

SYNTHESIS OF TRIAZOLIDINE-1,3,5,7-TETRAONE AND PYRIMIDIN[1,5]DIAZEPINE DERIVATIVES BY CARBON SUBOXIDE

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Abstract – A one step synthesis of 6*H*-pyrazolidin[1,2-*a*][1,2,4]-triazolidine-1,3,5,7-tetraones and pyrimidino[1,5]diazepine- and thiazepines by carbon suboxide is here described.

In previous papers ¹ we reported the synthesis of heterocyclic derivatives by carbon suboxide. Starting from bifunctionalized aromatic and aliphatic compounds with this reagent it was possible to carry out a one step heterocyclization reaction in high yields.

Pyrazolidine-3,5-dione and 1,2,4-triazolidine-3,5-dione derivatives are an important compounds for their biological activity, ² especially as anti-inflammatory activity.³

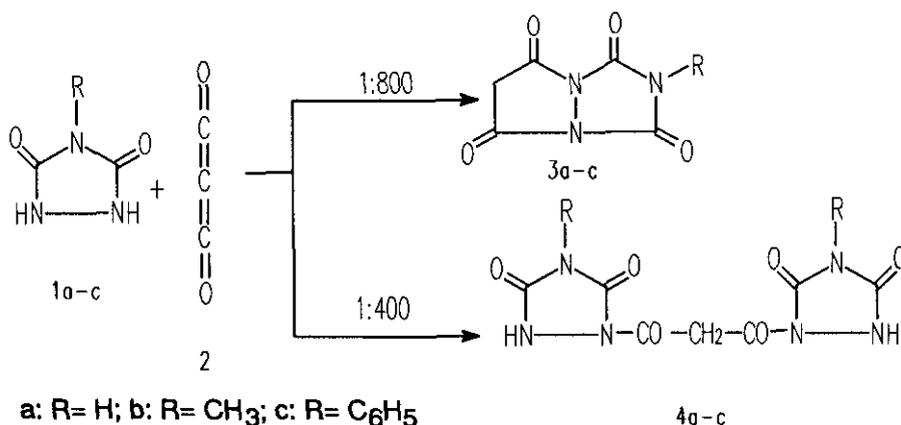
It is, moreover, well known that benzodiazepines are an important class of psychotherapeutic compounds. Normally they need benzene ring for pharmacological activity, but in recent years some examples of heterocyclic rings fused to the seven-member diazepine ring system have appeared in literature. ⁴ In particular a good CNS activity was reported ⁵ for various pyrazolodiazepines.

Considering the biological importance of these heterocycles, in this work we report a preliminary study on the reactivity of carbon suboxide with 1,2,4-triazolidine-3,5-dione derivatives and polifunctionalized pyrimidines.

The reaction of 1,2,4-triazolidine-3,5-diones (1a-c) with carbon suboxide (2) leads to

6*H*-pyrazolidin[1,2-*a*][1,2,4]triazolidine-1,3,5,7-tetraones (**3a-c**). Only compounds (**3a-c**) were obtained when the reaction was carried out in dilute solutions (C_3O_2 :solvent 1:800), while in more concentrated solutions (1:400) malonic derivatives (**4a-c**) were also obtained in less than 25% yields (Scheme 1).

The structure of compounds (**3a-c**) was confirmed by ir, 1H nmr and mass spectra. In particular, the molecular ion was determined in their mass spectra and the loss of the $[C_3HO_2]^+$ ion, m/z 69, identified as the protonated carbon suboxide, was observed for all compounds. This elimination pathway was in accord with literature.⁶

