

AMIDOALKYLATION OF DIENES WITH ADDUCTS OF GLYOXYLIC ACID -
SYNTHESIS OF α -ACYLAMINO- γ -ALKENYL- γ -BUTYROLACTONES

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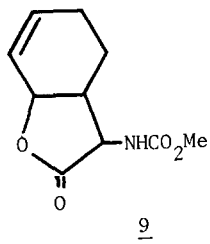
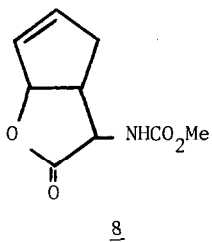
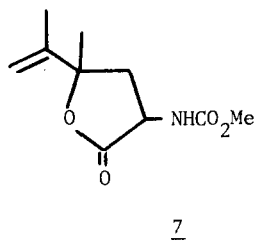
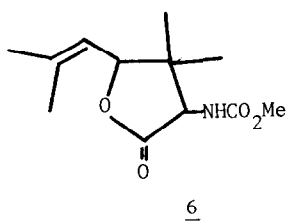
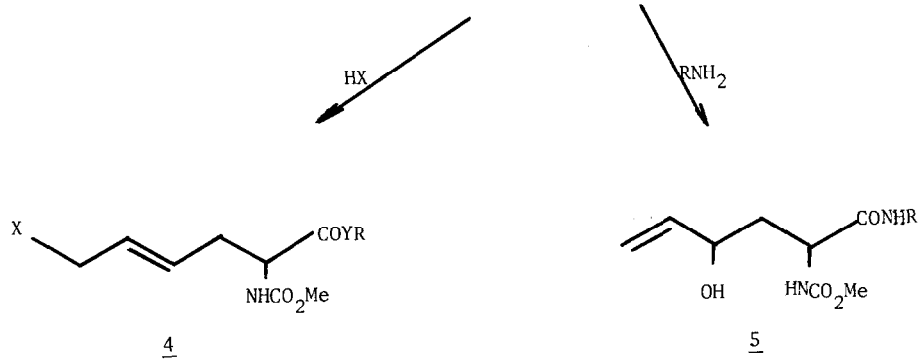
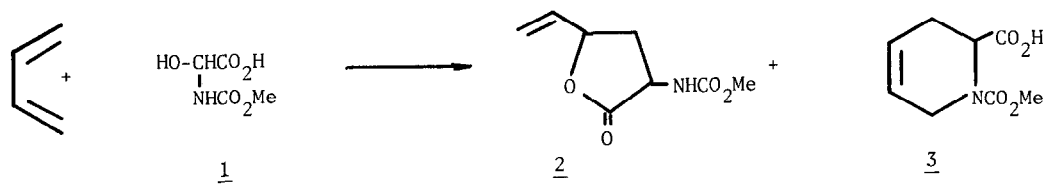
Abstract: Amidoalkylation of 1,3-dienes with the adduct of glyoxylic acid-methyl carbamate (1) afforded α -acylamino- γ -alkenyl- γ -butyrolactones (e.g. 2, 6-9) in 40-80% yield and the pipercolic acid derivatives (e.g. 3) in less than 20% yield. An explanation is suggested to account for the above results.

In the course of our studies on the chemistry of glyoxylic acid-primary amides adducts (e.g. 1)¹ and their reactions with aromatic and olefins² we were puzzled by the claims^{3,4} and our own observations⁵ that the yields of the acid catalyzed Diels-Alder reactions of dienes with open chain acylimines as dienophiles are rather low.^{3,4,5} We have now found, in the case of glyoxylic acid-methyl carbamate adduct (1) that the competing reaction with the normal cycloaddition reaction (e.g. 3) is the formation of α -methoxycarbonylamino- γ -alkenyl- γ -butyrolactones (e.g., 2, 6-9). In all the cases studied (10 dienes) the lactones were found to be the major reaction products.

Thus reacting adduct 1⁶ with butadiene in methylene chloride at room temperature and in the presence of methanesulfonic acid afforded the neutral α -methoxycarbonylamino- γ -vinyl- γ -butyrolactone (2) in 70-75% yield and the pipercolic acid derivative, the N-methoxycarbonylbaikiain (3) in only 7-9% yield. This observation was found to be quite general: piperylene, isoprene, 2,3-dimethylbutadiene, 2,4-hexadiene, 2,5-dimethyl-2,4-hexadiene, cyclopentadiene, 1,3-cyclohexadiene and 1,3-cyclooctadiene were all found to react with the adduct 1, in an acid catalyzed reaction, to give lactones as the major reaction products (40-80%). The normal Diels-Alder adducts were obtained in less than 20% yield.

