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α,β-UNSATURATED OXIMES

ISOXAZOLINE FORMATION BY THERMAL CYCLISATION OF COMPOUNDS RELATED TO BENZALACETOPHENONE OXIME AND ISOXAZOLINE THERMAL CYCLOREVERSION REACTIONS

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Abstract—At about 300° the title compounds yield fragments attributed to cyclisation to isoxazolines and subsequent cycloreversion. Isoxazolines are formed at about 200° and can usually be isolated. At 300° they yield the same products as the oximes.

Thus benzalacetophenone oxime gives 3,5-diphenylisoxazoline which then largely undergoes two distinct cycloreversions: (a) 1,3-*cleavage* (numbers refer to isoxazoline bonds) yielding benzonitrile and acetophenone and (b) *reductive* 1,4-*cleavage* yielding benzaldehyde and 1-phenylethylimine hydrolysis products. By-products are 2,4,6-triphenylpyridine, water and ammonium benzoate. With α-methylchalcone oxime reductive 1,4-cleavage is suppressed and with β-methylchalcone oxime both modes of cleavage are suppressed and 5-methyl-3,5-diphenylisoxazole is the stable product. An analogue of α-methylchalcone oxime, 2-methyl-1-phenyl-3-(2-thienyl)prop-2-ene-1-one oxime gives fragments attributed to both cleavage modes of an unisolatable and hitherto unknown isoxazoline.

Possible mechanisms for the cyclisation and cycloreversions are discussed and the reductive 1,4-cleavage is believed to be a cycloreversion of a vinyl-nitrene.

It is well-known that oximes of chalcones (derivatives of **1a**) decompose at or above their m.ps but the compositions of the resulting products have not been reported except for one partially investigated example. Blatt and Stone[1] found that α-bromochalcone oxime, **1b**, evolved hydrogen bromide and ammonia on heating but the nature of the other possible products was not discussed. Our studies were concerned with the thermal transformations of a number of chalcone oximes and related compounds in which we chose not to have halogen atoms present in the α or β positions since we considered that the expected elimination of hydrogen halides which would otherwise occur, constituted a complicating process and gave rise to undesired catalysts.

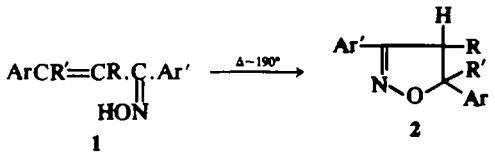
When benzalacetophenone oxime, **1a** (syn isomer[2]), was heated at 280° until no further changes were observed, there was obtained a distillate containing benzonitrile (36%), acetophenone (30%), benzaldehyde (4%), ammonium benzoate (6%) and some water and ammonia (the figures in brackets are yields calculated on a mole for mole basis). The residue contained 2,4,6-triphenylpyridine, **4** (7%). The formation of almost equimolar quantities of benzonitrile and acetophenone is accounted for by the prior cyclisation of the oxime to 3,5-diphenylisoxazoline, **2a**, followed by the rupture of this ring system (see Scheme I, eqns 1 and 2). We refer to the latter process as 1,3-cleavage of the isoxazoline ring where the numbers indicate the bonds broken. Conclusive evidence for the formation of the cyclic intermediate was obtained from two further experiments. When the oxime was heated at 190° for 10 min there was obtained a nearly quantitative yield of the isoxazoline and a pure specimen of this heated to 280° gave a mixture very similar to that obtained from the directly heated oxime.

Benzaldehyde results from a competing mode of rupture of the isoxazoline ring and not from α,β-cleavage of the oxime since it was obtained in almost the same yield from the similarly heated isoxazoline. The fragment accompanying benzaldehyde is expected to be the imino derivative of acetophenone but in the presence of water from a side reaction it was isolated as acetophenone and ammonia (Scheme 1, Eqn 3). Reduction must occur during this reaction and it is referred to as reductive 1,4-cleavage of isoxazolines. This is written as a hydride ion transfer process in Eqn (3) but the source of the ion, free or incipient, has not been identified.

The two cleavage modes are clearly distinguished when all four possible fragments are different as is the case when the aryl groups possess substituents (Table 1).

