Syntheses and properties of new herbicidal 2-arylthio-1,2,4-triazolo[1,5-a]pyrimidine derivatives

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In search of novel herbicides with high activity, a series of 2-arylthio-1,2,4-triazolo[1,5-a]pyrimidines (3) were synthesized by cyclization of 5-amino-3-arylthio-1,2,4-triazoles with 1,3-diketones or by the nucleophilic substitution of substituted thiophenols with 2-methylsulfonyl-1, 2, 4-triazolo [1, 5-a]-pyrimidine. The structures of all compounds prepared were confirmed by ^{1}H NMR and MS spectroscopy along with elemental analyses. Preliminary bioassays indicated that some of the compounds 3 had good herbicidal activity against rape. In addition, the regioselectivity in the reaction of 5-amino-3-substituted arylthio-1,2,4-triazoles with benzoylacetone was studied.

Keywords 1,2,4-Triazolo[1,5-a]pyrimidine, cyclization reaction, regioselectivity, herbicidal activity

Introduction

The synthesis of biologically active triazolopyrimidine compounds has been of continuing interest to us over the years.[1-4] Many 1,2,4-triazolo[1,5-a]pyrimidines are developed as effective herbicides (such as metosulam and flumetsulam), and others have been used as therapeutic agents.[5,6] Therefore, various 1,2,4-triazolo[1,5-a]pyrimidines and their derivatives are in great demand now. Recently, we became interested in the syntheses of novel herbicidal triazolo[1,5-a]pyrimidines, some of which have shown potential herbicidal activities.[7,8] Herein, we wish to report in detail the preparation of a novel series of 2-arylthio-1,2,4-triazolo-[1,5-a]pyrimidine derivatives **3** via different synthetic routes.

Results and discussion

Synthetic methods for preparing the title compounds **3**

The title compounds **3a—r** were synthesized via two different routes outlined in Schemes 1 and 2, respectively. The molecular structures of the products **3a—r** were confirmed by ^{1}H NMR and MS spectroscopy as well as elemental analyses. The experimental data for **3a—r** were listed in Tables 1 and 2, respectively.

In method A, the key intermediates are 5-amino-3-arylthio-1,2,4-triazoles **2**, which were synthesized by nucleophilic substitution at the substituted chlorobenzene bearing electron-withdrawing groups by 5-amino-3-mercapto-1,2,4-triazole (**1**). Compounds **2** cyclized on reaction with different 1,3-diketones to give the title compounds in good to excellent yields. This method is suitable for synthesizing the title compounds with strong electron-withdrawing groups in the benzene ring.

The other convenient synthetic approach to **3** is the reaction of substituted thiophenols with 2-methylsulfonyl-1,2,4-triazolo[1,5-a]pyrimidines, which are novel synthetic intermediates readily prepared by oxidation of 2-methylthio-1,2,4-triazolo[1,5-a]pyrimidines using

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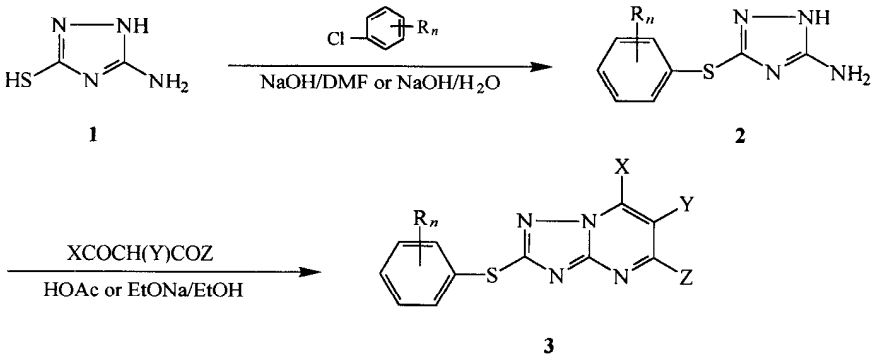
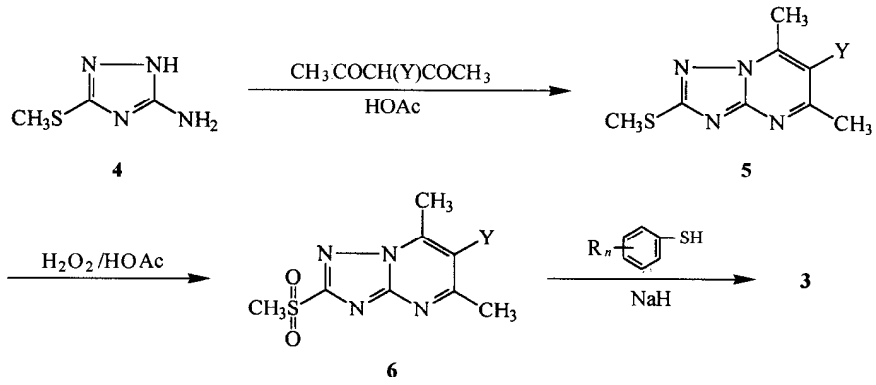
Scheme 1 (Method A)



