REGIOSELECTIVE ADDITION OF 5-AMINO-1,2,4-TRIAZOLES AND ITS ANALOGUES WITH ARYLSULFONYL ISOCYANATES

Guangfu Yang*[a] and Huazheng Yang[b]

[a]Institute of Organic Synthesis, Central China Normal University, Wuhan 430079, P. R. China

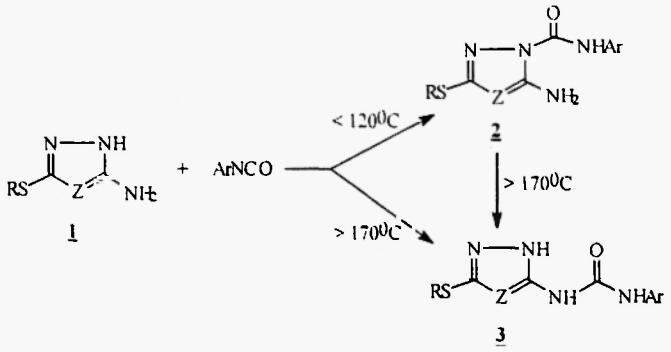
[b]Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, P. R. China

Abstract: The regioselective addition reaction of 5-amino-1,2,4-triazoles and its pyrazole analogues **1** with arylsulfonyl isocyanates were described. Experimental results showed that the addition reaction of **1** with arylsulfonyl isocyanates at room temperature took placed at the 5-position amino group and adducts **4** were obtained, however, the reaction proceeded at 1-N at the presence of sodium hydride to give products **5**, which suggested that the amino nitrogen at C-5 is more nuclophilic than 1-N in this reaction system. In addition, molecular mechanic calculations were applied to explain the regioselectivity.

Introduction

5-Amino-3-benzyl(aryl)thio-1,2,4-triazoles and its pyrazole analogues **1** are important intermediates for the syntheses of a lot of biological active compounds (1,2). In the course of synthetic programe of biological heterocyclic compounds, we reported in our previous paper (3) the regioselective addition of **1** with aryl isocyanates and the experimental results showed that the orientation of the addition of 5-amino-3-benzyl-(aryl)thio-1,2,4-triazoles and its analogues with the aryl isocyanates can be directed by controlling the reaction temperature .The 1-position adduct **2** was obtained regiospecifically below 120^{0}C, whereas the 5-position adduct **3** was obtained selectively when the reaction temperature was raised to 170^{0}C as depicted in Scheme **1**.

* To receive any correspondence (*e-mail*: gfyang@mail.ccnu.edu.cn)



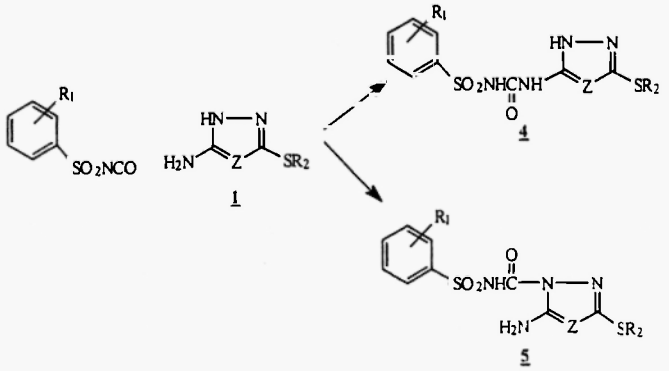
R = $PhCH_2S$, Z = N, C-CN, C-COOEt

Scheme 1

As a continuation of our research work, we needed a series of sulfonylurea compounds containing five-member heterocycles. Interestedly, when we applied the addition reaction of 5-amino-3-benzyl(aryl)thio-1,2,4-triazoles and its pyrazole analogues **1** with arylsulfonyl isocyanates to synthesize our target sulfonylureas, a different regioselectivity from that of arylisocyanate systems was observed. Herein we reported in detail the experimental results.

Results and Discussion

Experimental results as shown in scheme **2** indicated that the addition reaction of **1** with arylsulfonyl isocyanates at room temperature took placed at the 5-position and adducts 5-arylsulfonylureylene-3-substituted-1,2,4-triazoles (pyrazoles) **4** were obtained , which differed from the results of our previous paper and suggested that the amino nitrogen at C-5 is more nuclophilic than 1-N in this reaction system. In the presence of sodium hydride, the reaction proceeded at 1-N to give products 5-amino-1-arylsulfonylaminocarbonyl-3-substituted-1,2,4-triazoles(pyrazoles) **5**.



4a, 5a R_1 = H, Z = C-CN, R 2 = $C_6H_5CH_2$
4b, 5b R_1 = 2-COOEt, Z = C-COOEt, R 2 = $C_6H_5CH_2$
4c, 5c R_1 = H, Z = N, R 2 = 2-NO 2-4-$CF_3C_6H_3$

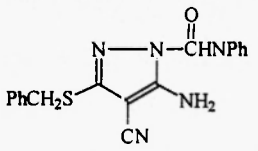
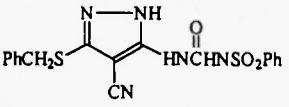
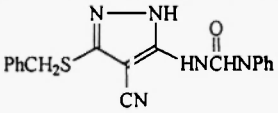
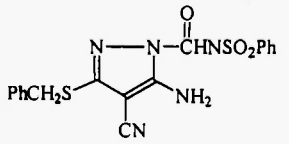
Scheme 2

The structures of **4** and **5** were determined on the basis of the proton nuclear magetic resonance (^{1}H-NMR) data. Take **4a** and **5b** as examples, the ^{1}H-NMR spectrum of **4a** showed the signals of three NH protons at δ 13.62 ppm, 11.18 ppm and 9.56 ppm as broad absorptions, while that of **5b** showed the signals of NH_2 at δ 9.38 ppm as a broad absorption and an NH proton at δ 10.76 ppm as a single absorption. The structure of all compounds prepared were confirmed using ^{1}H-NMR and CHN analyses.