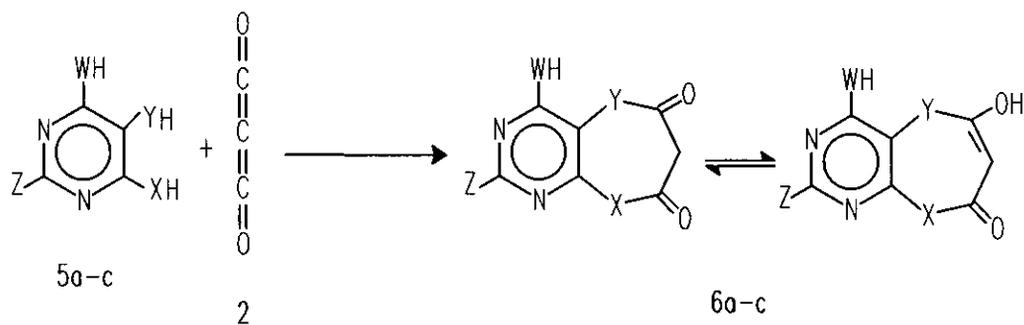


Scheme 1

Reaction of the polyfunctionalized pyrimidines (**5a-c**) with carbon suboxide (**2**) gave pyrimidin[1,5]thiazepine (**6a**) and pyrimidin[1,5]diazepines (**6b,c**).

As shown in Scheme 2 carbon suboxide (**2**) reacts with the $-NH_2$ groups of **5b,c** to give the diamides (**6b-c**). Starting from **5a** we only isolated the heterocycle (**6a**) in which the carbon suboxide reacts with the $-NH_2$ and SH groups.

The structure of compounds (**6a-c**) was confirmed by their 1H nmr spectra. In fact, in compounds (**6b-c**) we observed complete disappearance of the NH_2 groups at ca. 6 ppm and appearance of two new signals due to the NH groups. We detected disappearance of the signal of only one $-NH_2$ group and observed the tautomerism shown in Scheme 2 only in the 1H nmr spectrum of compound (**6a**).



a: X=S, Y=NH, W=NH, Z=SH

b: X=NH, Y=NH, W=O, Z=SH

c: X=NH, Y=NH, W=O, Z=H

Scheme 2

EXPERIMENTAL

Melting points were determined on a Kofler apparatus and are uncorrected. The ^1H nmr spectra were determined using a Varian Unity 300 spectrometer and the chemical shifts (δ) refer to tetramethylsilane. The ir spectra were recorded on a Perkin Elmer 1310 spectrophotometer on NaCl mulls.

Elemental analyses were carried out on a Carlo Erba 1106 Elemental analyzer. Mass spectra were taken with a QMD 1000 instrument (Fisons Instruments) at 70 eV using a direct inlet system. All compounds were purchased from Aldrich Chemical Co. and the solvents were dried rigorously before use according to standard methods.⁷

The carbon suboxide was prepared from pyrolysis of di-*O*-acetyltartaric anhydride.⁸

General procedure for the synthesis of 3a-c and 4a-c.

Carbon suboxide (2) was slowly added at $-70\text{ }^\circ\text{C}$ to stirred solutions of 1a-c (16 mmol) in 800 ml of anhydrous 1,4-dioxane:acetonitrile (1:1) (for 1a), acetone (for 1b) and acetonitrile (for 1c). At completion, the mixture was kept under stirring at $0\text{ }^\circ\text{C}$ for 5 h and at room temperature for 48 h. The solution was then evaporated under reduced pressure, and the crude residue was crystallized from acetone to give 3a-c.

Using the same procedure but starting from solutions of **1a-c** (16 mmol) in 400 ml of the previously mentioned solvents, the crude residue was flash chromatographed using 3:1 acetone:ethyl acetate as eluant. The first eluate was **3a-c**, while the second eluate gave **4a-c**.

The analytical and spectral data for compounds (**3a-c**) and (**4a-c**) are shown in Table 1.

General procedure for the synthesis of pyrimidine (**6a-c**).

Carbon suboxide (**2**) (16 mmol) was slowly added at -70°C to stirred suspensions of **5a-c** (16 mmol) in 500 ml of anhydrous acetone:1,4-dioxane (2:1). At completion, the mixture was kept at room temperature and under stirring for 72 h. The reaction mixture was then filtered off. The solid proved to be the unreacted pyrimidines after comparison with commercial samples. Evaporation of the clear filtrate under reduced pressure gave a crude solid that was crystallized from acetone to yield **6a-c**.