1 2 3

Scheme 2 (Method B)



4 5 6 3

Table 1 Physical data for compounds **3**

Compd.	R_n	X	Y	Z	Method	mp (℃)	Yield (%)
3a	2,6-$(NO_2)_2$-4-CF_3	CH_3	H	CH_3	A	222—223	85
3b	2,4-$(NO_2)_2$	CH_3	H	CH_3	A	183—184	90
3c	2,6-$(NO_2)_2$-4-CF_3	CH_3	CH_3	CH_3	A	178—181	89
3d	2,4-$(NO_2)_2$	CH_3	CH_3	CH_3	A	198—200	84
3e	2,6-$(NO_2)_2$-4-CF_3	CF_3	H	CF_3	A	87—89	71
3f	2-NO_2	CH_3	H	CH_3	A	210—212	91
3g	2-NO_2	CH_3	CH_3	CH_3	A	195—196	90
3h	2-NO_2	CH_3	H	C_6H_5	A	205—207	18
3i	2-NO_2	C_6H_5	H	CH_3	A	199—200	76
3j	2-NO_2	CF_3	H	CF_3	A	120—121	98
3k	2-NO_2-4-CF_3	CH_3	H	CH_3	A	174—175.5	92
3l	2-NO_2-4-CF_3	CH_3	CH_3	CH_3	A	183—184.5	93
3m	2-NO_2-4-CF_3	CH_3	H	C_6H_5	A	163—164	18
3n	2-NO_2-4-CF_3	C_6H_5	H	CH_3	A	157—158	60
3o	2-NO_2-4-CF_3	CF_3	H	CF_3	A	125—127	91
3p	H	CH_3	H	CH_3	B	154—155	83
3q	H	CH_3	CH_3	CH_3	B	117—118	75
3r	2-$COOCH_3$	CH_3	H	CH_3	B	191—193	72

H_2O_2/HOAc system in good yields. It appears that the electronic effect is the dominant factor affecting theyields of the products **3**: the reaction of the substituted thiophenols bearing an electron-donating group with the intermediates **6** occurred more easily than those bearing a strong electron-withdrawing group, such as nitro group which did not react with **6** at all.

