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A FACILE SYNTHESIS OF A NEW TYPE OF OXADIAZABICYCLO[3,3,1]NONANES

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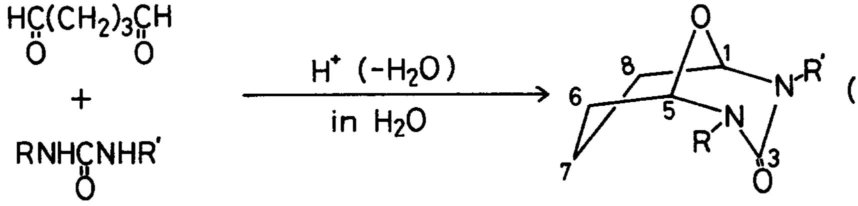
Abstract: 2,4-Dialkyl-9-oxa-2,4-diazabicyclo[3,3,1]nonan-3-ones were easily prepared by the acid-catalyzed reactions of glutaraldehyde with 1,3-dialkylureas in aqueous conditions, whereas in the absence of water only the copolymerization was observed.

Bicyclo[3,3,1]nonanes and their heterocyclic analogs have been well studied on the transannular reactions and others, where a double-chair conformation has been postulated.[1] While a many of heterobicyclo[3,3,1]nonanes containing N, O, S, or B atoms have been prepared,[2] the synthesis of a 9-oxa-2,4-diaza type of bicyclo[3,3,1]nonane has not been prepared as yet.

We report herein a facile synthesis of the 2,4-dialkyl-9-oxa-2,4-diazabicyclo[3,3,1]nonan-3-ones (1) by the acid-catalyzed reactions of glutaraldehyde with 1,3-dialkylureas. Although glutaraldehyde is a useful reagent for the synthesis of dihydropyridine derivatives by the reactions with amides,[3] the reaction with ureas has been little known except for the production of the copolymer of unsubstituted urea.[4] In contrast with the reactions of the amides under the anhydrous conditions,[3] the reactions of 1,3-dialkylureas must be carried out under the aqueous conditions for the synthesis of the compounds 1.[5]



(1)

1,3-Dimethylurea was most active and gave 2,4-dimethyl-9-oxa-2,4-diazabicyclo[3,3,1]nonan-3-one (1a) in 75.5% yield. Moreover, 1,3-diisopropylurea gave no product, but 1-isopropyl-3-methylurea could produce the corresponding compound 1. From these facts, the order of the reactivity is apparently due to the bulkiness of the alkylsubstituents of the ureas. In the ^{13}C-nmr spectra of the compounds 1,[6] the C-7 absorbed in the range of 12.7-13.3 ppm. This characteristic upfield absorption, other spectral and analytical data fully supported this ring system. The stereochemistry of them is tentatively assinged to the double-chair conformation which is generally most stable. In this structure, the two methyl substituents are not hindered, but the two isopropyl ones are highly hindered.

Although the consuming rate of 1,3-dimethylurea is similar under the anhydrous conditions to that under the anhydrous conditions, the former gave the compound 1a and the latter the copolymer.[7] It seems that the water does not depress the reactivity of glutaraldehyde with the urea. The copolymer obtained under the anhydrous conditions was heated in water in the presence of hydrochloric acid, but no change was observed (run 9). In addition, 1a was treated in dry benzene as well, but no polymerization was occured (run 8). Hence, no reversible interconversion between 1a and the copolymer may exist. On the basis of these results, the reaction path is considered as follows. At first an adduct of glutaraldehyde with an urea may be produced, and then the intramolecular dehydration may predominantly proceed to yield the corresponding compounds 1 by the presence of water. Under the anhydrous conditions the intermolecular reaction may occur to give the copolymer. However, its detailed structure is under investigation, and so the preparation path is not clear.

Table: Reaction Results[a]

run	R	R'	Solvent(vol/vol)	Yield of 1 (%)[b]	b.p. of 1 (°C/mmHg)
1	Me	Me	H_2O	75.5(53.9)[c]	69-70 °C(m.p.)
2	Et	Et	H_2O	33.3	91/1.5
3	^{n}Bu	^{n}Bu	H_2O-EtOH(1/1)	4.7(29.8)[d]	146/2.0
4	Me	Benzyl	H_2O-EtOH(1/1)	13.3(51.5)[d]	150-152/0.4
5	Me	^{i}Pr	H_2O	18.0(26.6)[e]	104-106/0.5
6	^{i}Pr	^{i}Pr	H_2O-EtOH(1/1)	0	
7	Me	Me	Benzene	0(copolymer 92%)	
8	1a		Benzene	no reaction	
9	copolymer		H_2O	no reaction	

[a] Urea 30mmol, glutaraldehyde 30mmol, cat. 3mmol, solv. 30ml, temp: 80°C except for run 6 at 120°C, time: 2hr except for run 6 for 20hr, cat: HCl in runs 1-6 and 9; p-$MeC_6H_4SO_3H$ in runs 7 and 8. [b] Determined by the glc. [c] H_2O-EtOH (1/1) solv. [d] For 10hr. [e] For 4hr.

References and notes

1 For example: T. Sasaki, S. Eguchi, and T. Kiriyama, J. Am. Chem. Soc., 91, 212 (1969); H. C. Brown and R. Norman, Tetrahedron Lett., 3007 (1977); N. S. Zefirov and S. V. Rogozina, Tetrahedron, 30, 2345 (1974).

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5 The products 1 were prepared as follows. A reaction mixture was heated as shown in Table. After neutralized by NaOH, the solvents were removed under vacuo, and then the residue was extracted with hexane. All products were purified by distillation.

6 The ^{13}C-nmr data of 1a($CDCl_3$,ppm): 12.7(C-7), 29.7(C-6,8), 31.1(CH_3), 83.5(C-1,5), 154.4(C-3).

7 The consuming rates were detected by the glc. The production of the copolymer was accompanied by dehydration. Copolymer: $\bar{M}n$ = 476, containing equimolar amount of the urea and glutaraldehyde (by elemental anal.), and the ^{1}H-nmr spectrum showed very little olefinic protons.

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