Identification of the Intermediate in the Reaction of Primary Nitroalkanes with Acetic anhydride in the Presence of Sodium acetate

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(Received 25th November, 1982)

Summary: The reaction of primary nitroalkanes with acetic anhydride and sodium acetate has been studied in the presence of dipolarophiles and the formation of nitrile oxide as a reaction intermediate has been proved by its cycloaddition reaction with the dipolarophiles to give isoxazolines.

Oxidation of primary nitroalkanes to carboxylic acids has been known for more than hundred years. This type of reaction was first discovered by Meyer and Wurster in 1873 [1]. Since then various interpretations of the nature of the reaction and the intermediate involved, have been advanced but none of these appeared to be satisfactory. Aldol-type condensation of primary nitroalkanes with aldehydes and ketones is seldom a straight-forward process and a variety of different types of products can be obtained depending [2] upon the reaction conditions employed. Primary nitroalkanes are inert to acetic anhydride alone but in the presence of basis such as triethylamine [3] and sodium acetate [4], oxidation to carboxylic acids has been observed. Even in this case the detailed mechanism and the nature of the intermediate involved in the overall oxidation to carboxylic acid, has been poorly understood.

It has been shown [5] that treatment of primary nitroalkanes with isocyanates in the presence of a catalytic amount of triethylamine in ether, gives furoxan through the intermediate formation of nitrile oxide which dimerises to the product. The presence of nitrile oxide as an intermediate was confirmed by the formation of isoxazoles when the reaction was carried out in the presence of acetylenes. Nitrile oxide was also reported [3] as an intermediate when isocyanate was replaced by acetic anhydride in the above reaction, which was established by its conversion to an isoxazoline when an active dipolarophile was also present in the reaction mixture. However, in the absence of the dipolarophile, a carboxylic acid was reported to be formed instead of a furoxan, due to the presence of acetic anhydride as a medium of reaction. Formation of carboxylic acid as one of the products, was also reported by Norris and Stermitz [6] and Urbanski [7] when they treated primary nitroalkanes with acetic anhydride in the presence of basic compounds.

McKillop and Kobylecki [4] have investigated the reaction of primary nitroalkanes with acetic anhydride in the presence of Sodium acetate in some detail. The major product in this case also was a carboxylic acid alongwith small amounts of acetanilide under standard hydrolytic work-up procedure whereas under strictly anhydrous conditions using non-aqueous work-up procedure, the products were benzoic anhydride and triacetylated hydroxylamine. They explained the formation of these products by suggesting a mechanism involving acetate of nitrile oxide, R-CH=

$N\text{-}OCOCH_3$ as an intermediate which isomerises to an unstable intermediate, oxazirane. Oxaziranes are known to undergo a rapid acid catalysed isomerism [8]. It therefore, rapidly decomposes to hydroxamic acid derivatives from which the various reaction products are formed.

The argument given against the involvement of nitrile oxide as an intermediate was the formation of carboxylic acid instead of the expected furoxan [5], and the inability of the intermediate to undergo cycloaddition reaction with dipolarophile to form isoxazoline. In fact, the experimental conditions in this case were different from that of the earlier work in which the furoxan was formed by the dimerization of the intermediate, nitrile oxide. It has been shown[9] that a nitrile oxide dimerizes to give furoxan only in the absence of an active dipolarophile with which it undergoes a cycloaddition reaction to form an isoxazoline or isoxazole, and in the absence of a polar solvent by which it is hydrolysed to a carboxylic acid [10]. The formation of furoxan in the reaction of primary nitroalkane with acetic anhydride in the presence of sodium acetate, therefore, is not expected even if nitrile oxide is formed as an intermediate. Also, the dipolarophiles used in this case were relatively less reactive for a cycloaddition reaction with 1,3-dipolar species[11]. It is, therefore, not surprising if these dipolarophiles did not react with nitrile oxide which also is a moderately stable compound. However, when an active dipolarophile like dimethylacetylenedicarboxylate, was used, cycloaddition reaction did occur and the corresponding isoxazole was isolated in a fairly good yield (82%). The possibility of nitrile oxide as an intermediate in the reaction of primary nitroalkanes with acetic anhydride in the presence of sodium acetate, therefore, cannot be ruled out.

In the present investigations, it has been shown that the reaction of primary nitroalkanes with acetic anahydride in the presence of sodium acetate, is similar in mechanism to the reaction of primary nitroalkanes with acetic anhydride in the presence of triethylamine [3], and involes nitrile oxide as an intermediate the presence of which has been substanciated by carrying out the reaction in the presence of active dipolarophiles such as diethyl maleate, dimethyl fumarate and vinyl acetate. The formation of isoxazolines [12] as a result of the cycloaddition reaction indicates the presence of nitrile oxide in the reaction sequence. Although, addition of a dipolarophile to a nitrile oxide is expected to be stereospecific [13], a trans-isoxazoline was obtained in each case. In fact, a cis-isoxazoline formed in the cycloaddition reaction isomerizes easily to its trans-isomer under basic as well as polar conditions [14]. It is, therefore, suggested that the reaction of primary nitroalkanes with acetic anhydride in the presence of sodium acetate follows a mechanism (shown in the scheme) which involves nitrile oxide as an intermediate which then functions both as the 1,3-dipolar species in the cycloaddition reaction and as the precursor to the various products formed in the oxidation reaction.