Table 2 ^{1}H NMR and elemental analysis data for compounds **3**

Compd.	^{1}H NMR (δ, $CDCl_3$)	Elemental analysis (Found/Calcd)		
		C	H	N
3a	2.58(s, 3H, CH_3), 2.67(s, 3H, CH_3), 6.78(s, 1H, CH), 8.40(s, 2H, C_6H_2)	40.84 (40.58)	2.16 (2.17)	20.13 (20.29)
3b	2.70(s, 3H, CH_3), 2.81(s, 3H, CH_3), 6.92(s, 1H, CH), 7.88—9.06(m, 2H, C_6H_3)	45.15 (45.08)	3.17 (2.89)	24.11 (24.28)
3c	2.26(s, 3H, CH_3), 2.54(s, 3H, CH_3), 2.64(s, 3H, CH_3), 8.91(s, 2H, $C_6H_)$	42.23 (42.06)	3.07 (2.57)	19.29 (19.63)
3d	2.35(s, 3H, CH_3), 2.64(s, 3H, CH_3), 2.77(s, 3H, CH_3), 7.54—8.93(m, 2H, C_6H_3)	46.69 (46.67)	3.79 (3.33)	23.66 (23.33)
3e	7.72(s, 1H, CH), 8.46(s, 2H, $C_6H_)$	32.48 (32.18)	0.58 (1.07)	16.26 (16.09)
3f	2.68(s, 3H, CH_3), 2.79(s, 3H, CH_3), 6.87(s, 1H, CH), 7.26—8.22(m, 4H, C_6H_4)	52.07 (51.82)	3.65 (3.68)	23.40 (23.24)
3g	2.37(s, 3H, CH_3), 2.68(s, 3H, CH_3), 2.82(s, 3H, CH_3), 7.26—8.22(m, 4H, C_6H_4)	53.20 (53.32)	4.06 (4.15)	22.19 (22.21)
3h	2.91(s, 3H, CH_3), 7.38—8.23(m, 10H, C_6H_5 + C_6H_4 + CH)	59.10 (59.49)	3.70 (3.61)	19.01 (19.27)
3i	2.78(s, 3H, CH_3), 7.14(s, 1H, CH), 7.57—8.22(m, 9H, C_6H_5 + C_6H_4)	59.61 (59.49)	3.42 (3.61)	19.22 (19.27)
3j	7.73(s, 1H, CH), 7.54—8.21(m, 4H, C_6H_4)	38.38 (38.14)	1.17 (1.22)	17.01 (17.11)
3k	2.71(s, 3H, CH_3), 2.82(s, 3H, CH_3), 6.91(s, 1H, CH), 7.66—8.48(m, 3H, C_6H_3)	45.71 (45.53)	2.97 (2.73)	19.04 (18.96)
3l	2.39(s, 3H, CH_3), 2.69(s, 3H, CH_3), 2.84(s, 3H, CH_3), 7.63—8.48(m, 3H, C_6H_3)	47.12 (47.00)	3.00 (3.16)	18.62 (18.27)
3m	2.93(s, 3H, CH_3), 7.36(s, 1H, CH), 7.50—8.50(m, 8H, C_6H_5 + C_6H_3)	52.78 (52.90)	2.57 (2.78)	16.11 (16.24)
3n	2.79(s, 3H, CH_3), 7.18(s, 1H, CH), 7.59—8.48(m, 8H, C_6H_5 + C_6H_3)	52.81 (52.90)	2.67 (2.78)	16.20 (16.24)
3o	7.79(s, 1H, CH), 7.84—8.48(m, 3H, C_6H_3)	37.57 (37.70)	0.84 (0.90)	15.60 (15.73)
3p	2.58(s, 3H, CH_3), 2.69(s, 3H, CH_3), 6.71(s, 1H, CH), 7.33—7.69(m, 5H, C_6H_5)	60.81 (60.94)	4.83 (4.69)	21.56 (21.88)
3q	2.26(s, 3H, CH_3), 2.56(s, 3H, CH_3), 2.69(s, 3H, CH_3), 7.30—7.68(m, 5H, C_6H_5)	61.94 (62.22)	5.36 (5.19)	20.45 (20.74)
3r	2.96(s, 3H, CH_3), 3.10(s, 3H, CH_3), 4.48(s, 3H, CH_3), 7.62(s, 1H, CH), 8.00—8.96(m, 4H, C_6H_4)	57.40 (57.32)	4.80 (4.46)	18.06 (17.82)

Regioselectivity in the reaction of **2** *with benzoylacetone*

Although the regioselectivity of the reaction of aminoazoles with some unsymmetrical 1, 3-dicarbonyl compounds, such as β-ketoesters and β-ketoaldehyde derivatives, is well established,[9,10] the outcome of the reaction of aminoazoles, especially arylthio substituted aminoazoles with unsymmetrical 1, 3-diketones is unknown. Herein, we use the reaction of 5-amino-3-(2-nitro) phenylthio-1, 2, 4-triazole with benzoylacetone to exemplify the influence of the reaction conditions on the regioselectivity (Table 3).

Under acidic conditions, 2-(2-nitro)phenylthio-7-phenyl-5-methyl-1,2,4-triazolo[1,5-a]pyrimidine (**3i**) was obtained as the main product in high yield. Under basic conditions at low temperature, the yield was low, but the ratio of **3h/3i** was relatively large. When the reaction temperature was raised to 60℃, the yield was increased, but the ratio (**3h/3i**) was decreased. It is therefore concluded that the regioselectivity of the cyclization reaction of 5-amino-1,2,4-triazole with asym-1,3-dicarbonyl compounds is decreased with increasing of the reaction temperature.

The structures of isomers **3h/3i** and **3m/3n** were assigned on the basis of the comparison of ^{1}H NMR spectral data to those of known model compounds.[4] For examples, the signal for the Py-H in **3h** appeared in the range of δ 7.381—8.225, which overlapped with that for the aryl groups and was therefore more intense than that of **3i** (δ 7.137). Mass spectroscopy showed obvious difference between **3h** and **3i**, there was a signal at *m/z* 103 $(PhC\equiv N)^+$ in the spectrum of **3h** but not in that of **3i**.

