Synthesis of novel herbicidal sulfonylureas

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Novel sulfonylurea derivatives containing five-membered heterocycle 3a—l and 4a—d were synthesized in good yields by the regioselective addition of aryl sulfonylisocyanates 1 to 5-amino-3-benzyl (aryl) thio-1, 2, 4-triazoles and its pyrazole analogues 2. The structures of all these compounds were evaluated by elemental analyses and ^{1}H NMR spectroscopy. The preliminary biological tests showed that the products displayed herbicidal activity against rape to some extent.

Keywords 5-Amino-1,2,4-triazoles, 5-amino-1*H*-pyrazoles, sulfonylurea, regioselectivity

Introduction

A large number of sulfonylurea compounds with high herbicidal activity and excellent crop selectivity has been synthesized and their biological characteristics as plant acetolacetate synthase (ALS) inhibition have been studied[1-4] since the original discovery of these compounds by Levitt. The extremely low application rates and low mammalian toxicity give them distinct commercial advantages, and some of them are on the market. Much attention has been focused on the structural modification of sulfonylurea herbicides in last decades.[5] However, most modifications of the B-ring of this class of herbicides are still kept in six-membered heterocycles,[6] such as pyrimidine and triazine. We are interested in these aspects and have paid attention to the diverse biological activity of triazole and pyrazole systems. As a continuation of our work searching for new ALS inhibitors with high herbicidal activity,[7,8] we designed and synthesized two kinds of novel sulfonylurea derivatives by introducing five-membered heterocycles, such as 1,2,4-triazole and pyrazole, into the structure of sulfonylurea herbicides.

Results and discussion

The title compounds **3** and **4** were prepared by condensation of 5-amino-1, 2, 4-triazole and its pyrazole analogues **2** with substituted aryl sulfonylisocyanates **1** as outlined in Scheme 1.

5-Amino-1,2,4-triazole and its pyrazole analogues **2** were prepared according to the previous paper.[7] The reaction of aryl sulfonylisocyanates **1** with 5-amino-1,2,4-triazole and its pyrazole analogues **2** can give two products, 5-arylsulfonylureylene-3-substituted-1, 2, 4-triazoles (pyrazoles) (**3**) and 5-amino-1-arylsulfonylaminocarbonyl-3-substituted-1,2,4-triazoles(pyrazoles) (**4**). When aryl sulfonylisocyanates **1** were treated with heterocyclic amines **2** at room temperature, products **3a—l** were obtained in good yields. Otherwise, in the presence of sodium hydride aryl sulfonyl-isocyanates **1** reacted with heterocyclic amines **2** to give **4a—d**.

The structures of **3a—l** and **4a—d** were determined on the basis of the proton nuclear magetic resonance (^{1}H NMR) data. Taking **3a** and **4b** as examples, the ^{1}H NMR spectrum of **3a** showed the signals of three NH protons at δ 13.62, 11.18 and 9.56 as broad peaks, while that of **4b** showed the signals of NH_2 at δ 9.38 as a broad absorption and an NH proton at δ 11.89 as a single absorption. The structure of all compounds prepared were confirmed using ^{1}H NMR and CHN analyses. Physical properties and spectral data are recorded in Tables 1 and 2, respectively.

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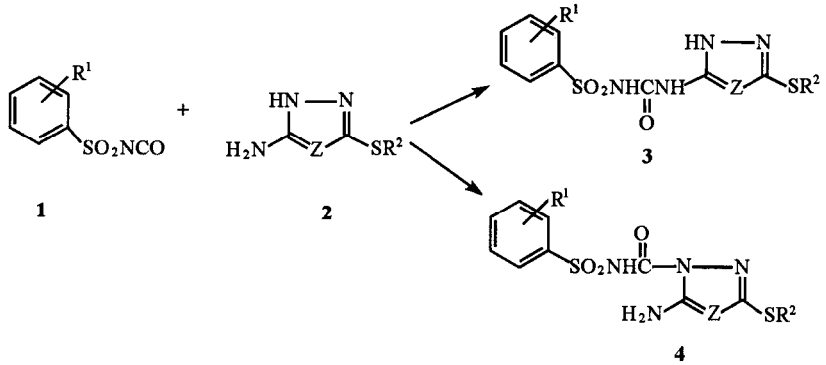
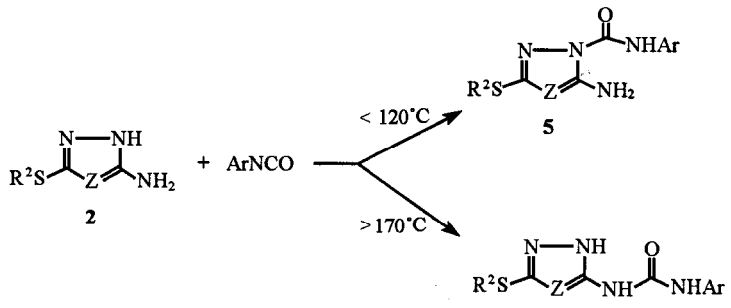
Scheme 1



