Ketene. Part 25.[1] Mechanistic Studies of the Reaction of Nitrile Oxides with Ketenes

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The reaction of ^{17}O-labelled 2,4,6-trimethylbenzonitrile *N*-oxide (**4**) with dimethylketene gives the dihydro-oxazolone adduct (**5b**), with isotopic labelling predominantly, but not exclusively, in the carbonyl group. Thermal scrambling of the label is observed, presumably *via* the zwitterion (**6**). The dioxazole (**8**) is proposed as an intermediate in the conversion of (**4**) into (**5b**). Alkaline hydrolysis of (**5b**) gives (**10b**) by predominant hydroxide attack on the carbonyl group. Attempts to generate the α-lactone (**11**) (by thermal decomposition of alkali α-halogenoisobutyrates) and add it to benzonitrile and fluorenone anil were unsuccessful. No traces of compounds (**5**; Ar = Ph, R = Me) or (**2**; R^1 = Ph, R = Me) could be detected, suggesting that α-lactones are not intermediates in the formation of adducts of dimethylketene with nitrile oxides and nitrones.

The reactions of ketenes with nitrones lead to a wide range of products. Where the reaction involves *C*,*C*-biphenylene nitrones (**1**) and related compounds, oxazolidinones (**2**) are commonly formed[2,3] along with other compounds. Several, wholly conjectural mechanisms have been proposed for this transformation[2,4] but no experimental evidence had so far been published which helps to explain the formation of the adducts (**2**). One aspect of this problem which any mechanistic rationalisation must accommodate is the provenance of the oxygen atoms in (**2**), and isotopic labelling of the oxygen atoms of the ketene or nitrone is an obvious means of investigation. However, although most of the published examples of this type of reaction involve nitrones of the general structure (**1**), these are unsuitable for oxygen labelling studies since there is good evidence for the adducts (**2**) undergoing easy, reversible conversion into the zwitterion (**3**), which is believed to be the intermediate in reactions of (**2**) with nucleophiles such as hydroxylamine, or during decarboxylation to form ylides.[3] Such a process would scramble specific labelling in the adducts (**2**). We have recently shown that the nitrile oxide (**4**) reacts with several ketenes to give the dihydro-oxazolines (**5**) analogous to (**2**),[5] and during this work no sign of the reversible formation of the zwitterion (**6**) was noticed, although no attempt was made to check this point specifically. Compound (**5a**) was apparently thermally stable, unlike (**2a**). For this reason the oxygen-labelling study was performed using the nitrile oxide–ketene reaction.

^{18}O-Labelled nitrile oxide (**4**) has already been synthesized,[6] and for this work the n.m.r. detectable ^{17}O-labelled material was prepared by an identical procedure. Treatment of ^{17}O-labelled (**4**) with dimethylketene in diethyl ether gave (**5b**) and (**7**), which were isolated by column chromatography.[5] Throughout the whole of this work care was taken to avoid heating the reaction mixture or products above 25 °C to minimize the risk of scrambling *via* the reversible formation of (**6b**). The ^{17}O n.m.r. spectrum of the adduct (**5b**) so obtained showed two signals at δ 343 and 260, corresponding to the carbonyl and ring oxygen atoms respectively,[7] the carbonyl signal being much stronger. Because these signals were characteristically broad and superimposed on a very broad background absorption arising from the glass of the container no reliable electronic integration could be obtained. Comparison of the areas under the peaks by cutting these out of 20 copies and weighing the paper gave a ratio of *ca.* 8:1. If it is assumed that the relaxation times of the oxygen atoms are approximately equal, this shows that the nitrile oxide oxygen atom is converted predominantly into the carbonyl oxygen of (**5**). The presence of a small proportion of ring-labelled adduct could arise either by partial scrambling of exclusively carbonyl-labelled adduct or by

