THE SYNTHESIS OF NOVEL 1-SUBSTITUTED 4H-[1,2,4]TRIAZOLO[3,4-c][1,4]BENZOXAZIN AND BENZTHIAZIN-4-ONES

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Abstract - The synthesis of novel 1-substituted 4H-[1,2,4]triazolo[3,4-c][1,4] benzoxazin and benzthiazin-4-ones is described. A minor modification in the synthetic sequence resulted in an entirely different heterocyclic system, i.e. a 2-(2-oxo-3H-1,3,4-oxadiazol-5-yl)benzoxazole.

The chemistry and biology of the 4H-[1,2,4]triazolo[3,4-c][1,4]benzoxazine and benzthiazine ring systems have not been extensively explored. The one report that we were aware of concerned the synthesis of the 4-phenyl-substituted ring system[2]. These compounds were found to be useful as central nervous system depressants and in particular as antianxiety agents.

We now report a short, efficient synthesis of 1-substituted 4H-[1,2,4]triazolo[3,4-c][1,4] benzoxazin and benzthiazin-4-ones. Our compounds inhibit histamine release from passively sensitized rat mast cells and as such have utility as anti-allergic agents.[3] In addition, we wish to report the details of an interesting ring contraction reaction.

RESULTS AND DISCUSSION

Reaction of 1a (prepared from the treatment of 1,4-benzoxazine-2,3-dione[4] with thionyl chloride) with formylhydrazine in 1,2-dimethoxyethane at reflux produced 4H-[1,2,4]triazolo[3,4-c][1,4]-benzoxazin-4-one (2a) (Scheme). In the same way, using appropriate starting materials, the products shown in the Table were prepared. However, when 1g was treated with ethyl carbazate in 1,2-dimethoxyethane at reflux a mixture was obtained. Instead of immediately trying to solve this problem, we decided to prepare the uncyclized ethyl carbazate intermediate.

Therefore, treatment of 1g with ethyl carbazate in acetonitrile at reflux gave the desired intermediate 3. Thermal cyclization of 3 in Dow Therm^{R} at 250°C produced 8-methyl-4H-[1,2,4]-triazolo[3,4-c][1,4]benzoxazine-1,4-dione (5). The ir spectrum of compound 5 contained absorptions at 1760 and 1725 cm^{-1} corresponding to carbonyls at C-4 and C-1, respectively. In the NMR spectrum, the C-9 methine of 5 was shifted 1.1 ppm downfield relative to starting material (3). This is due to the deshielding effect of the neighboring C-1 carbonyl of 5.

A minor modification of the reaction conditions in the first step of the above synthetic route, however, produced an entirely different result.

Reaction of 1g with ethyl carbazate in acetonitrile with triethylamine at room temperature did not give 3; instead a compound with the physical properties recorded for 4 was isolated (for a comparison of properties see the Experimental section). We reasoned that the presence of triethylamine shifted attack of ethyl carbazate away from the imino chloride to the lactone carbonyl and that subsequent ring contraction gave compound 4. Thermal cyclization of 4 in Dow Therm^{R} at 250°C produced 5-methyl-2-(2-oxo-3H-1,3,4-oxadiazol-5-yl)benzoxazole (6). The ir spectrum of compound 6 contained absorptions at 1780-1820 and 3300-3500 cm^{-1} which are consistant with values reported for oxadiazol-5-one systems.[5] Futhermore, we have investigated the synthesis of 2-(2-oxo-3H-1,3,4-oxadiazol-5-yl)benzoheterocycles as orally active antiallergic agents in detail and have reported the results elsewhere.[6]

In summary , we have reported the synthesis of 1-substituted 4H-[1,2,4]triazolo[3,4-c][1,4] benzoxazin and benzthiazin-4-ones. In addition, we have shown that a slight modification of the reaction conditions in the route to 5 resulted in an entirely different heterocyclic system (6).

