained in low yield under the same conditions. They were achieved in good yield by using anhydrous potassium carbonate as a base and refluxing in chloroform. Because bromoacetyl-substituted benzene and dibromoacetyl-substituted benzene react with thiourea, they could afford the same compound,[4] Treatment of **3** with light excessive bromine in the presence of sodium acetate in acetic acid below 50°C, followed by heating with thiourea in ethanol, and alkalification with ammonia solution (5%) via a Hantzsh reaction, afforded compounds **4a**–**4p** (Scheme 1).



Scheme 1. Synthetic routes of compounds **4a**–**4q**: R = H (a), *p*-F (b), *p*-Cl (c), *o*-Cl (d), *m*-Cl (e), *p*-Br (f), *o*-Br (g), *m*-Br (h), *p*-OCH_3 (i), *p*-Ph (j), 2,4-Cl (k), 3,4-Cl (l), 2,5-Cl (m), 2,3,4-Cl (n), 2,5-OCH_3 (o), benzo[2,3-*b*](p) 2,4-F (q).

The reaction was investigated under various conditions, including solution (methanol, ethanol, water, and acetone), temperature, and ratio of reagents (Table 1). The best yield was attained when compound **3** and thiourea (1:2 molar ratios) were reacted in ethanol at reflux. In addition, we cannot get the target production **4a** if compound **3a**, without being bromated, directly reacted with thiourea under the effect of iodine.

Additionally, compound **4q** was prepared in four steps starting from **2**, 4-difurobenzene, and α-chloroacetyl chloride by the Friedel–Crafts acylation reaction, and subsequent steps use the same method as that of **4b**–**4p** (Scheme 1).

Structure

Figure 1 shows the molecular structure of **4c**, which contains the following three-plane subunit: the substituted phenyl ring C6-C11 (*p1*), the thiazole ring (*p2*), and the triazole ring (*p3*). The dihedral angles between *p1* and *p2* and between *p2* and *p3* are 34.9 and 49.9°, respectively. In the crystal structure, weak intermolecular N-H...N interaction are found [N (5)-H (5B)...N3: N-H = 0.851Å, H...N = 2.311 Å, N...N = 3.005 Å, and N (5)-H (5B)...N3 = 109.3°; symmetry code: (i) $3/2 - x, 2 - y, 1/2 + z$].

Biological Activities

Antifungal Activity

The assessments of in vitro fungicidal activity for some 2-aminothiazole containing 1*H*-1,2,4-triazole compounds (**4**) were proceeding against five selected fungi including *P. zeae*, *A. solani*, *C. fulvum*, *P. piricola*, and *C. ara*. Their relative inhibitory ratios (%) against these fungi were determined, and the results are reported in Table 2. The screening data revealed that the inhibitory

Table 1. Reaction conditions

Solution and condition	Ratio of reagents (mol) **3a**:thiourea	Yield of **4a** (%)
Acetone/reflux	1:1	0
Water/room temperature	1:1	0
Ethanol/room temperature	1:1	0
Methanol/reflux	1:1	21.6
Ethanol/reflux	1:1	34.0
Ethanol/reflux	1:1.5	50.4
Ethanol/reflux	1:2	60.1