The mechanism of unsaturated oxime cyclisation may be (a) a two step process involving a zwitterion, $PhC^{+}H.CH_2.C(Ph)=NO^{-}$, or a diradicaloid species or (b) a pericyclic reaction as shown in **3**†. In case (a) a proton or H atom is required to bond with C2 in the aliphatic chain. The sulphuric acid-catalysed cyclisation of a similar oxime has been reported[1] but the present conditions are much less conducive to ionisation. Analogous acetylenic oximes isolated from the reaction products of benzonitrile oxide and acetylenes, were found to cyclise very easily by heating or by standing, especially in neutral or alkaline solutions, but were more stable in acidic media.[3] In case (b) the molecule is required to coil rather tightly but the two new σ bonds are unlikely to be generated at the same rate and this may ease the steric requirements. Further mechanistic studies are required before a decision can be made between these possibilities.

By analogy with the behaviour of other 5-ring heterocyclic systems such as those cited by Gilchrist and Storr[4] it is believed that the mechanisms for both modes of cleavage are examples of retro-1,3-dipolar cycloadditions. However, in the case of the 1,3-cleavage of isoxazolines the incipient dipolar ion, $CH_2^{+}–CH(Ph)–O^{-}$, does not possess the 4π electrons on the C–C–O system which is usual with other 1,3-dipolar ions and it cannot be

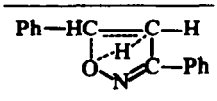


(1)

1

2

1a,2a: Ar = Ar′ = Ph, R = R′ = H
1b: Ar = Ar′ = Ph, R = Br, R′ = H
1c,2c: Ar = Ar′ = Ph, R = H, R′ = CH_3
1d,2d: Ar = Ar′ = Ph, R = CH_3, R′ = H
1e,2e: Ar = *p*-$MeOC_6H_4$–, Ar′ = Ph, R = R′ = H
1f,2f: Ar = Ph, Ar′ = *p*-$MeOC_6H_4$–, R = R′ = H
1g,2g: Ar = 2-thienyl, Ar′ = Ph, R = CH_3, R′ = H



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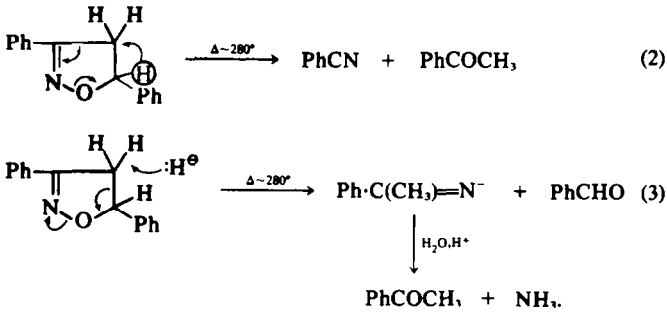
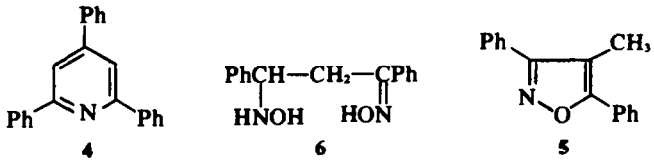


Scheme 1. The action of heat on α, β-unsaturated oximes and isoxazolines



4 **6** **5**

transposed into its alternative canonical form, CH_2^-–CH(Ph)–O^+, by the movement of electrons in the usual way. In the case of the reductive 1,4-cleavage of isoxazolines the incipient dipolar ion is a vinyl-nitrene,

$$N^-{=}C(Ph){-}CH_2^+ \leftrightarrow :N{-}C(Ph){=}CH_2 \leftrightarrow N^+{=}C(Ph){-}CH_2^-.$$

It is noteworthy that the third possible mode of cleavage, namely the retro-Grünanger addition of benzonitrile oxide to olefins was not detected in the present experiments.