Table 3 Regioselectivity of the cyclization of **2c** with benzoylacetone

Conditions	HOAc / reflux	EtONa / EtOH			KF/CH_3CN
Temperature (℃)	110	25	40	60	40
Yield (%, **3h/3i**)	18 / 76	40 / 14	45 / 37	43 / 41	39 / 29
Total yield (%)	94	54	82	84	68
Ratio (**3h/3i**)	19 / 81	74 / 26	55 / 45	51 / 49	57 / 43

Herbicidal activities of **3**

The preliminary biological activities were tested by spraying the seedlings of the plants with the solutions of the compounds **3a**—**r**, respectively, in acetone at the dosage of 300 g/ha. It was found that most of the products showed inhibiting effect (38—89%) against rape. For example, at 300 g/ha, the growth-inhibitory rate of compound **3f** to rape attained 89%. Furthermore, it was found that some of compounds **3** displayed certain fungicidal activity **3p**: the inhibition rate against wheat leaf rust for 500 ppm is 67.8%).

Experimental

Melting points were obtained on a Yanaco MT-500 apparatus without correction. IR spectra were recorded on a Shimadzo-IR 435 infrared spectrophotometer. Mass spectra were recorded on a VG-7070E spectrometer using a direct inlet probe in EI mode. ^{1}H NMR spectra were measured on a Bruker AC-P200 spectrometer using TMS as internal standard and elemental analyses were performered on a Perkin-Elmer 240-C instrument. The reagents and solvents were available commercially and purified according to conventional methods. 5-Amino-3-mercapto-1,2,4-triazole (**1**) and 5-amino-3-methylthio-1,2,4-triazole (**4**) were prepared according to the literatures.[11,12]

General procedure for the syntheses of 5-*amino*-3-*arylthio*-1,2,4-*triazoles* (**2**)

2a, R_n = 2,6-$(NO_2)_2$-4-CF_3 *and* **2b**, R_n = 2,4-$(NO_2)_2$: Sodium hydroxide (22 mmol) was dissolved in 50 mL of water and 20 mmol of 5-amino-3-mercapto-1,2,4-triazole (**1**) was added. After stirring for 15 minutes, a solution of 20 mmol of 2,6-dinitro-4-trifluoromethylchloro-benzene or 2,4-dinitro-chlorobenzene in 30 mL of methanol was added dropwise over 20 minutes. After the addition was completed, the solution was stirred at room temperature for about 2 h. The solid was filtered and recrystallized from acetone to give pure products as a yellow crystal. **2a**: yield 71%, mp 184—187℃. Anal. $C_7H_5F_3N_6O_4S$. Cacld.: C, 25.77; H, 1.53; N, 25.77. Found: C, 25.63; H, 1.85; N, 25.96. **2b**: yield 83%, mp 215—217℃. Anal. $C_6H_6N_6O_4S$. Calcd.: C, 27.91; H, 2.32; N, 32.56. Found: C, 27.66; H, 2.55; N, 32.89.

2c, R_n = 2-NO_2: A solution of 0.104 mol of 5-amino-3-mercapto-1,2,4-triazole (**1**), 0.104 mol of 2-nitrochlorobenzene and 0.104 mol of sodium hydroxide in 150 mL of DMF was heated at 75—80℃ for about 12 h. The resulting mixture was poured into 200 mL of water. The solid was filtered and washed with ethyl ether to give the product. The pure product was

obtained by recrystallization from acetone-petroleum ether as a yellow crystal in a yield of 81%, m. p. 200—202℃. Anal. $C_6H_7N_5O_2S$. Calcd.: C, 33.80; H, 3.29; N, 32.86. Found: C, 34.06, H; 3.45; N, 33.19.

2d, R_n = 2-NO_2-4-CF_3: A solution of 50 mmol of 5-amino-3-mercapto-1, 2, 4-triazole (**1**), 50 mmol of 2-nitro-4-trifluoromethylchloro-benzene and 50 mmol of sodium hydroxide in 100 mL of DMSO was stirred at room temperature for about 1 h. Then, 200 mL of water was added and the resulting solid was filtered and recrystallized from acetone-petroleum ether to give the pure product as a yellow crystal in a yield of 91%, mp 218—221℃. Anal. $C_7H_6F_3N_5O_2S$. Calcd.: C, 29.89; H, 2.13; N, 24.91. Found: C, 30.17, H; 2.42; N, 25.16.