Z = N, CCN, CCOOEt; R^1 = H, Me, NO_2, COOEt; R^2 = Ar, $CH_2C_6H_5$

In our previous paper,[10] we reported the regioselective addition of **2** with aryl isocyanates and the experimental results showed that the 1-position adduct **5** was obtained regiospecifically below 120℃, whereas the 5-position adduct **6** was obtained selectively when the reaction temperature was raised to 170℃ as depicted in Scheme 2.

Scheme 2



R^2 = $PhCH_2S$; Z=N, CCN, CCOOEt

Table 1 Physical constants of compounds **3a—l** and **4a—d**

No.	R^1	Z	R^2	mp (℃)	Yield (%)
3a	H	CCN	$C_6H_5CH_2$	270	79.2
3b	2-$COOC_2H_5$	$CCOOC_2H_5$	$C_6H_5CH_2$	157—159	72.5
3c	4-CH_3	CCN	$C_6H_5CH_2$	290	82.4
3d	4-CH_3	N	2-$NO_2C_6H_4$	> 300	76.0
3e	4-CH_3	N	2-NO_2-4-$CF_3C_6H_3$	212	85.7
3f	H	N	2-$NO_2C_6H_4$	261	84.7
3g	H	N	2-NO_2-4-$CF_3C_6H_3$	255	84.0
3h	2-$COOCH_3$	N	2-NO_2-4-$CF_3C_6H_3$	> 300	50.5
3i	2-$COOCH_3$	N	2,6-$(NO_2)_2$-4-$CF_3C_6H_2$	130	75.0
3j	2-NO_2	N	2-NO_2-4-$CF_3C_6H_3$	247	74.0
3k	2-NO_2	N	2,6-$(NO_2)_2$-4-$CF_3C_6H_2$	177	42.0
3l[a]	2-$COOC_2H_5$	N	2-$NO_2C_6H_4$	144—147	67.8
4a	H	CCN	$C_6H_5CH_2$	200—202	82.3
4b	2-$COOC_2H_5$	$CCOOC_2H_5$	$C_6H_5CH_2$	91—93	75.8
4c	H	N	2-NO_2-4-CF_3-C_6H_3	197—199	85.0
4d	2-$COOCH_3$	$CCOOC_2H_5$	$C_6H_5CH_2$	145—147	78.0

[a] containing an acetone molecule.

At low temperature, aryl isocyanates reacted with 5-amino-1,2,4-triazoles and its analogues **2** to give 1-N addition products as the only isomers. In contrast, in the case of reaction of **2** with arylsulfonyl isocyanates at room temperature, only 5-NH_2 addition products were obtained. Why? In order to answer this question, we performed molecular mechanic calculations using the program Sybyl (version 6.22, Tripos force field). Take **3a**, **4a**, **5a** and **6a** as representative examples, the results are outlined in Table 3.

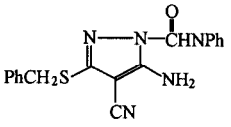
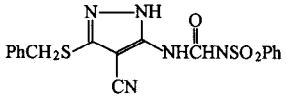
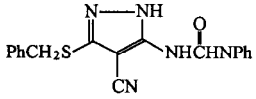
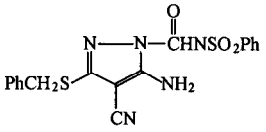
From Table 3 we can conclude that **6a** and **4a** are more stable than **3a** and **5a** respectively. We can assume that **6a** and **4a** are thermodynamics control products and **5a** and **3a** are dynamics control products. So, based on the dynamics and thermodynamics control analysis, the different regioselectivity of addition reaction of aryl isocyanates and arylsulfonyl isocyanates with 5-amino-1,2,4-triazoles and its analogues **2** can be explained easily. Fortunately, we investigated the rearrangement of adducts **3a—b** and found that, **3a—b** could be indeed converted to **4a—b** under N_2 at 170℃ in yields of 56.8% and 76.5%, respectively, as shown in Scheme 3, which suggested the reasonableness of the above assumption.