The formation of 2,4,6-triphenylpyridine is attributed to the condensation of two molecules of acetophenone with one of benzonitrile and the elimination of water in a manner similar to a previously reported reaction.[5]

The results of heating 4- and 4′-methoxychalcone oximes, **1e** and **1f** respectively, are summarised in Table 1. They provide clearcut examples of both cleavage modes occurring together. Isoxazolines, isolated in good yields from the 200° reaction products, were identified by chromic acid oxidations to isoxazoles which were identical to those whose structures were determined previously by Johnston and Shotter.[6]

The main product from heating β-methylchalcone oxime, **1c**, to 290° for 1 hr was 5-methyl-3,5-diphenylisoxazoline, **2c** (69%). Evidently this isoxazoline is resistant to both types of thermal rupture. Because the requisite hydride ion shift is not possible, 1,3-cleavage is almost entirely prevented and only a trace of benzonitrile was formed. Reductive 1,4-cleavage is possible and this should give rise to two molecules of acetophenone after hydrolysis of the imine. The yield of acetophenone was 8% so that the extent to which this reaction occurred was only 4%.

The isomeric α-methylchalcone oxime, **1d**, steadily decomposed at 310° during 0·5 hr and gave a distillate containing only benzonitrile (50%) and propiophenone (56%) both of which are expected to be formed by 1,3-cleavage of the unisolated 4-methyl-3,5-diphenylisoxazoline, **2d**. The residue contained the aromatisation product, 4-methyl-3,5-diphenylisoxazole, **5** (22%). Reductive 1,4-cleavage was not observed as shown by the absence of benzaldehyde.

The action of heat on a heterocyclic analogue of α-methylchalcone was also studied. 2-Methyl-1-phenyl-3-(2-thienyl)prop-2-en-1-one oxime, **1g**, began to decompose at 230° with the evolution of a little hydrogen sulphide but the reaction was not completed until the temperature was held at 310° for 25 min. Benzonitrile (25%) and 2-propionylthiophene (17%) were found in the distillate and these are expected to be formed by 1,3-cleavage of the

Table 1. Thermal reactions of α,β-unsaturated oximes and 3,5-diphenylisoxazoline.

Compound	Bath temp.	Time (min.)	Products	
			Volatile	Residual
1a	280	45	PhCN 36%; PhCOMe 30%; PhCHO 4%; $PhCO_2NH_4$ 6%; NH_3; H_2O	4 7%[a]
1a	190	10	None	2a ~ 100%
2a	290	45	PhCN 28%; PhCOMe 27%; PhCHO 6%; NH_3; H_2O	4 23%[a]
1c	290	60	PhCN 1%; PhCOMe 8%; NH_3	2c 65%
1d	330	30	PhCN 50%; PhCOEt 56%	5 22%
1e	200	15	None	2e 75%
1e	310	50	PhCN 15%; *p*-methoxyacetophenone 10%; PhCOMe 23%; anisaldehyde 4%; trace of ammonium anisate; NH_3; H_2O	Tar.
1f	200	15	None	2f 85%
1f	320	50	Anisonitrile 27%[b]; PhCOMe 37% PhCHO 6%; *p*-methoxyacetophenone 10%; trace of $PhCO_2NH_4$; NH_3; H_2O	Tar.
1g	220	10	Trace of H_2S	1g ~ 100%
1g	310	25	PhCN 25%; 2-propionylthiophene 17%; PhCOEt 7%; 2-thienylcarboxaldehyde 10%; $PhCO_2NH_4$ 4%; NH_3; H_2S	Tar.
6	310	15	$PhCO_2NH_4$ 26%; NH_3; H_2O; PhCOMe and 4 unknown compounds (sepd. by GLC)	4 12%[a]
Benzalacetone oxime	240	20	PhCOMe; MeCN[c]	
Cinnamaldehyde oxime	240	20	Cinnamonitrile[c]	—

[a] Calculated on a mole for mole basis.

[b] Anisaldehyde was proved absent under conditions where anisonitrile and anisaldehyde were shown to be separated by GLC.

[c] The amounts of these compounds were not measured.

unisolated and unknown 4-methyl-3-phenyl-5-(2-thienyl)isoxazoline, **2g**. In contrast to α-methylchalcone oxime, competition from reductive 1,4-cleavage was pronounced and both expected fragments, 2-thienylcarboxaldehyde (10%) and propiophenone (7%), were isolated together with some ammonia and ammonium benzoate (4%). An attempt was made to isolate the intermediate isoxazoline, **2g**, by conducting the experiment at a lower temperature. At 220° the oxime was molten but otherwise unchanged whereas at 230° fragmentation commenced and, for this reason, it is believed that the isoxazoline, although formed, has only a transient existence at this temperature.