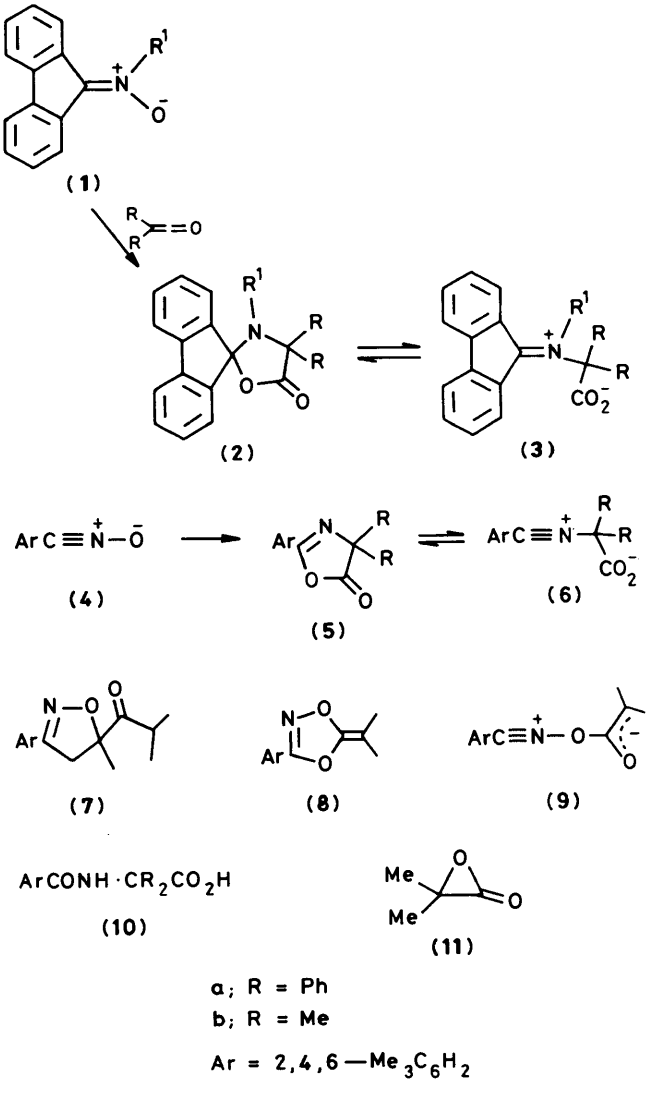

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Table. ^{17}O N.m.r. chemical shifts

	δ (w.r.t. H_2O)
$H_3N^+OH\ Cl^-$ (D_2O)	65
H_2NOH (D_2O/O^-H)	45
2,4,6-$Me_3C_6H_2CH{=}NOH$ (*E*/*Z* mixture, $CDCl_3$)	176
2,4,6-$Me_3C_6H_2C{\equiv}N^+{-}O^-$ ($CDCl_3$)	127
(**5b**) ($CDCl_3$)	343 (C=O), 260 (C–O–C)
(**7**) Ring oxygen only ($CDCl_3$)	245
(**10b**) [$(Me)_2CO$]	357 (CONH), 252 (CO_2H)

an alternative, parallel mechanism involving loss of oxygen-atom integrity. To test the possibility of scrambling *via* zwitterion (**6b**), the labelled reaction product was heated in acetonitrile at 100 °C for 18 h. The recovered adduct showed two, equally strong ^{17}O n.m.r. signals. We therefore believe that (**5b**) is formed from (**4**) with complete retention of oxygen-atom integrity followed by limited scrambling during subsequent manipulation.

We suggest that the formation of (**5b**) proceeds *via* the intermediate dioxazole (**8**). Several examples of cycloaddition of 1,3-dipoles across the carbonyl group of ketenes have been reported[8] and, in one case,[9] the preservation of stereochemistry suggests that the addition is a concerted process. Similar cycloadditions to the thiocarbonyl group of thioketenes are known.[10] Although the formation of (**8**) from (**4**) might be a concerted reaction, this seems unlikely to be the case since the zwitterion (**9**) is implicated in the pathway leading to (**7**).[5] The subsequent rearrangement of (**8**) to (**5b**) by a 1,3-migration has several parallels in the literature involving the cleavage of N–O bonds,[11] though whether these processes are concerted or stepwise is unclear.

The adducts (**5**) undergo alkaline hydrolysis to form the amido acids (**10**). In principle, three mechanisms are possible for this process with the hydroxide ion attacking either at the carbonyl carbon atom or at the hindered imino carbon atom of (**5**), or alternatively the hydroxide ion might intercept the zwitterion (**6**). Alkaline hydrolysis of the scrambled ^{17}O-labelled adduct gave (**10b**) in which both amide and carboxylic acid groups appeared to be equally labelled with the ^{17}O- n.m.r. spectrum having two very broad signals of approximately equal intensity. Hydroxide ion attack on the carbonyl group appears to be the most important, if not the exclusive, mode of hydrolysis.

Before the results of the ^{17}O-labelling experiments were available, another mechanistic proposal had been investigated. In the early study of the conversion of (**1**) into (**2**)[2] the possibility of deoxygenation of (**1**) by the ketene to give an imine and an α-lactone followed by recombination to form (**2**) had been rejected, although it was known then that deoxygenation of *N*-oxides by ketenes could give α-lactones.[12] Subsequently several cases of α-lactone formation by oxygen atom transfer to ketenes have been reported.[13] The deoxygenation–recombination mechanism was later proposed in a review[4] and an increasing number of reports of cycloadditions of three-membered ring compounds to π-bonds,[14] some of which are undoubtedly concerted processes, led to a reconsideration of the α-lactone pathway for the formation of (**2**) and (**5**).