Table 2 ^{1}H NMR and elemental analysis data of compounds **3a—l** and **4a—d**

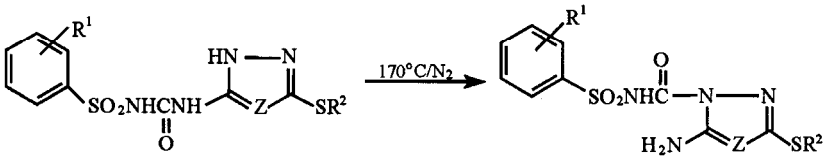
No.	^{1}H NMR (δ, **3a—l** from DMSO-d_6, **4a—d** from $CDCl_3$)	Elemental analysis (calcd.) C	H	N
3a	4.24(s, 2H, CH_2), 7.25(s, 5H, C_6H_5), 7.62—7.97(m, 5H, C_6H_5), 9.56(br.s, 1H, NH), 11.18(br.s, 1H, NH), 13.62(br.s, 1H, NH)	52.36 (52.30)	3.78 (3.63)	16.96 (16.95)
3b	1.28—1.37(m, 6H, $2CH_3$), 4.32—4.47(m, 6H, $3CH_2$), 7.18—7.75(m, 9H, C_6H_5 + C_6H_4), 9.88(br.s, 1H, NH), 11.76(br.s, 1H, NH), 13.02(br.s, 1H, NH)	51.67 (51.88)	4.73 (4.51)	10.79 (10.53)
3c	2.38(s, 3H, CH_3), 4.24(s, 2H, CH_2), 7.25(s, 5H, C_6H_5), 7.39—7.85(m, 4H, C_6H_4), 9.76(br.s, 1H, NH), 11.38(br.s, 1H, NH)	52.82 (53.39)	3.99 (3.98)	16.42 (16.39)
3d	2.81(s, 3H, CH_3), 7.63—9.65(m, 8H, $2C_6H_4$), 8.98(br.s, 1H, NH), 11.30 (br.s, 1H, NH), 13.02(br.s, 1H, NH)	44.02 (44.24)	3.14 (3.23)	19.30 (19.35)
3e	2.40(s, 3H, CH_3), 7.25—8.51(m, 7H, C_6H_3 + C_6H_4), 9.04(br.s, 1H, NH), 10.96(br.s, 1H, NH), 14.03(br.s, 1H, NH)	40.88 (40.63)	2.88 (2.59)	16.75 (16.73)
3f	7.04—8.25(m, 9H, C_6H_4 + C_6H_5), 10.02(br.s, 1H, NH), 11.46(br.s, 1H, NH), 13.35(br.s, 1H, NH)	42.49 (42.86)	3.13 (2.86)	20.31 (20.00)
3g	7.21—8.51(m, 8H, C_6H_3 + C_6H_5), 9.75(br.s, 1H, NH), 11.14(br.s, 1H, NH), 12.38(br.s, 1H, NH)	39.22 (39.34)	2.50 (2.25)	17.55 (17.21)
3h	3.86(s, 3H, CH_3), 7.28—8.52(m, 7H, C_6H_3 + C_6H_4), 9.77(br.s, 1H, NH), 11.67(br.s, 1H, NH)	39.65 (39.56)	2.41 (2.38)	15.59 (15.38)
3i	3.86(s, 3H, CH_3), 7.77—8.12(m, 4H, C_6H_4), 8.81(s, 2H, C_6H_2), 10.13(br.s, 1H, NH), 11.59(br.s, 1H, NH)	36.83 (36.55)	2.39 (2.03)	16.71 (16.58)
3j	7.22—8.50(m, 7H, C_6H_3 + C_6H_4), 9.87(br.s, 1H, NH), 11.32(b, 1H, NH), 13.14 (br.s, 1H, NH)	36.59 (36.02)	1.89 (1.88)	18.10 (18.39)
3k	7.61—8.12(m, 4H, C_6H_4), 8.76(s, 2H, C_6H_2), 9.69(br.s, 1H, NH), 11.65(br.s, 1H, NH), 13.78 (br.s, 1H, NH)	32.94 (33.22)	1.95 (1.56)	19.46 (19.38)
3l[a]	1.29(d, J = 7.20 Hz, 3H, CH_3), 2.07(s, 6H, $2CH_3$), 4.31(t, J = 7.26 Hz, 2H, CH_2), 7.09—8.22(m, 8H, C_6H_4 + C_6H_4)	46.25 (45.82)	3.79 (4.00)	15.34 (15.27)
4a	4.24(s, 2H, CH_2), 7.25(s, 5H, C_6H_5), 7.62—7.97(m, 5H, C_6H_5), 6.79(br.s, 2H, NH_2), 10.38(br.s, 1H, NH)	52.48 (52.30)	3.33 (3.63)	17.12 (16.95)
4b	1.33—1.42(m, 6H, $2CH_3$), 4.30—4.44(m, 6H, $3CH_2$), 7.23—7.69(m, 9H, C_6H_5 + C_6H_4), 9.38(br.s, 2H, NH_2), 11.89(br.s, 1H, NH)	52.03 (51.88)	4.12 (4.51)	10.78 (10.53)
4c	7.35—8.51(m, 10H, C_6H_5 + C_6H_3 + NH_2), 10.15(br.s, 1H, NH)	39.15 (39.34)	2.55 (2.25)	17.50 (17.21)
4d	1.29(t, J = 7.19 Hz, 3H, CH_3), 3.92(s, 3H, CH_3), 4.16—4.25(m, 4H, $2CH_2$), 6.56(br.s, 2H, NH_2), 7.18—7.98(m, 9H, C_6H_5 + C_6H_4), 11.21(br.s, 1H, NH)	51.23 (50.96)	4.55 (4.25)	11.01 (10.81)