Scheme

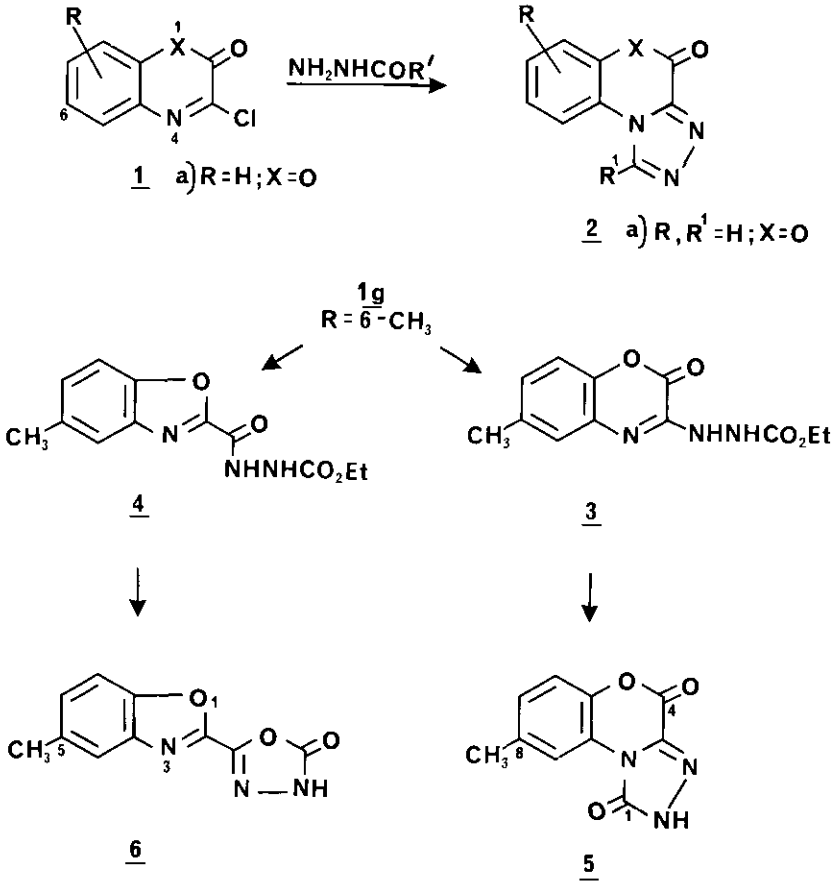
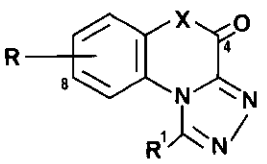


Table Synthesis of 1-Substituted 4H-[1,2,4]Triazolo[3,4-c][1,4]benzoxazin and Benzthiazin-4-ones.



No.	X	R	R^1	MP°C	Yields[a]	Molecular Formula	Analysis	
							Calcd.	Found
2a	O	H	H	270-275	50%	$C_9H_5N_3O_2$	C 57.76	57.73
							H 2.69	2.59
							N 22.45	22.36
2b	O	7-CH_3	H	273-275	73%	$C_{10}H_7N_3O_2$	C 59.70	59.54
							H 3.51	3.53
							N 20.89	20.64
2c	O	7-CH_3	CH_3	258-261	61%	$C_{11}H_9N_3O_2$	C 61.39	61.39
							H 4.22	4.24
							N 19.53	19.74
2d	O	8-Cl	H	>300	35%	$C_9H_4ClN_3O_2$	C 48.77	49.06
							H 1.81	1.83
							N 18.96	18.79
2e	O	H	CH_3	>300	31%	$C_{10}H_7N_3O_2$	C 59.70	59.83
							H 3.51	3.55
							N 20.89	21.02
2f	S	H	H	288-292	54%	$C_9H_5N_3OS$	C 53.19	53.32
							H 2.48	2.08
							N 20.68	20.74

a) Compounds 2b-2e were recrystallized from acetonitrile and compounds 2a and 2f were recrystallized from 1,2-dimethoxyethane.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were taken on a Varian 60 MHz spectrophotometer. Microanalysis were performed by the Analytical Chemistry Department, Revlon Health Care Group. Dow Therm^R is a product of Dow Chemical Company. All reactions were done under a nitrogen atmosphere.

