Molecules **1996**, *1*, 89 – 92

Synthesis of 3,6-Disubstituted Tetrahydro-*S*-triazolo[3,4-b][1,3,5]thiadiazines

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Received: 25 September 1996 / Accepted: 22 November 1996 / Published: 18 December 1996

Abstract

Ten novel 3,6-disubstituted tetrahydro-*S*-triazolo[3,4-b][1,3,5]thiadiazines **2** have been synthesized by the double Mannich reaction of 3-aryl-5-mercapto-1,2,4-triazole with various aromatic amines and formaldehyde in the presence of ethanol-HCl solution. The structure of these compounds was determined by elemental analysis, IR, NMR and MS. Their antibacterial activities against *E. coli*, *B. bob* and *S. aureus* have been tested.

Keywords: Mannich reaction, 3-aryl-5-mercapto-1,2,4-triazole, 3,6-disubstituted tetrahydro-*S*-triazolo[3,4-b][1,3,5] thiadiazines.

Introduction

In recent years, some fused heterocycles have been found to possess many unique properties in synthesis of condensed *S*-triazole heterocycles, and have attracted a great deal of attention from chemists and pharmacologists because of their broad spectra of biological activities such as antifungal [1], antibacterial [2], hypotensive and CNS depressant [3] activities. Even though there are many reports [4-6] on the synthesis of triazolo[3,4-b][1,3,4]thiadiazole derivatives, there has been no report on the synthesis of 3,6-disubstituted tetrahydro-*S*-triazolo[3,4-b] [1,3,5]thiadiazine. A triazo-thiadiazole system may be viewed as a cyclic analog of two very important components, which display diverse biological activities. These results inspired us to synthesize a system which combines these two biolabile components in a ring together to give the title structure **2** for screening their antibacterial activities.

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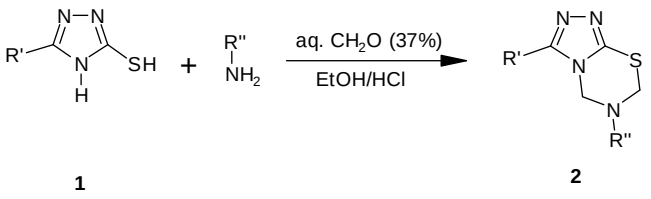
Table 1. *3,6-Disubstituted tetrohydro-*S*-triazolo[3,4-b] [1,3,5]thiadiazines* ***2a-j****.*

Compound	R'	R''	Yield (%)	M.p. (°C)
2a	*p*-$O_2NC_6H_4$	Ph-	85	275 (decomposed)
2b	*p*-$O_2NC_6H_4$-	*p*-$CH_3C_6H_4$-	87.82	290 (decomposed)
2c	*p*-$O_2NC_6H_4$-	*m*-$O_2NC_6H_4$-	80.92	250-251
2d	*p*-$O_2NC_6H_4$-	$(CH_3)_3CH$-	74.63	270 (decomposed)
2e	*m*-$O_2NC_6H_4$-	*p*-$CH_3C_6H_4$-	52	294 (decomposed)
2f	*m*-$O_2NC_6H_4$-	Ph-	77	178 (decomposed)
2g	Ph-	Ph-	61.22	204-205.5
2h	Ph-	*o*-$CH_3C_6H_4$-	84.42	198-199
2i	*m*-Py-	Ph-	81.2	213-214.5
2j	*o*-$CH_3OC_6H_4$-	*o*-$O_2NC_6H_4$-	50	217-218

Results and Discussion

The required 3-aryl-5-mercapto-1,2,4-triazole derivatives (**1)** were prepared according to the method in the literature [7]. Compound **1** contains NH and SH groups. The di-Mannich reaction with aromatic amines and a formaldehyde solution in the presence of ethanol-HCl solution at 45-65 °C was used to produce the Mannich base in good yields. The synthesis route is outlined in Scheme 1:



1 **2**

Scheme 1

The most reactive systems appeared to be those for which both R' and R'' were aromatic and those for which R'' was aliphatic and R' aromatic. However, if R'' contained an electron donating group, it was introduced hydroxyl methyl group easily. The reaction was also influenced by temperature. If the reaction was run at the refluxing temperature of the reaction mixture, no Mannich base **2** could be isolated. The rate of reaction decreased at low temperature, the most suitable temperature is 45–65 °C.