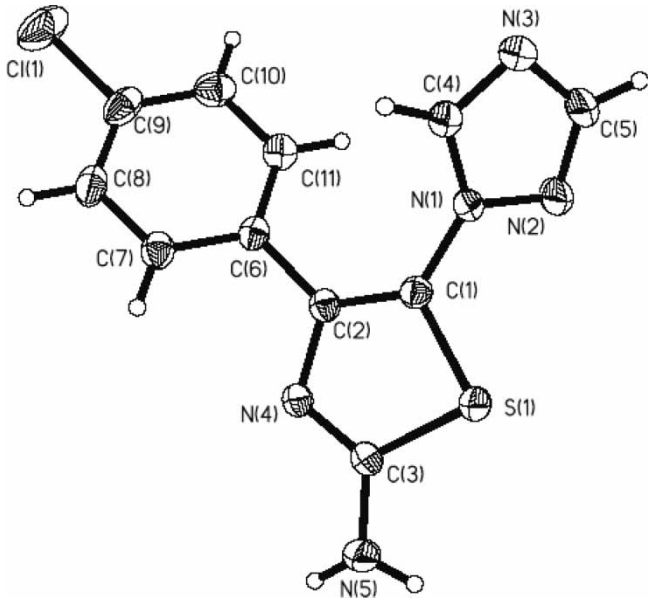


Figure 1. Molecular structure and crystallographic numbering scheme for compound **4c**. Selected bond lengths (Å): S(1)–C(1) 1.758(4); S(1)–C(3) 1.764(4); Cl(1)–C(9) 1.758(4); N(1)–C(4) 1.356(4); N(1)–N(2) 1.370(4); N(1)–C(1) 1.414(4); N(2)–C(5) 1.314(4); N(3)–C(4) 1.318(4); N(3)–C(5) 1.363(4); N(4)–C(3) 1.311(4); N(4)–C(2) 1.405(4); N(5)–C(3) 1.359(4); C(1)–C(2) 1.364(4); C(2)–C(6) 1.494(4). Selected bond angles (°): C(1)–S(1)–C(3) 87.7(12); C(4)–N(1)-N(2) 109.7(2); N(2)–N(1)–C(1) 119.2(2); C(4)–N(3)–C(5) 102.0(2); C(3)–N(4)–C(2) 111.2(3); C(2)–C(1)–N(1) 129.7(2); C(2)–C(1)–S(1) 111.50(18); N(4)–C(2)–C(6) 117.4(2); N(4)–C(3)–S(1) 115.3(2); N(3)–C(4)–N(1) 110.4(2); C(11)–C(6)–C(2) 122.4(3); C(7)–C(6)–C(2) 118.8(2).

ratios against *A. solani* and *P. piricola* of these compounds were slightly higher than that of the other three.

The screening data indicated that compounds **4** showed a slight degree of antifungal activity. Compared with known commercial agents, the antifungals of this type of compounds were not encouraged (Table 2).

Plant-Growth Regulatory Activity

The plant-growth regulatory activity test adopted the wheat coleoptil segment elongation and excised cucumber cotyledon root approaches. The results showed that compounds **4k**, **4l**, and **4m** could restrain the growth of wheat coleoptile to a certain degree, and compound **4o** has the activity to accelerate the rootage of cucumber cotyledon when concentration was 10^{-5} mg/mL (Table 3).

Table 2. Antifungal activity of selected compound **4** (relative inhibitory ratio %)

Comp. ($c = 5 \times 10^{-5}$ mg/mL)	*P. zeae*	*A. solzni*	*C. ara*	*P. piricola*	*C. fulvum*
4a	0	26.0	0	18.4	20.0
4b	18.4	26.0	0	18.4	0
4c	0	30.0	0	32.7	20.0
4f	15.8	30.0	0	32.7	0
4i	0	16.0	0	20.4	0
4j	0	30.0	17.4	36.7	20.0
4k	15.8	26.0	0	32.7	0
4l	27.1	26.0	0	28.6	0
4m	15.8	14.0	0	32.7	0
4p	0	14.0	0	22.5	0

SUMMARY

To summarize, we synthesized a series of 2-amino-1,3-thiazole containing 1*H*-1,2,4-triazole derivatives **4a**–**4q**, and their structures were established on the basis of ^{1}H NMR spectral data and elemental analysis. Finally, the structure of compound **4c** was confirmed by X-ray crystallographic studies. These novel 2-amino-1,3-thiazole derivatives were also screened for their fungicidal activities on five selected fungi and for plant-growth regulatory activities. The structure of compound **4** waits for further modification, in expectation of getting better activities.