4H-[1,2,4]-Triazolo[3,4-c][1,4]benzoxazin-4-one (2a)

A hot solution of formyl hydrazine (2.32g, 38.6 mmol) in 1,2-dimethoxyethane (50 ml) was added (2 min) to a solution of 3-chloro-1,4-benzoxazin-2-one in 1,2-dimethoxyethane (90 ml). The reaction was refluxed for 18 h, the resulting precipitate was filtered and recrystallized from 1,2-dimethoxyethanol, mp 270-275°C (50% yield).

In the same way, using appropriate starting materials, the products shown in the Table were prepared.

Ethyl (6-Methyl-2-oxo-2H-benzoxazin-3-yl)hydrazinocarboxylate (3)

A mixture of 3-chloro-6-methy-1,4-benzoxazin-2-one (44.0 g), ethyl carbazate (25.7 g) and dry

acetonitrile (1 L) was refluxed for 4 h. The resulting solution was partially concentrated and cooled. A crystalline solid formed which was filtered and dried, mp 214-217°C (70% yield). NMR ($DMSOd_6$): 7.1 (m, 3H); 4.2 (q, 2H); 2.3 (s, 3H); 1.2 ppm (t, 3H). IR (KBr): 1760, 1695 cm^{-1}. Anal. calcd. for $C_{12}H_{13}N_3O_4$: C, 54.75; H, 4.98; N,15.96. Found: C, 54.77; H,4.87; N, 15.94.

Ethyl 3-(5-Methyl-2-benzoxazoyl)hydrazinocarboxylate (4)

A mixture of 3-chloro-6-methyl-1,4-benzoxazin-2-one (15 g) and ethyl carbazate (8.4 g) in dioxane (80 ml) and triethylamine (12 ml) was stirred for 4 h at room temperature. The organic solvent was removed in vacuo and the residue was triturated with water, filtered and dried. Recrystallization from acetonitrile gave white crystals, mp 130-133°C (63% yield). NMR ($DMSOd_6$): 7.6 (q, 2H); 6.8 (s, 1H); 4.2 (q, 2H); 2.3 (s, 3H); 1.2 ppm (t, 3H). IR (KBr): 1735, 1690 cm^{-1}. MS: m/e 263(M+).

8-Methyl-4H-[1,2,4]triazolo[3,4-c][1,4]benzoxazine-1,4-dione (5)

A suspension of ethyl (6-methyl-2-oxo-2H-benzoxazin-3-yl)hydrazinocarboxylate (37.0 g) in Dow Therm^R (100 ml) was heated at 250°C for 3 h. After cooling, ether was added and the resulting precipitate was filtered and dried. The precipitate was then suspended in acetonitrile, refluxed for 2 h and filtered hot. The resulting solid was dried, mp >300°C (73% yield). NMR ($DMSOd_6$): 8.2 (s, 1H); 7.2 (m, 2H); 2.4 ppm (s, 3H). IR (KBr): 1760, 1725 cm^{-1}. MS: m/e 217 (M^+). Anal. calcd for $C_{10}H_7N_3O_3$: C, 55.30; H, 3.25; N, 19.35. Found: C, 55.41, H, 3.19; N, 19.21.

5-Methyl-2-(2-oxo-3H-1,3,4-oxadiazol-5-yl)benzoxazole (6)

Intermediate 4 (12 g) was added with stirring to Dow Therm^R (250 ml) at 230-240°C. After heating for 1 h, the reaction mixture was cooled, filtered and the resulting solid was washed with hexane. Recrystallization from acetonitrile gave the product, mp 207-210°C, in 77% yield. NMR ($DMSOd_6$): 7.4 (m, 3H); 2.5 ppm (s, 3H). IR (KBr): 1780-1820 and 3300-3500 cm^{-1}. MS: m/e 217 (M^+). Anal. calcd. for $C_{10}H_7N_3O_3$: C, 55.30; H, 3.25; N, 19.35. Found: C, 55.51; H, 3.07; N, 19.61.

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