The lactones showed characteristic I.R. absorptions at 1770-1790 cm^{-1} for the five-membered carbonyl lactone and at 3340, 1720 and 1550 cm^{-1} for the NH and CO of the carbamate group. Lactones 6, 7 and 8 were obtained as crystalline materials. An X-ray crystal structure analysis showed the lactone 6 (m.p. 108°, 65%) to have the trans configuration. The mother liquor of the crystalline products 6 and 7 did show the presence of isomers which had not yet been obtained pure.

Reacting cyclopentadiene with 1 in THF and in the presence of MSA afforded the crystalline lactone 8 (m.p. 80-82°) in 76% yield. Only a trace of an acidic product was detected in this



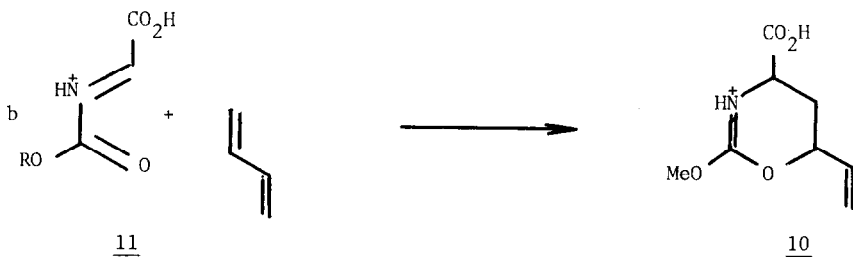
reaction. 1,3-Cyclohexadiene reacted similarly with 1 in 50% yield. The normal Diels-Alder product was obtained in only 6% yield. The lactones showed in the NMR characteristic absorptions of the α and γ hydrogens. In compound 6 the α and γ hydrogens appeared as doublets at 4.51 and 4.90 ppm and the methyl groups appeared as five singlets. In compound 8, the α hydrogen appeared as a triplet at 4.00 ppm. The β -methylene group of 7 (m.p. 84-86°, 52%) appeared as a ABX system at 2.10-3.30 ppm and the α hydrogen as a multiplet at 4.10-4.65 ppm.

The vinyl lactone 2 was found to react in an S_N1 fashion with HBr in AcOH and with MeSH in the presence of an acid catalyst to give the corresponding ω -bromo (4, RY=HO; X=Br) and ω -methylmercapto (4, RY=X=MeS) derivatives of γ,δ -unsaturated α -aminohexanoic acid. Primary and secondary amines opened the lactone ring to give the corresponding unsaturated hydroxyamino acid amides 5. The structures assigned to these products are based on their IR, NMR, mass spectra and elemental analysis.

The intermediates in the formation of the γ -alkenyl lactones are most probably the oxazine-4-carboxylic acid derivatives (e.g. 10) which rearranges to the lactones (e.g. 2) in the acid media. This suggestion is based on the observations made by Seelinger⁷ and R.R. Schmidt⁸ who have isolated alkenyloxazine in the reactions of N -hydroxymethylbenzamide with dienes and on the observation that a 4-carbomethoxyoxazine was found to rearrange partly to the corresponding lactone on heating in the presence of an acid catalyst²:



If the oxazines (e.g. 10) are the kinetically controlled products in the above reactions, it means that we are dealing with two competitive 4+2 cycloadditions:



In the first reaction (path a) the acyliminium 11, formed from 1 in the acid medium, reacts as a dienophile in a normal Diels-Alder reaction. In the second reaction (path b) the same acyliminium intermediate 11 reacts as the diene in a 4+2 cycloaddition with an inverse electron demand while butadiene functions as the dienophile in this reaction. The competition between the two reactions will depend on the conformation of the two dienes and on steric and stereoelectronic effects. The results obtained by us and by Seelinger⁷, Schmidt⁸ and C. Giordano¹⁰ suggest that the favoured conformation of the acyliminium intermediate 11 is s-cis⁹ and that the steric effect and probably the secondary orbital interactions favours the cycloaddition with the inverse electron demand (path b).

The above suggested mechanism explains the low yields which are often encountered in the acid catalyzed normal Diels-Alder reactions with acylimines as dienophiles^{3,4,5}.

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(Received in UK 20 December 1982)