Tetrahedron Letters No. 44, pp 3983 - 3984, 1976. Pergamon Press. Printed in Great Britain.

NITRILE OXIDES IN A NEW APPROACH TO THE SYNTHESIS OF GLUTARIMIDE ANTIBIOTICS

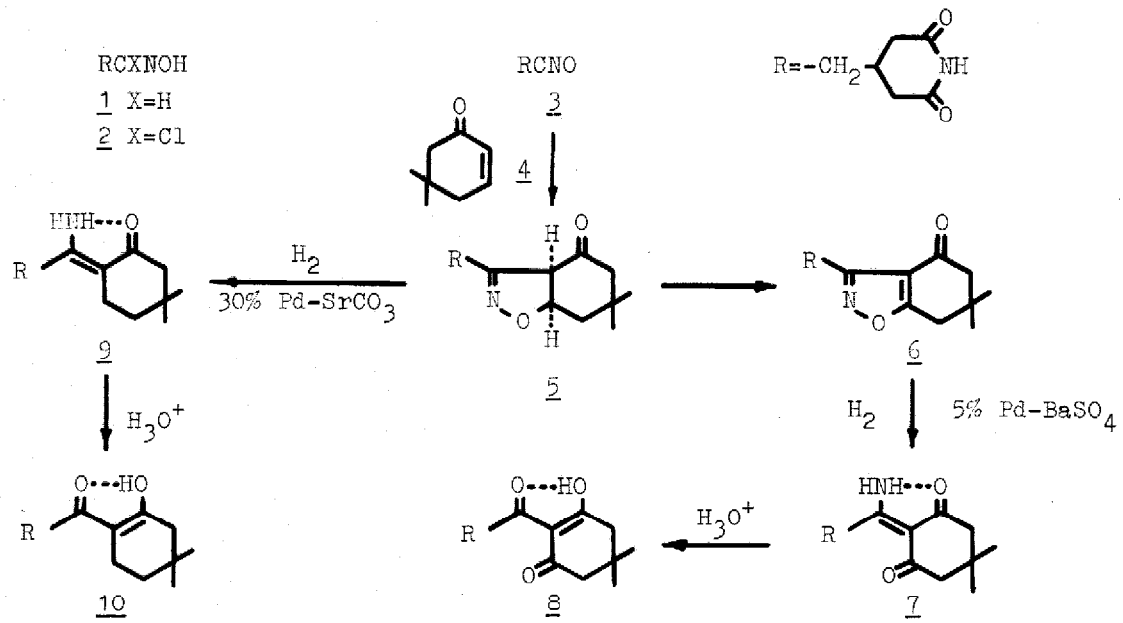
A. A. Akhrem, F. A. Lakhvich, V. A. Khripach and I. B. Klebanovich

Institute of Bioorganic Chemistry Byelorussian SSR Academy of Sciences, Minsk, USSR

(Received in UK 7 June 1976; accepted for publication 16 September 1976)

Nitrile oxides are versatile tools of modern theoretical and preparative organic chemistry[1]. We now report application of the reaction of 3-glutarimidylacetonitrile oxide 3 with the cyclohexenone 4 to a new synthesis of the polycarbonyl derivatives 7-10. Compounds of this type are analogs of glutarimide antibiotics and key intermediates in the synthesis of the latter[2].

The synthesis of the nitrile oxide 3 has been achieved by the following way[3]. The oxime 1 (mp 156-158°), prepared by the usual method from 3-glutarimidylacetaldehyde[4], was chlorinated in ethanol at -50° to give the hydroxamic acid chloride 2 (100%, mp 145° dec.). The nitrile oxide 3 obtained by the treatment of 2 with a base proved to be sufficiently stable. The time of its complete dimerization in chloroform solution at 20° was about 100 hours (disappearance of the C≡N absorption at 2310 cm^{-1} in the ir spectrum).



Reaction of the nitrile oxide 3 with the enone 4 proceeded upon treatment of the mixture of 2 and 4 in chloroform with a dilute solution of triethylamine. The reaction of the nitrile oxide in situ and the use of a considerable excess of dipolarophile avoided self-condensation processes significantly reducing the yield of the desired products. Separation of the reaction mixture on a silica gel column gave the expected isoxazoline 5 (mp 184-186°) along with a considerable amount of its dehydro-derivative 6 (mp 198-201°). The total yield of 5 and 6 was 70% based on 2. Rapid chromatography under high pressure allowed isolation of the isoxazoline 5 as a single product of the cycloaddition. Obviously, the formation of the isoxazole 6 is a result of the adsorbent dehydrogenation of the isoxazoline 5 in the course of its isolation. The isoxazole 6 was also prepared in 94% yield by heated under reflux a solution of 5 with chloranil in t-BuOH. The structure of the adduct as 5 rather than the isomeric 5-acylisoxazoline follows both from the values of chemical shifts and from the spin-spin coupling of the C-4 and C-5 protons in the pmr spectrum: δ ($CDCl_3$) 3,68 (d, J=11 Hz) and 5,03 (m) ppm, respectively. Finally, the structure of the isoxazoline 5 was confirmed by its conversion into the isoxazole 6 and by the hydrogenation of the latter over 5% Pd-$BaSO_4$. The resulting enaminodiketone 7 was isolated in quantitative yield and then hydrolysed into the β-triketone 8. Compounds 7 and 8 were identical with the samples obtained by an independent method[2a].

It should be noted, that the hydrogenation of the isoxazoline 5 using 30% Pd-$SrCO_3$ as catalyst proceeded with formation of the enaminoketone 9 (100%, mp 222-225°), which can be further hydrolysed into the diketone 10. The latter is the gem-dimethyl isomer of dehydrocycloheximide obtained by Johnson et al. and used as a key compound in the total synthesis of cycloheximide[2b].

Application of the transformations discussed to the adducts of the nitrile oxide 3 with the conveniently substituted cyclohexenones will provide a synthetic route to the streptovitacins and other glutarimide antibiotics[5].

References and Notes

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