EXPERIMENT

Melting points (°C) were determined with X-4 digital melting-point apparatus and are uncorrected. The ^{1}H NMR spectra were measured on a Brucker AC-300 spectrometer in DMSO-d_6 solution with TMS as internal standard. Elemental analysis was determined on Yanaco CHN Corder elemental analyzer. X-ray diffraction data were recorded at 293 K on a Bruker

Table 3. Plant-growth regulatory activity of selected compound **4**

$c = 10^{-5}$ mg/mL	**4h**	**4k**	**4l**	**4m**	**4o**
Wheat coleoptile	−	+	+	+	−
Cucumber cotyledon root	−	−	−	−	+

Note. Wheat coleoptile: + ≤10% <25%; cucumber cotyledon root: + ≤50% <100%.

Smart1000 diffractometer (graphite-monochromatized Mo Kα radiation, $\lambda = 0.71073$ Å). The substituted phenacyl bromide **2** was prepared by the literature method.[5]

Synthesis of α-(1*H*-1,2,4-Triazol-1-yl)-substituted acetophenone (3a–3q)

Compound **3a** was prepared by the literature method,[6] and compounds **3b**–**3q** were synthesized as follows.

Anhydrous potassium carbonate (0.04 mol) and 1*H*-1,2,4-triazole (0.04 mol) were added to a solution of compounds **2** (0.02 mol) in 250 ml of chloroform. The reaction mixture was stirred and refluxed for 5–10 h (tracked with thin-layer chromatography, TLC). Then the mixture was cooled and filtered. The filtration was washed with water, dried, and evaporated in vacuum to afford **3**. They were purified by chromatography on silica gel with the solvent system of ethyl acetate/petroleum ether (v/v = 1:1).

Synthesis of 2-Amino-4-aryl-5-(1*H*-1,2,4-triazol-1-yl)-1,3-thiazole (4a–4q)

Sodium acetate (4 mmol) was added to a solution of compound **3** (3 mmol) in acetic acid (40 ml), then a solution of bromine (4 mmol) in acetic acid (10 ml) was added dropwise at temperatures below 50°C with continuous stirring. After complete addition, the reaction mixture was stirred for another 3 h. Following that, some water (60 ml) was added, and the formed precipitate dissolved. Then the mixture was extracted in chloroform (3 × 15 ml), and the organic solution was washed with saturated sodium bicarbonate untill no gas was emitted washed with water, dried over magnesium sulfate, and freed from the solvent by evaporation in vacuum.

With that, the residue was heated with thiourea (6 mmol) in ethanol under reflux for 8 h, and the mixture was alkalified by ammonia solution (5%) and allowed to cool overnight. The precipitated product was collected by filtration, washed with water, and dried. Recrystallization from methanol or ethanol afforded the desired 2-amino-4-aryl-5-(1*H*-1,2,4-triazol-1-yl)-1,3-thiazole **4** in various yields. The physical properties, elemental analysis data, and ^{1}H NMR spectra data of compounds **4** thus synthesized are reported in Tables 4 and 5, respectively.

Crystallographic Measurement

The colorless crystals with dimensions 0.22 mm × 0.16 mm × 0.14 mm were mounted in a fiber. The structure was solved by direct methods and