[a] $C_{18}H_{16}N_6O_7S_2 \cdot C_3H_6O$.

Table 3 Results of molecule mechanic calculations

No.	Structure	Energy (kcal/mol)	No.	Structure	Energy (kcal/mol)
5a		15.344	**3a**		7.974
6a		10.421	**4a**		3.507

Scheme 3



3 **4**

The preliminary biological tests were carried out by spraying the seedings of the plants with the solutions of the compounds **3a—l** and **4a—d**, respectively, in acetone at the dosage of 1500 g/ha. The results showed that the products displayed herbicidal activity against rape to some extent. The inhibiting rate ranged from 15% to 92%. The further study on the ALS (acetolacetate synthase) inhibition activity of the products is on the way.

Experimental

Melting points were obtained on a Yanaco MT-500 apparatus without correction. ^1H NMR spectra were recorded on a Bruker AC-P200 spectrometer using TMS as internal standard and elemental analyses were performed on a Perkin-Elmer 240-C instrument. Starting materials **1** and **2a—e** were prepared according to the literature.[6,7,9]

The reagents and solvents were available commercially and purified according to conventional methods.

General procedure for the syntheses of **3a—l**

A solution of 2.2 mmol of arylsulfonyl isocyanate in 5 mL of dry CH_3CN was added dropwise to a solution of 2.2 mmol of **2** in 15 mL of the same solvent at room temperature. After being stirred for about 2 h, the mixture was filtered and the solid collected was recrystallized from acetone-petroleum mixture to give the pure products.

General procedure for the syntheses of **4a—d**

A mixture of 2 mmol of **2** and 0.06 g of NaH (80%) in 15 mL of dry THF was stirred at room temperature for half an hour. Then, 2 mmol of arylsulfonyl isocyanate in 5 mL of dry THF was added. After being stirred at room temperature for about 2 h, the mixture was poured into 100 mL of ice-water. While the mixture was adjusted to pH = 6—7, the resulting precipitate was collected by filtration. The pure product **4** was obtained by column chromatography using petroleum/acetone (*V*/*V*, 10:1) as eluant.

General procedure for the rearrangement of **3a—b** *to* **4a—b**

In a N_2 atmosphere, 1.25 mmol of **3a—b** was heated at 170℃ for about 3 hours. After being cooled to room temperature, the mixture was purified by flash column chromatography using petroleum/acetone (*V*/*V*, 10:1) as eluant to give rearrangement products **4a—b** in yields of 56.8% and 76.5%, respectively.

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