The reaction mechanism is proposed as follows (Scheme 2).

The structures of compounds **2a-j** were determined by elemental analysis, IR, NMR and MS. For example, from the IR spectral data of **1** characteristic peaks at 2560–2859 cm^{-1} and 3093–3427 cm^{-1} were found. These peaks were assigned to SH and NH. However, the peaks of SH and NH disappeared when **1** reacted with aromatic amines and cyclized to compound **2** and the characteristic peak of C-S-C appeared at 618–725 cm^{-1}. Comparing the ^{1}H-NMR spectra of **1** with **2**, we could see that the noticeable change is that the signals of the imino proton at 13.70–14.20 ppm and the mercapto proton at 13.20–13.75 ppm disappeared. The chemical shift of methylene protons of **2** was at lower field than normal methylene. This was due to the influence of deshielding effect in *S*-triazolo[3, 4-b][1, 3, 5]thiadiazine.

Analyzing the MS spectra of **2a-j** which contained many heteroatoms, we found that the molecular ion peaks of the compound **2a-j** have a high intensity.

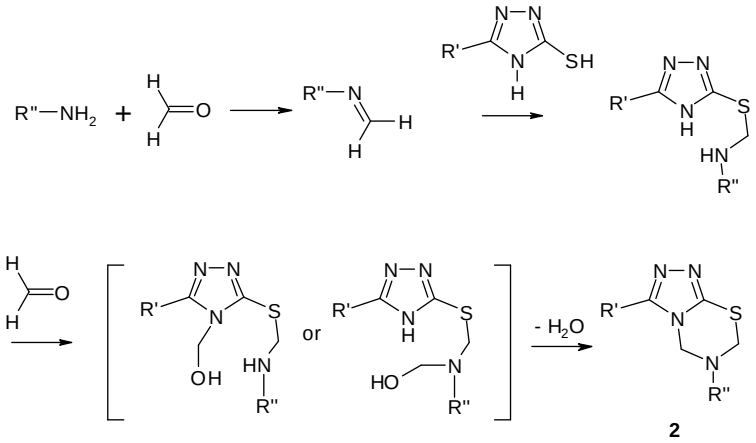
Ten compounds were screened for their antibacterial activity against *B. bob*; *S. aureus* and *E. coli* at 800,100 and 50 ppm concentrations. The results showed that compounds **2a**, **2b**, **2c**, **2e**, **2f**, **2h** and **2j** have significant activity. Detailed results will be described elsewhere.

Experimental Section

The melting points were recorded on an X4 microscopic melting point apparatus and uncorrected. Elemental analyses were determined on a PE-2400 instrument, IR spectrum on an FTS-40(KBr) and ^{1}H-NMR spectra on a Brukar AM (100 MHz) instrument (DMSO-d_6). MS spectra were recorded on a ZAB-HS (EI, 70ev) instrument.

Table 2. *Properties of 3,6-disubstituted tetrohydro-S-triazolo[3,4-b][1,3,5]thiadiazines* ***2a-j***

