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SYNTHESIS OF HYDROXYISOXAZOLIDINES ON ADSORBENTS

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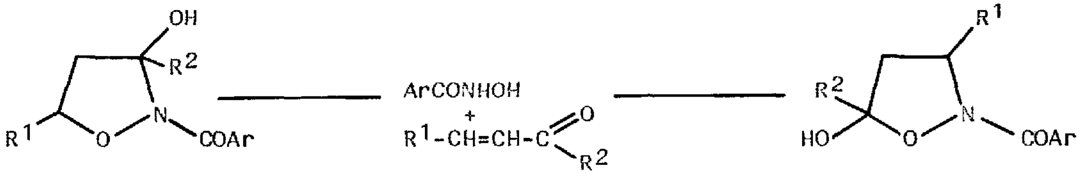
Abstract. 3- And 5-hydroxyisoxazolidines can be synthesized in solution and on the surface of an adsorbent. The regioselectivity depends on the type of adsorbent used.

The reaction of N-substituted hydroxylamines and alkenals has been shown to proceed with the formation of 3- or 5-hydroxyisoxazolidines [1]. As these compounds have a hemiaminal or hemiacetal fragment in their structure, they are very unstable and in most cases only products of the elimination of a water molecule can be isolated[2]. Recently we have described an efficient method of synthesizing previously undescribed 3- and 5-hydroxyisoxazolidines[3] It was found that arylhydroxamic acids and α,β-unsaturated carbonyl compounds interact in the presence of the heterophase catalyst triethylaminoethylcellulose (TEAE-cellulose) yielding cyclic compounds 1 or 2 (see Scheme) depending on the aryl substituent[4].



1

2

$Ar=C_6H_2(CH_3)_3$-2,4,5;
C_6H_4X-p , X=H,Br,NO_2

R^1,R^2=H,CH_3

$Ar=C_6H_4X$-p
X=OCH_3, CH_3, H

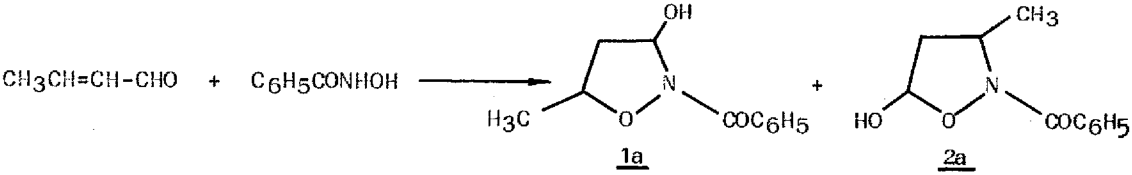
The interaction of benzohydroxamic acid and crotonaldehyde in methanol solution yields a mixture of 3- (98%) and 5-hydroxyisoxazolidines (≈2%) [5] .

Ring-chain tautomerism is characteristic of compounds 1 and 2. The present note is devoted to the comparison of the reaction of hydroxamic acids and α,β-unsaturated aldehydes in solution and in an adsorbed state in the absence of any solvent.

Our experiments have shown that adsorption causes an acceleration of the reaction. Thus, the complete conversion into 2-benzoyl-3-hydroxy-5-methylisoxazolidine under conventional conditions (0 °C, methanol solution, TEAE-cellulose catalysis) is achieved only after prolonged stirring (5-7 h) and the yield of product after isolation and purification is about 60%. The same conversion in an adsorbed state (20 °C, SiO_2)[6] is complete within 30-40 minutes (yield 90%).

Quite surprisingly it turned out that the isolated product structure (3- or 5-isomer) depends on the type of adsorbent (see Table 1). It may be supposed that these results can be explained by the difference in basic properties of adsorbents.

Table 1. Effect of adsorbent on the composition of the reaction products*.



Adsorbent	Total yield,%	3-OH isomer, % total	5-OH isomer, % % total
Neutral alumina	70-75	80-85	20-15
Neutral alumina/KF	70	75-80	25-20
Acid alumina	60-70	85-80	15-20
Florisil	50-70	85-90	15-10
Inerton AW	73	68	32
Silica gel	80-90	100	0
Cellulose	43	75	25
CM-cellulose	41	70	30
DEAE-cellulose	95-98	0	100
TEAE-cellulose	98	0	100

It was found that different diastereomers form in equal amounts in the case of 2-benzoyl-3-hydroxy-5-methylisoxazolidine, but only one diastereomeric pair of 2-benzoyl-5-hydroxy-3-methylisoxazolidine forms on DEAE-cellulose[7].