Attempts to investigate the possibility of α-lactone (**11**) addition to the nitrile were made by thermal decomposition of alkali (Li^+, Na^+, and K^+) 2-chloro- and 2-bromo-isobutyrates in the presence of benzonitrile. Support for the formation of (**11**) by this route came from observing the thermal decomposition of potassium 2-chloroisobutyrate on the probe of a mass spectrometer, when a volatile material with a parent ion of *m/z* 86.0366$^+$ ($C_4H_6O_2$) was produced. However, although heating the halogenoisobutyrate salts in the presence of benzonitrile with or without glyme as a solvent led to the formation of alkali halides, no trace of the dihydro-oxazolone (**5**; Ar = Ph, R = Me) could be detected. Benzonitrile when heated with the free 2-halogenoisobutyric acids did form this product, presumably *via* a nitrilium zwitterion like (**6**). Likewise, no trace of the oxazolidinone (**2**; R^1 = Ph, R = Me) could be detected when the alkali 2-halogenisobutyrates were decomposed by heating in a glyme solution of fluorenone anil. We conclude that the addition of α-lactones to nitriles or imines is very unlikely as a pathway for the formation of cyclic adducts from the reactions of ketenes with nitrones and nitrile oxides.

Experimental

^{17}O N.m.r. spectra were measured with a Bruker AM250 spectrometer, and mass spectra with Kratos MS25 and MS80 spectrometers.

^{17}O-Labelled hydroxylamine (4% enriched) was prepared from $H_2{}^{17}O$ (15.6% enriched) and converted into mesitonitrile *N*-oxide (**4**) as previously described for the ^{18}O-labelled compound.[6]

^{17}O N.m.r. chemical shifts of all labelled compounds prepared are listed in the Table. Ether refers to diethyl ether and glyme to 1,2-dimethoxyethane.

Reaction of [^{17}O]-2,4,6-*Trimethylbenzonitrile* N-*Oxide* (**4**) *with Dimethylketene*[5].—An excess of dimethylketene (from pyrolysis of the dimer[15]) was passed into a solution of the isotopically labelled nitrile oxide (0.5 g) in dry ether (20 ml) at 0 °C. After 12 h the solvent was evaporated and the residue separated by column chromatography (silica gel and ether–light petroleum) into compounds (**5b**) (0.2 g) and (**7**) (0.3 g). Throughout this procedure, the temperature of the reaction mixture and products was maintained below 25 °C.

Hydrolysis of the ^{17}O-*Labelled Adduct* (**5b**)[5].—This was achieved by stirring a solution of the adduct and an excess of sodium hydroxide in aqueous ethanol for 3 d. Evaporation of the ethanol and acidification of the residue with hydrochloric acid precipitated the amido acid (**10b**).

Preparation of Alkali α-*Halogenoisobutyrates.*—(**A**). Solutions of sodium or potassium hydroxide in dry methanol or ethanol were neutralised by addition of the calculated amounts of 2-chloroisobutyric or 2-bromoisobutyric acids dissolved in dry ether. Addition of large volumes of dry ether precipitated the salts as crystalline solids which decomposed to gummy solids after storage at room temperature for a few days. The i.r. spectra of these compounds showed broad absorption at 3 300—3 500 cm^{-1}, attributable to hydration.

(**B**). An excess of 2-halogenoisobutyric acid in dry ether was added slowly to a stirred, ice-cooled suspension of sodium hydride powder in dry ether. After gas evolution had ceased the amorphous solid was collected, washed with dry ether, and used in subsequent experiments immediately.

Attempted Addition of the α-*Lactone* (**11**) *to Benzonitrile and Fluorenone Anil.*—A suspension of alkali 2-halogenoisobutyrate in glyme containing either benzonitrile or fluorenone anil was stirred and heated to boiling and maintained at b.p. for 0.5 h. T.l.c. analysis of the reaction mixture showed no signs of either compound (**5**; Ar = Ph, R = Me) or (**2**; R^1 = Ph, R = Me). Addition of a saturated solution of sodium 2-chloroisobutyrate in glyme either to a boiling solution of benzonitrile in glyme or to boiling benzonitrile alone likewise gave no adduct. In the former experiment sodium chloride was precipitated from the hot reaction mixture almost immediately.

The addition of solid sodium 2-chloro- or 2-bromo-isobutyrates to boiling benzonitrile gave no detectable formation of compound (**5**; Ar = Ph, R = Me).

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