General procedure for the syntheses of 2-*methylthio*-1,2,4-*triazolo*[1,5-a]*pyrimidines* (**5**)

A solution of 0.5 mol of 5-amino-3-methylthio-1, 2,4-triazoles (**4**) and 0.5 mol of 1,3-diketone in 150 mL of glacial AcOH was heated at reflux for 18 h. The reation mixture was cooled to room temperature and evaporated at reduced pressure. The residual solid was recrystallized from ethanol to afford the pure products as white crystals. **5a**: Y = H, yield 90%, mp 154—156℃. δ_H($CDCl_3$): 2.52(s, 3H, CH_3), 2.64(s, 3H, CH_3), 2.68(s, 3H, CH_3), 6.72(s, 1H, CH). **5b**: Y = CH_3, yield 87%, mp 148—149℃. δ_H($CDCl_3$): 2.26(s, 3H, CH_3), 2.50(s, 3H, CH_3), 2.64 (s, 3H, CH_3), 2.69(s, 3H, CH_3).

General procedure for the syntheses of 2-*methylsulfonyl*-1,2,4-*triazolo*[1,5-a]*pyrimidines* (**6**)

To a stirred mixture of 27 mmol of 2-methylthio-1, 2,4-triazolo[1, 5-a] pyrimidines (**5**) and 20 mL of acetic acid, 0.08 mmol of sodium tungstate dihydrate at room temperature was added. To the vigorously stirred solution, 6.12 g (54 mmol) of hydrogen peroxide as a 30% aqueous solution was added slowly at 40℃. Stirring was continued at 50℃ for additional 3 h. The excess hydrogen peroxide was destroyed by the addition of an aqueous solution of sodium sulfite, the solid filtered and recrystallized from ethanol to give the pure products as colourless crystals. **6a**: Y = H, yield 85%, mp 186—188℃. δ_H($CDCl_3$): 2.53(s, 3H, CH_3), 2.64 (s, 3H, CH_3), 3.36(s, 3H, CH_3), 6.71(s, 1H, CH). **6b**: Y = CH_3, yield 83%, mp 179—180℃. δ_H($CDCl_3$): 2.26(s, 3H, CH_3), 2.52(s, 3H, CH_3), 2.65(s, 3H, CH_3), 3.37(s, 3H, CH_3).

Reaction of 5-*amino*-3-*arylthio*-1, 2, 4-*triazoles* (**2**) *with symmetrical* 1,3-*diketones* (*Method A*)

A solution of 2 mmol of **2** and 2 mmol of 1,3-diketone in 30 mL of glacial AcOH was heated at reflux for 7.5—18 h. The reation mixture was cooled to room temperature and evaporated at reduced pressure. The residual solid was recrystallized from acetone-petroleum ether to afford the pure products.

Reaction of 5-*amino*-3-*arylthio*-1, 2, 4-*triazoles* (**2**) *with benzoylacetone*

Acidic condition A solution of 2 mmol of **2** and 2 mmol of benzoylacetone in 30 mL of glacial AcOH was heated at reflux for 14 h. The reation mixture was cooled to room temperature and evaporated at reduced pressure. The residual solid contained **3h** and **3i** in a ratio of 19:81 as determined by HPLC (HP1090 instrument, equipped with a Hypersil 5μm 200 × 4.6 mm (79916 SI-574) column at 210 nm, using petroleum ether (60—90℃), methanol and isopropanol as solvent). The isomers were separated by column chromatography on silical gel (petroleum ether/acetone, *V*/*V* 8:5, as the eluent).

Basic condition Sodium (1.25 mmol) was dissolved in 6 mL of absolute ethanol and 2.5 mmol of **2** was added. After stirring for 15 minutes, a solution of 2.5 mmol of benzoylacetone in 6 mL of absolute ethanol was added dropwise over 20 minutes. After the addition was completed, the solution was stirred at different temperature for 16 hours. The ratios of **3h** to **3i** were determined by HPLC.

Substituted reaction betweem thiophenols and 2-*methylsulfonyl*-1,2,4-*triazolo*[1,5-a]*pyrimidine* (**6**) (*Method B*)

A mixture of 2 mmol of thiophenols and 2 mmol of sodium hydride in 20 mL of anhydrous toluene was

stirred at room temperature in a stream of N_2 for about 20 min. Then, 2 mmol of 2-methylsulfonyl-1,2,4-triazolo[1,5-a]pyrimidines (**2**) was added, the resulting reaction mixture was refluxed for about 10—20 h. After filtration, the solvent was removed under reduced pressure and the residue was purified by column chromatography on silical gel (petroleum ether/acetone, *V*/*V* 8:5, as the eluent).

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