At room temperature, aryl isocyanates reacted with 5-amino-1,2,4-triazoles and its analogues **1** to give 1-N addition products as the only isomers. In contrast, in the case of reaction of **1** 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 **2a**, **3a**, **4a** and **5a** as representative examples, the results are outlined in Table **1**.

From Table **1** we can conclude that **3a** and **5a** are more stable than **2a** and **4a** respectively. we can assume that **3a** and **5a** are thermodynamics control products and **2a** and **4a** are dynamics control products. So, based on the dynamics and thermodynamics control analysis, the different regioselectivety of addition reaction of aryl isocyanates and arylsulfonyl isocyanates with 5-amino-1,2,4-triazoles and its analogues **1** can be explained easily.

Table 1 The results of molecule mechanic calculations

No.	Structure	Energy (Kcals/mol)	No.	Structure	Energy (Kcals/mol)
2a		15.344	**4a**		7.974
3a		10.421	**5a**		3.507

In summary, we developed a regioselective route for the syntheses of 5-arylsulfonylureylene-3-substituted-1,2,4-triazoles (pyrazoles) **4** and 5-amino-1-arylsulfonylaminocarbonyl-3-substituted-1,2,4-triazoles(pyrazoles) **5** in good yields. Further studies on the bioactivety and structure-activity relationships of the products is on the way.

Experimental

Melting points were observed with a Yanaco MT-500 apparatus without correction. ^{1}H-NMR spectra were measured with a Bruker AC-P200 spectrometer using TMS as internal standard and elemental analyses were performered on a Perking-Elemer 240-C instrument. Staring materials 1a~e were prepared according to the literature (4,5).

General procedure for the preparation of **4***a~c:*

A solution of 2.2 mmoL of arylsulfonyl isocyanate in 5ml of dry CH_3CN was added dropwise to a solution of 2.2

mmoL of **1** in 15ml of the same solvent at room temperature. After stirring for about 2 hours, the mixture was filtered and the solid collected was recrystallized from acetone-petroleum mixture to give the pure products.

General procedure for the preparation of **5***a~c:*

A mixture of 2 mmoL of **1** and 0.06g (80%) NaH 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 stirring at room temperature for about 2 hours, the mixture was poured into 100 mL of ice-water. While the mixture was adjusted to pH = 6~7 and the resulting precipitate was collected by filtration. The pure product **5** was obtained by column chromatography using petroleum / acetone as eluant.

Spectral data and elemental analyses are as follows:

4a: Yield 79.2%; m.p 270~273°C; δ_H (DMSO-d_6) 4.24(s, 2H, CH_2), 7.25(s, 5H, C_6H_5), 7.62~7.97 (m,5H,C_6H_5), 9.56 (b,1H, NH), 11.18 (b,1H, NH), 13.62 (b,1H, NH). (Found: C, 52.36; H, 3.78; N, 16.96. $C_{18}H_{15}N_5O_3S_2$ requires C, 52.30; H, 3.63; N, 16.95). **4b:** Yield 72.5%; m.p 157~159°C; δ_H (DMSO-d_6) 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(b, H, NH), 11.76(s,1H, NH), 13.02 (b,1H, NH). (Found: C, 51.67; H, 4.73; N, 10.79. $C_{23}H_{24}N_4O_7S_2$ requires C, 51.88; H, 4.51; N, 10.53). **4c:** Yield 84.0%; m.p 255°C; δ_H (DMSO-d_6) 7.21~8.51 (m, 8H.C_6H_3 +C_6H_5), 9.75(b, H. NH), 11.14(s,1H,NH), 12.38 (b,1H, NH). (Found: C, 39.22; H, 2.50; N, 17.55. $C_{16}H_{11}F_3N_6O_5S_2$ requires C, 39.34; H, 2.25; N, 17.21). **5a:** Yield 82.3%; m.p 200~202°C; δ_H ($CDCl_3$) 4.24 (s, 2H, CH_2), 7.25 (s, 5H, C_6H_5), 7.62~7.97 (m,5H,C_6H_5), 6.79 (b,2H, NH_2), 10.38 (b,1H, NH). (Found: C, 52.48; H, 3.33; N, 17.12. $C_{18}H_{15}N_5O_3S_2$ requires C, 52.30; H, 3.63; N, 16.95). **5b:** Yield 75.8%; m.p 91~93°C; δ_H ($CDCl_3$) 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(b, 2H, NH_2), 11.89 (b,1H, NH). (Found: C, 52.03; H, 4.12; N, 10.78. $C_{23}H_{24}N_4O_7S_2$ requires C, 51.88; H, 4.51; N, 10.53). **5c:** Yield 85.0%; m.p 197~199°C; δ_H ($CDCl_3$) 7.35~8.51(m,10H,C_6H_5+C_6H_3+NH_2), 10.15 (b,1H,NH). (Found: C, 39.15; H, 2.55; N, 17.50. $C_{16}H_{11}F_3N_6O_5S_2$ requires C, 39.34; H, 2.25; N, 17.21).

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