Table 4. Physical data and elemental analysis of compounds **4a**–**4q**

Compound	R	Yield (%)	Mp (°C)	Formula (g/mol)	Elemental analysis (%) found (calcd).		
					C	H	N
4a	H	60.1	223–224	$C_{11}H_9N_5S$ (243.29)	54.31 (54.34)	3.73 (3.87)	28.79 (28.79)
4b	*p*-F	49.8	228–229	$C_{11}H_8FN_5S$ (261.05)	50.51 (50.57)	3.15 (3.09)	26.58 (26.80)
4c	*p*-Cl	54.8	247–248	$C_{11}H_8ClN_5S$ (277.73)	47.56 (47.57)	3.02 (2.90)	25.25 (25.22)
4d	*o*-Cl	47.48	239–240	$C_{11}H_8ClN_5S$ (277.73)	47.30 (47.57)	3.11 (2.90)	24.98 (25.22)
4e	*m*-Cl	46.72	223–225	$C_{11}H_8ClN_5S$ (277.73)	47.64 (47.57)	3.03 (2.90)	25.32 (25.22)
4f	*p*-Br	54.2	239–241	$C_{11}H_8BrN_5S$ (322.18)	41.05 (41.01)	2.54 (2.50)	21.60 (21.74)
4g	*o*-Br	69.81	218–220	$C_{11}H_8BrN_5S$ (322.18)	21.65 (41.01)	2.48 (2.50)	21.65 (21.74)
4h	*m*-Br	82.01	226–228	$C_{11}H_8BrN_5S$ (322.18)	41.03 (41.01)	2.70 (2.50)	21.70 (21.74)
4i	*p*-CH_3O	60.5	242–244	$C_{12}H_{11}N_5OS$ (273.31)	52.67 (52.73)	4.11 (4.06)	25.78 (25.62)
4j	*p*-Ph	67.5	187–189	$C_{17}H_{13}N_5S$ (319.38)	63.85 (63.93)	4.01 (4.10)	21.78 (21.93)
4k	2,4-Cl	56.6	241–243	$C_{11}H_7Cl_2N_5S$ (312.18)	42.22 (42.32)	2.30 (2.26)	22.41 (22.43)
4l	3,4-Cl	50.1	259–261	$C_{11}H_7Cl_2N_5S$ (312.18)	42.22 (42.32)	2.30 (2.26)	22.41 (22.43)
4m	2,5-Cl	48.3	197–199	$C_{11}H_7Cl_2N_5S$ (312.18)	42.42 (42.32)	2.26 (2.26)	22.20 (22.43)
4n	2,3,4-Cl	32.5	255–256	$C_{11}H_6Cl_3N_5S$ (346.62)	37.91 (38.12)	2.00 (1.74)	19.99 (20.20)
4o	2,5-CH_3O	30.2	167–169	$C_{13}H_{13}N_5O_2S$ (303.34)	51.51 (51.47)	4.20 (4.32)	22.95 (23.09)
4p	Benzo[2,3-*b*]	63.5	215–217	$C_{15}H_{11}N_5S$ (293.35)	61.32 (61.42)	3.98 (3.78)	23.77 (23.87)
4q	2,4-F	33.2	224–226	$C_{11}H_7F_2N_5S$ (279.27)	47.36 (47.31)	2.51 (2.53)	25.16 (25.08)