No.	Analysis	Found	Calc	IR (cm^{-1})	^{1}H-NMR (δ, ppm)	MS (%)
2a	C	49.78	49.99	3035, 2854, 2673	8.24–8.38 (4H, m)	340 (M,1.4), 325
	H	3.21	3.15	1662, 1614, 1435	7.31–8.22 (5H, m)	277, 237, 221
	N	22.06	21.87	1366, 1467, 1246	6.49 (2H,s)	207, 134, 65
				853, 732, 618	5.26 (2H,s)	
2b	C	57.49	57.77	3095, 3031, 2923	8.35–8.25 (4H,m)	353 (M,25), 323
	H	4.34	4.28	2798, 1673, 1604	7.35–7.12 (4H, m)	234, 176, 177,
	N	19.54	19.82	1570, 1384, 880	5.97 (2H, s)	119, 75
				809, 1265, 725	5.57 (2H, s)	
					2.23 (3H, s)	
2c	C	49.8	49.9	3078, 2824, 2729	8.26–8.33 (4H, m)	384 (M,65), 354
	H	3.20	3.15	1628, 1579, 1527	7.61–8.1 (4H, m)	236, 222, 177
	N	21.60	21.87	1455, 1348, 793	6.20 (2H, s)	176, 150, 104
				732, 1267, 690	5.75 (2H, s)	
2d	C	51.04	51.18	3071, 2964, 2853	8.14–8.38 (4H, m)	306 (M, 0.69)
	H	4.87	4.95	1697, 1627, 1576	5.40 (2H, s)	223, 191, 177
	N	23.23	22.94	1481, 1519, 1348	6.22 (2H, s)	
				868, 1293, 705	1.22 (6H, d)	
					3.33 (1H, m)	
2e	C	57.98	57.77	3090, 3072, 2910	8.93–8.22 (4H, m)	353 (M, 18), 236
	H	4.19	4.28	2822, 2793, 1675	7.6–7.11 (4H, m)	235, 207, 177
	N	19.64	19.82	1635, 1589, 1517	5.6 (2H, s)	119, 91, 75
				1347, 803, 734	6.52 (2H, s)	
				1280, 678	2.03 (3H, s)	
2f	C	56.76	56.62	3030, 2859, 2764	7.17–6.91 (5H, m)	339 (M, 18), 307
	H	3.71	3.86	1660, 1613, 1524	7.97–7.51 (4H, m)	236, 177, 147
	N	20.93	20.64	1433, 1470, 1372	6.52 (2H, s)	135, 118, 57
				1247, 693	5.47 (2H, s)	
2g	C	65.42	65.28	3063, 2970, 2936	7.55 (5H, s)	294 (M, 3), 235
	H	4.68	4.97	2790, 1628, 1517	7.40 (5H, s)	207, 191, 177
	N	19.31	19.03	1450, 1358, 810	6.20 (2H, s)	118, 77
				765, 1280, 705	5.66 (2H, s)	
2h	C	66.37	66.21	3040,3020,2912	7.89 (5H,s)	308 (M, 0.86)
	H	5.38	5.23	2785, 2720, 1633	7.65–6.83 (4H, m)	278, 206, 178
	N	18.41	18.17	1504, 1480, 1352	6.37 (2H, s)	104, 77
				1271, 710, 763	5.40 (2H, s)	
				805	2.23 (3H, s)	
2i	C	61.21	60.99	3041, 2845, 2909	7.74–6.82 (5H, m)	295 (M, 0.61)
	H	4.26	4.44	1660, 1600, 1546	9.14–7.95 (4H, m)	235, 207, 179
	N	23.96	23.71	1452, 1372, 1505	6.45 (2H, s)	147, 106
				1246, 701	5.25 (2H,s)	
2j	C	55.35	55.27	3025, 2953, 2853	8.85–8.0 (4H, m)	369 (M, 2), 340
	H	4.17	4.09	2764, 1611, 1512	7.65–7.45 (4H, m)	207, 177, 119
	N	18.68	18.96	1480, 1450, 1341	3.95 (3H, s)	91, 77
				822, 738, 1275	6.75 (2H, s)	
				663	5.75 (2H, s)	



Scheme 2

General procedure for the preparation of 3,6-disubstituted-S-triazolo[3,4-b][1,3,5]thiadiazine

The aromatic amine (10 mmol) was dissolved in absolute EtOH (10 ml) then ethanol-HCl (10 ml), formaldehyde solution (37%) (3 ml) and 3-aryl-5-mercapto-1,2,4-triazole (10 ml) was added. The mixture was stirred at 40–50 °C for 3 h then at 65–70 °C for 7–8 h and allowed to stand overnight. The precipitate was filtered, washed with 10% Na_2CO_3 and 95% EtOH. The pure product was obtained by recrystallization from acetone/95%EtOH (1:2), 95% EtOH/Et_2O (1:1), or acetone/ethylacetate (1:1).

Acknowledgement. This work was supported by the Natural Science Foundation of Education Commission of Anhui Province.

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Supporting samples are available from MDPI:
2a, MDPI 671; **2b**, MDPI 672; **2d**, MDPI 676; **2e**, MDPI 678; **2g**, MDPI 682; **2a**, MDPI 683; **2i**, MDPI 689.