In the presence of excess amount of acetic anhydride, di- and tri-acetylated derivatives of hydroxylamine are formed as reported by earlier workers [4,6,7].

Experimental

Nitroethane and anhydrous sodium acetate were used as supplied. Phenylnitromethane was prepared by standard literature procedure [15]. Acetic anhydride was purified by distillation from phosphorus pentaoxide.

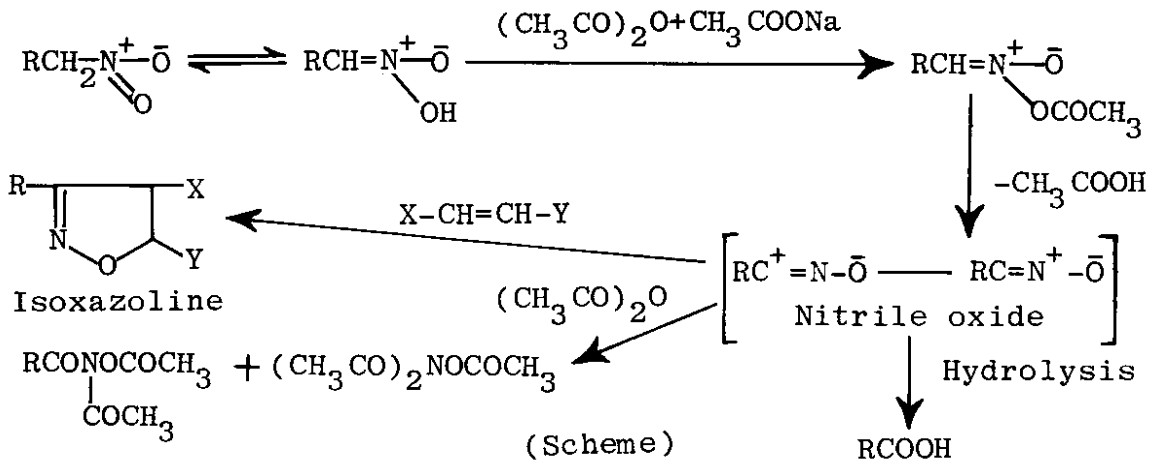
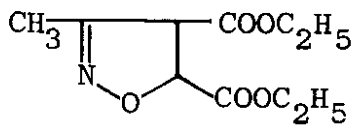
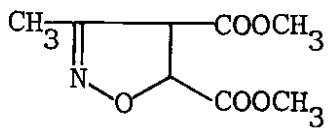
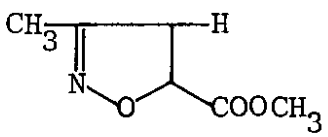
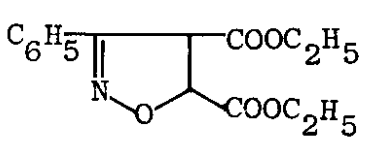


Table 1. Reaction of nitroalkanes with acetic anhydride and sodium acetate in the presence of dipolarophiles to from isoxazolines.

Nitroalkane	Dipolarophile	Isoxazoline	Yield (%)	B.pt./mm (M.pt.°C)
Nitroethane	Diethyl maleate		25	145/4
Nitroethane	Diethyl fumarate		20	(90-1)
Nitroethane	vinyl acetate		48	(76-7)
Phenylnitro-methane	Dimethyl maleate		50	159/0.2

Melting points were determined by the capillary tube method. Infrared spectra were recorded on an I.R.'Spektromom 2000' Spectrophotomer using standard film and Nujol mull techniques.

Preparation of Isoxazolines:

A mixture of 0.1 mole of nitroalkane, 8.2 gm (0.1 mole) of anhydrous sodium acetate, 0.12 mole of dipolarophile and 40 ml of acetic anhydride, was placed in a 250 ml round bottommed flask fitted with a reflux condenser, and heated to 70-80°C for 4-5 hours. The mixture was then allowed to cool and excess acetic anhydride was removed by distillation under reduced pressure. The residue was diluted with 200 ml of chloroform and the resulting precipitate of sodium acetate was removed by vacuum filtration through keiselguhr. The filtrate was shaken with 100 ml of 10% solution of sodium hydroxide. The organic layer was separated, washed twice with 50 ml portions of water, dried over anhydrous sodium sulphate and the solvent removed by evaporation under reduced pressure. The residual viscous mass of the isoxazoline solidified on cooling and was recrystallised from 95% ethanol. Where the residual viscous mass did not solidify, it was distilled under reduced pressure.

The identification of isoxazolines was made by comparison of their physical data with those of the authentic samples of these compounds prepared by standard methods. The yields and the m.pts/b.pts. of different isoxazolines are given in the Table 1.

The I.R. spectra of all the isoxazolines showed a broad carbonyl band at 1720-1740 cm^{-1} and C=N stretching bands at 1605-1610 cm^{-1}.

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