Table 5. ^{1}H NMR spectral data of compounds **4a**–**4q**

Compound	^{1}H NMR (DMSO/TMS, δ)
4a	8.73 (s, 1H, Tr-H), 8.30 (s, 1H, Tr-H), 7.54 (s, 2H, NH_2), 7.30–7.14 (m, 5H, Ar-H)
4b	8.76 (s, 1H, Tr-H), 8.30 (s, 1H, Tr-H), 7.56 (s, 2H, NH_2), 7.22–7.11 (m, 4H, Ar-H)
4c	8.76 (s, 1H, Tr-H), 8.30 (s, 1H, Tr-H), 7.58 (s, 2H, NH_2), 7.39–7.36 (q, 2H, Ar-H), 7.16–7.13 (q, 2H, Ar-H)
4d	8.40 (d, 1H, Tr-H, $J = 1.2$ Hz), 8.09 (d, 1H, $J = 1.2$ Hz), 7.50 (s, 2H, NH_2), 7.45–7.33 (m, 4H, Ar-H)
4e	8.80 (s, 1H, Tr-H), 8.34 (s, 1H, Tr-H), 7.62 (s, 2H, NH_2), 7.40–7.00 (m, 4H, Ar-H)
4f	8.76 (s, 1H, Tr-H), 8.30 (s, 1H, Tr-H), 7.60 (s, 2H, NH_2), 7.53–7.49 (q, 2H, Ar-H), 7.10–7.07 (q, 2H, Ar-H)
4g	8.36 (s, 1H, Tr-H), 8.09 (s, 1H, Tr-H), 7.50 (s, 2H, NH_2), 7.42–7.29 (m, 4H, Ar-H)
4h	8.80 (s, 1H, Tr-H), 8.34 (s, 1H, Tr-H), 7.62 (s, 2H, NH_2), 7.51–7.02 (m, 4H, Ar-H)
4i	8.73 (s, 1H, Tr-H), 8.29 (s, 1H, Tr-H), 7.49 (s, 2H, NH_2), 7.10–7.07 (q, 2H, Ar-H), 6.86–6.83 (q, 2H, Ar-H), 3.820 (s, 3H, OCH_3)
4j	8.79 (s, 1H, Tr-H), 8.33 (s, 1H, Tr-H), 7.56 (s, 2H, NH_2), 7.67–7.23 (m, 9H, Ar-H)
4k	8.48 (s, 1H, Tr-H), 8.10 (s, 1H, Tr-H), 7.54 (s, 2H, NH_2), 7.63–7.44 (t, 3H, Ar-H)
4l	8.81 (s, 1H, Tr-H), 8.34 (s, 1H, Tr-H), 7.64 (s, 2H, NH_2), 7.60–6.99 (m, 3H, Ar-H)
4m	8.52 (s, 1H, Tr-H), 8.11 (s, 1H, Tr-H), 7.55 (s, 2H, NH_2), 7.51–7.45 (m, 3H, Ar-H)
4n	8.55 (s, 1H, Tr-H), 8.12 (s, 1H, Tr-H), 7.58 (s, 2H, NH_2), 7.68, 7.50 (d, 1H, Ar-H, $J = 8.4$), 7.43, 7.41 (d, 1H, Ar-H, $J = 8.4$)
4o	8.34 (s, 1H, Tr-H), 8.08 (s, 1H, Tr-H), 7.40 (s, 2H, NH_2), 6.97–6.82 (m, 3H, Ar-H), 3.40, 3.38 (d, 3H, 2-OCH_3), 3.35 (s, 3H, 5-OCH_3)
4p	8.36 (s, 1H, Tr-H), 8.04 (s, 1H, Tr-H), 7.43 (s, 2H, NH_2), 7.94–7.39 (m, 7H, Ar-H)
4q	8.60 (s, 1H, Tr-H), 8.13 (s, 1H, Tr-H), 7.47 (s, 2H, NH_2), 7.55–7.09 (m, 3H, Ar-H)

completed by difference Fourier map using the SHELXL-97 program and refined by full-matrix least-squares on F^2. The nonhydrogen atoms were refined anisotropically and hydrogen atoms were added according to theoretical models. Crystallographic data: orthorhombic, space group $P2(1)2(1)2(1)$ with cell dimensions of a = 7.540(15) nm, b = 11.27(2) nm, c = 14.65(3) nm, $\alpha = 90.00^\circ$, $\beta = 90.00^\circ$, $\gamma = 90.00^\circ$, $V = 1.245(4)$ nm^3, $Z = 4$, $\mu = 0.462$ mm^{-1}.

SUPPLEMENTARY MATERIAL

Crystallographic data for the structure **4c** has been deposited in the Cambridge Crystallographic Data Center, CCDC No. 283871. Copies of this information may be obtained free of charge from the director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, U.K. (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk, or http://www.ccdc.cam.ac.uk).

ACKNOWLEDGMENTS

We gratefully acknowledge the National Natural Science Foundation of China (NNSFC) (No. 20172030) and the Key Project of Chinese Ministry of Education (No. 105046) for financial support.

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