Lastly 3-(N-hydroxylamino)-1,3-diphenylpropan-1-one oxime, **6**, was studied. At 310° it gave a distillate containing water, ammonia, ammonium benzoate (26%) and an undetermined quantity of acetophenone together with small amounts of several unidentified compounds separated by means of GLC. A residue contained 2,4,6-triphenylpyridine (12%). It was therefore very similar in its behaviour to benzalacetophenone oxime from which it is formally made by the Michael addition of hydroxylamine.

Thermal cyclisation of α,β-unsaturated ketoximes provides a valuable method for the unambiguous synthesis of isoxazolines which in turn can be readily oxidised to isoxazoles. Fragments obtained by the thermolysis of isoxazolines yield further structural information. The main uses of the reactions described, however, is likely to be in the study of cycloadditions and cycloreversions.

EXPERIMENTAL

The following techniques were employed. Chromatography was done on alumina (Brockman activity No. 1) with 5% added water. GLC was conducted on a Perkin-Elmer F11 apparatus and compositions were determined by comparison of peak areas with those recorded for similarly composed standard mixtures. Elemental analyses were determined by Dr. Strauss of Oxford. The mass spectrum was measured by Mr. Clark of the School of Pharmacy, London.

Starting and reference compounds

1. *Unsaturated ketones.* These were prepared by standard Claisen-Schmidt condensations except for β-methylchalcone which was a commercial sample. 2-Methyl-1-phenyl-3-(2-thienyl)prop-2-en-one was prepared as follows. Sodium (**1g**) was dissolved in EtOH (250 cm^3) and then thienyl-2-carboxaldehyde (30 g, 0·268 mole) was added. Propiophenone (36 g, 0·268 mole) was added immediately with vigorous stirring. After several days in a refrigerator the green soln deposited yellow crystals. A second crop was obtained by adding a little water to the mother liquor. The combined material was washed with water and recrystallised (MeOH) to give 50 g (82%) of the required compound of m.p. 59–60°. An analytical sample of the *ketone*, m.p. 59–60° formed pale yellow prisms (MeOH) and gave a golden orange soln in H_2SO_4. IR spectrum (melt): ν (C=O), 1638 cm^{-1}; ν (C=C), 1603 cm^{-1}. ^1H NMR spectrum (20% in $CDCl_3$): τ 7·7 doublet (3H)(Me); τ 2·2–3·1 overlapping multiplets (9H)(aromatic and olefinic protons): J (allylic), 1·2 Hz (Me probably *trans* to olefinic proton). (Found: C, 73·85; H, 5·50; S, 14·00. $C_{14}H_{12}OS$ requires: C, 73·65; H, 5·30; S, 14·05%).

2. *Oximes.* These were prepared by the standard barium carbonate method as described by Unterhalt[7] except for **1g**, which was prepared by the standard pyridine method from the corresponding ketone described in Section 1. It was obtained in a yield of 84% and was best recrystallised from acetone. An analytical sample of the *oxime* had m.p. 199–202° (darkens) and formed needle-like rhombs (acetone) which gave a greenish-yellow soln in H_2SO_4. IR spectrum (in KBr): ν (OH), 3250 cm^{-1} (broad). (Found: N, 5·90%. $C_{14}H_{13}NOS$ requires: N, 5·75%). Compound **6** was prepared by a modification of Auwers and

Müller's method.[8] To a soln of benzalacetophenone (104 g, 0·5 mole) in EtOH (500 cm³) was added hydroxylamine hydrochloride (104 g, 1·5 mole) and 40% NaOHaq (150 cm³, 1·5 mole). The mixture was heated under reflux on a water bath for 4 hr and then refrigerated overnight. The ppt was removed by filtration, washed with a little EtOH then with water and dried. It was recrystallised from benzene and had m.p. 153° (lit.[8] 147°)(85 g, 66%). An analytical sample had m.p. 153° and formed a fine, crystalline powder. (Found: C, 68·60; H, 6·20; N, 10·60. Calc. for $C_{15}H_{16}N_2O_2$: C, 68·85; H, 6·60; N, 11·45%).