The analytical and spectral data are shown in Table 1.

Table 1. Analytical and spectral data for compounds (**3a-c**, **4a-c** and **6a-c**)

Compd.	Yield (%)	mp($^{\circ}\text{C}$)	ir (nujol) ν_{max} (cm^{-1})	^1H nmr (DMSO- d_6) δ (ppm)	Molecular Formula ^(a) M ⁺ (m/z)	Elemental Analyses		
						Calcd (%)	(Found)	
						C	H	N
3a	60	> 300	3580,1790,	10.71 (s, 1H, NH),	$\text{C}_5\text{H}_3\text{N}_3\text{O}_4$ 169	35.51 (35.45)	1.79 1.80	24.85 24.78)
			1710	3.67 (s, 2H, CH_2)				
3b	55	234-	1790,1770,	3.58(s, 2H, CH_2),	$\text{C}_6\text{H}_5\text{N}_3\text{O}_4$ 183	39.35 (39.46)	2.75 2.74	22.95 22.90)
		235	1700	2.80(s, 3H, CH_3)				
3c	63	288-	1780,1730,	7.53-7.38 (m, 5H, arom),	$\text{C}_{11}\text{H}_7\text{N}_3\text{O}_4$ 245	53.88 (53.90)	2.88 2.87	17.14 17.09)
		290	1710	3.86 (s, 2H, CH_2)				
4a	20	235-	3590-3280,	10.78 (s, 2H, 2NH),	$\text{C}_7\text{H}_6\text{N}_6\text{O}_6$ 270	31.12 (31.23)	2.24 2.23	31.11 31.08)
		237	1790,1720,	9.30 (s, 2H, 2NH),				
		1680	3.10 (s, 2H, CH_2)					
4b	20	241-	3580,1740,	9.97 (s, 2H, 2NH),	$\text{C}_9\text{H}_{10}\text{N}_6\text{O}_6$ 298	36.25 (36.38)	3.38 3.39	28.18 28.25)
		243	1680	3.20 (s, 2H, CH_2), 2.78 (s, 6H, 2 CH_3)				

4c	25	118-	3590,1720,	10.41 (s, 2H, 2NH),	C ₁₉ H ₁₄ N ₆ O ₆	54.03	3.34	19.90
		120	1670	7.45-7.32 (m, 10H, arom), 3.19 (s, 2H, CH ₂)		422	(53.96)	3.35
6a	62	225-	3420-3360,	3.22 (s, 2H, CH ₂),	C ₇ H ₆ N ₄ S ₂ O ₂	34.69	2.50	23.12
		227	1720	6.62 (s, 2H, NH ₂ D ₂ O exch), 8.88 (s, 1H, CH=), 8.97 (s, 1H, CH=), 11.89 (s, 1H, NH D ₂ O exch), 11.30 (s, 1H, OH D ₂ O exch)		242	(34.80)	2.51
6b	65	270-	3380-3310,	3.25 (s, 2H, CH ₂),	C ₇ H ₆ N ₄ SO ₃	37.17	2.67	24.76
		272	1730-1710	6.06 (s, 1H, SH, D ₂ O exch), 8.78 (d, J=9.3 Hz, 2NH, D ₂ O exch), 11.72 (s, 1H, OH, D ₂ O exch)		226	(37.22)	2.66
6c	59	205-	3320-3140,	3.27 (s, 2H, CH ₂),	C ₇ H ₆ N ₄ O ₃	43.31	3.12	28.85
		207	1730-1700	7.73 (s, 1H, Pyr-H), 8.91-8.95 (d, J= 9.3 Hz, 2H, 2NH D ₂ O exch), 11.87 (s, 1H, OH D ₂ O exch)		194	(43.41)	3.12

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