Further investigation of the reactions on DEAE-cellulose as adsorbent showed that for all starting hydroxamic acids and carbonyl compounds

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*-Reaction was carried out at 20 °C, reaction time in all cases was 15-16 h.

(acrolein, crotonaldehyde, methylvinylketone), only adducts 2 form in good yield (overnight incubation). The inversion of addition direction in comparison with that in methanol solution was observed for X=H,Br and Ar=$C_6H_2(CH_3)_3$. On the other hand, when the reaction time was reduced to 1-2 h, a mixture of the 3- and 5-isomers was obtained (see Table 2). Increasing the reaction time led to the transformation of 3-hydroxyisoxazolidines to 5-isomer on the surface of an adsorbent. Nevertheless, products 2 are not formed even on prolonged stirring in solution (20-40 days) for X=NO_2, Br and Ar=$C_6H_2(CH_3)_3$.

Table 2. The correlation between reaction time and amounts of isomers.

$$PhCONHOH + CH_3CH{=}CH{-}CHO \longrightarrow \underline{1a} + \underline{2a}$$

Reaction conditions	Time	Ratio of products, %	
		3-OH isomer(1a)	5-OH isomer(2a)
methanol solution	5 h	98	2
methanol solution	30 days	95-98	2-5
adsorbed state, silica gel	30 min	100	0
adsorbed state, DEAE-cellulose	1 h	60	40
adsorbed state, DEAE-cellulose	6 h	4	96

These data support the fact that the formation of 3-hydroxyisoxazolidines is reversible and DEAE-cellulose catalyzes not only the addition reaction, but also the transformation of the kinetic product 3-hydroxyisoxazolidine into the thermodynamically more stable 5-isomer[8].

Notes and references.

1. a) Y.Yamada, H.Noda, H. Okada, Agricul. and Biolog. Chem., 37, N9, 2201, (1973); b) J.E.Van Epp, Diss. Abstr. Int.,B, 40, 1727 (1979).
2. a) A.Belly, R.Jacquier, F.Petrus, J.Verducci, Bull. soc. chim. France, 330 (1972); b) A.Belly, F.Petrus, J.Verducci, Bull. soc. chim. France, 1395 (1973).
3. K.N.Zelenin, I.A.Motorina, L.A.Sviridova, G.A.Golubeva, I.P.Bezhan, A.Yu.Ershov, Yu.G.Bundel, Khim. Geterotsikl. Soed., N9, 1270 (1987).

4. The reaction was carried out in methanol solution, 0-5^{o}C, TEAE-cellulose catalysis, the reaction time being 5-20 h.
5. The structure of the compounds obtained was estimated on the basis of NMR ^{1}H and ^{13}C data. 3-Hydroxyisoxazolidines 1 have characteristic chemical shifts of 3-H proton at 5,6-6,1 ppm, and hemiaminal carbon atom $C_{(3)}$-- at 77-82 ppm, the analogous values for 5-hydroxyisoxazolidines being 5,2-5,8 and 95-100 ppm correspondingly. For more detailed information see also reference 3.
6. The general procedure of the reaction was as follows: 5 mmoles of p-substituted hydroxamic asid was dissolved in the minimum volume of anhydrous methanol and added to previously dried adsorbent (a) Silpearl "Chemapol" , CSSR, or b) acid alumina, activity I Brockman, pH 6-7, Poland c) neutral alumina, activity II Brockman, pH 9-10,"Reanal", Hungary; d) neutral alumina with 5% KF; e) Servacel TEAE, "Reanal", Hungary; f) DEAE-cellulose, "Reanal", Hungary and some other adsorbents). The solvent was evaporated under redused pressure. 5 mmoles of α,β-unsaturated carbonyl compound (acrolein, crotonaldehyde, methylvinylketone), stabilized by hydroquinone, was adsorbed on the another portion of adsorbent, the total mass of an adsorbent being 20 times as large as that of the reagents. Everything was thoroughly mixed and stirred during 30-40 min. The product was extracted from adsorbent by $CHCl_3$ and purified by recrystallization or column chromatography.
7. The existence of different diastereoisomers was estimated from NMR ^{1}H and ^{13}C spectra.
8. As follows from the kinetic data 3-OH and 5-OH isomers are prodused simultaneously and the ratio of production rates between 3-OH and 5-OH isomers is about 5.4.

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