3. *Isoxazolines.* Compound **2a** was obtained from the mother liquor from the preparation of **6**. The mother liquor was warmed to 60°, treated with water until just turbid and refrigerated overnight. The crystalline ppt was washed with EtOH/water (75/25) and then with water. After drying it was found to be pure, m.p. 75° (lit.[8] 75°) (28 g, 25%).

4. *Nitriles.* These were made by standard procedures. *p*-Methoxybenzonitrile had m.p. 61° (lit.[9] 60°) and 2-cyanothiophene had b.p. 192° (lit.[10] 192°). The latter was stored in the frozen state to prevent it darkening.

5. *2-Thienyl ethyl ketone* was prepared by a standard Friedel-Crafts method. Only the fraction b.p. 228° was used as a GLC standard.

6. *Isoxazoles.* 5-p-Anisyl-3-phenylisoxazole m.p. 126–7° and 3-*p*-anisyl-5-phenylisoxazole m.p. 120° were available from previous work.[6] 3,5-diphenyl-4-methylisoxazole was prepared by the method of Marshall[11] and had m.p. 127° (lit.[11] 127°).

7. *2,4,6-Triphenylpyridine* was prepared by the method of Dilthey and Kiefer[5] and had m.p. 138·5° (lit.[12] 138·5°).

The action of heat on oximes and 3,5-diphenylisoxazoline.

General directions. The compounds (4–5 g) were heated in a short path distillation apparatus on an oil bath. The temps recorded (Table 1) were those of the oil bath. For experiments conducted in the higher temp. range (280–330°) the precise temp. used was that at which slow distillation occurred (one drop per min). Heating was discontinued when distillation ceased.

A typical run is as follows. Compound **1a** (5 g, 0·0224 mole) was heated slowly. At 120° it melted and at 200° the condenser began to cloud up. At 280° steady distillation occurred and this temp. was held for 45 min. The distillate (1·9 g) smelled of benzonitrile and contained a small amount of aqueous ammonia. A sublimate of ammonium benzoate (free from benzamide) was removed from the inside of the condenser. The distillate was dissolved in benzene, dried ($MgSO_4$) and analysed by means of GLC (Table 1).

The residue in the distillation flask was worked up by means of chromatography on alumina and afforded 2,4,6-triphenylpyridine m.p. 140° (lit.[12] 138·5°)(7%) and mixed m.p. with an authentic specimen (m.p. 138·5°) was 138·5°. (Found: C, 89·50; H, 5·70; N, 5·15 and 5·20%; *m/e*, 307. Calc. for $C_{23}H_{17}N$: C, 89·85; H, 5·55; N, 4·55%; *m/e*, 307).

Identification of products. The identities of volatile products were established by means of GLC. Compounds isolated from the involatile residues were identified by the method of mixed m.ps except for the following: **2f**, m.p. 102–3° (lit.[7] 103–4°) was oxidised by chromic acid to 3-p-anisyl-5-phenylisoxazole, m.p. and mixed m.p. with an authentic specimen from previous work[6] 120°. **2e**, m.p. 101–2° (lit[7] 101–2°) gave by similar treatment 5-*p*-anisyl-3-phenylisoxazole m.p. and mixed m.p. with an authentic specimen from previous work[6] 126–7°. Auwers and Seyfried reported such oxidations but gave no experimental details.[13] Since the isoxazoles appear to be inseparable by fractional crystallisation from unchanged isoxazoline, pure products, albeit in reduced yields, were obtained as follows. The isoxazoline was dissolved in the minimum amount of AcOH to which a few drops of water had been added. To this was added 1·5 times the theoretical quantity of a 1 M soln of chromic oxide in acetic acid. During the initial reaction the temp. was not allowed to go above 80° and to complete the reaction the mixture was heated at 80° for 15 min. After pouring into water the ppt was recrystallised from benzene or EtOH. 5-Methyl-3,5-diphenylisoxazoline m.p. 75° (lit. 78–9°) was identified by its H^1 NMR spectrum (CCl_4): τ 8·3 singlet (3 H); τ 6·7 singlet (1 H); τ 7·9 singlet (1 H); τ 2·6 centre of overlapping multiplets (10 H); J(gem) ~ 0 Hz.

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