The Reaction of α-Nitro Ketones with the Ketene-Generating Compounds, Isopropenyl Acetate and α-Acetoxystyrene. Synthesis of 3-Acetyl- and 3-Benzoyl-5-Substituted Isoxazoles[1a]

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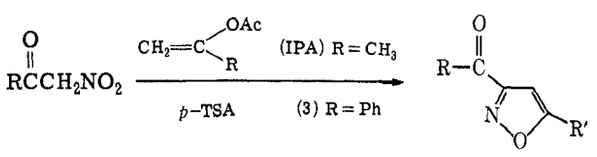
Reaction of α-nitroacetophenone (**1a**) with isopropenyl acetate (IPA) under acid-catalyzed conditions produced 3-benzoyl-5-methylisoxazole (**2a**) in 62% yield. A similar reaction with α-nitroacetone (**1b**) gave isoxazole **2b** although in much poorer yield (~5% by glc analysis). Reactions of **1a** and **1b** with α-acetoxystyrene (**3**) also produced the corresponding isoxazoles **4a** and **4b** in low but isolable yields (24 and 3%, respectively). A possible mechanism is suggested based on a study of the reaction of **1a** with IPA. Infrared, nmr, uv, and mass spectral data of the isoxazoles are reported.

As a possible facile entry into cyclopropyl analogs of the hormonal amines, epinephrine and norephrine, we envisaged a general route utilizing α-acetoxy-β-nitrostyrene as the key intermediate. Subsequent steps in the sequence were to involve formation of the cyclopropyl ring *via* condensation with dimethylsulfonium methylide[2] and reduction of the resultant nitrocyclopropane to the corresponding amine[3] followed by hydrolysis. In an attempt to prepare this intermediate by an acid-catalyzed enol acetate exchange reaction of α-nitroacetophenone (**1a**) with isopropenyl acetate (IPA), a solid product was obtained in reasonable yield which proved not to be the desired compound. This was demonstrated by the lack of asymmetric and symmetric ir stretching frequencies characteristic of a nitro group. The nmr spectrum showed the presence of five aromatic protons, a one-proton singlet at 6.42 ppm, and a three-proton singlet at 2.44 ppm. High-resolution mass measurement of the parent ion and combustion analysis showed that the compound had a molecular formula of $C_{11}H_9NO_2$. Analysis of the major peaks in the mass spectrum soon revealed that the compound was the isoxazole **2a**. Conclusive evidence for the proposed structure came from an independent synthesis of the isoxazole by the method of Ajello and Cusmano.[4]

Since the synthesis of isoxazoles by this method appeared to be novel, we decided to investigate whether the reaction was applicable to aliphatic nitro ketones. The reaction of α-nitroacetone (**1b**) and IPA did indeed produce the corresponding 3-acetyl-5-methylisoxazole (**2b**) (refer to Scheme I), although in very low yield and from consistently tarry reaction mixtures, an observation which will be discussed later in the text.

To further investigate the scope of the reaction the synthesis was extended by reacting the already prepared α-nitro ketones with an aromatic enol acetate, α-acetoxystyrene (**3**). As shown in Scheme I, the corresponding isoxazoles were isolated in both cases. Although the yields were poor, the isoxazoles formed were isomerically pure in contrast to the normal synthesis of

SCHEME I



1a, R = Ph
b, R = CH_3

2a, R = Ph; R′ = CH_3
b, R = CH_3; R′ = CH_3
4a, R = Ph; R′ = Ph
b, R = CH_3; R′ = Ph

3-keto 5-substituted isoxazoles using β diketones and nitric acid.[4a,b]

In recent years[5] 3-arylisoxazoles have been conveniently synthesized by a 1,3-dipolar cycloaddition of an aromatic nitrile oxide with some vinyl compound containing a leaving group. The reaction has been postulated[6] to proceed through a Δ^2-isoxazoline intermediate and recently Micetich[7] has in certain cases isolated such intermediates from the reactions between vinyl acetate or IPA and various nitrile oxides. The Δ^2-isoxazolines so obtained deacetylate to the corresponding isoxazoles upon heating or in the presence of acid.

Observation of a weak ir absorption[8] at 2260 cm^{-1} from a solution of 0.0003 mol of **1a** in 0.003 mol of IPA supports the postulated nitrile oxide intermediate. The intensity of this 2260-cm^{-1} peak increased when *p*-TSA was added to the solution, and an absorption at 1830 cm^{-1} also appeared suggesting the formation of acetic anhydride. This later observation was confirmed by isolation of acetic anhydride from the reaction mixture and is evidence for the formation of ketene under the reaction conditions.[9]

The formation of the nitrile oxide from the α-nitro ketone *via* Scheme II is consistent with these experimental data.

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(2) J. Asunskis and H. Shechter, *J. Org. Chem.*, **33**, 1164 (1968).

(3) S. Matin and N. Castagnoli, Department of Pharmaceutical Chemistry, University of California at San Francisco, private communication.

(4) (a) T. Ajello and S. Cusmano, *Gazz. Chim. Ital.*, **68**, 792 (1938); (b) S. Cusmano, *ibid.*, **78**, 622 (1948).

(5) (a) N. K. Kochetkov and S. D. Solokov in "Advances in Heterocyclic Chemistry," Vol. 2, Academic Press, New York, N. Y., 1963, p 375; (b) R. Scarpati, C. Santocroce, and D. Sica, *Gazz. Chim. Ital.*, **93**, 1706 (1963); (c) P. Rajagopalan and C. N. Talaty, *Tetrahedron Lett.*, **No. 38**, 4537 (1966).

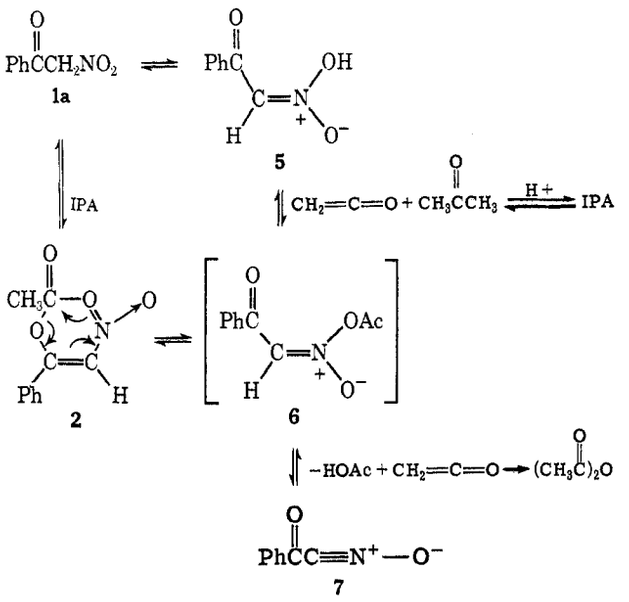
(6) P. Grunanger and S. Mangiapan, *Gazz. Chim. Ital.*, **88**, 149 (1958).

(7) (a) R. G. Micetich, *Can. J. Chem.*, **48**, 467 (1970); (b) *ibid.*, **48**, 3753 (1970).

(8) (a) S. Califano, R. Moccia, R. Scarpati, and G. Speroni, *J. Chem. Phys.*, **26**, 1777 (1957). (b) The C≡N stretching of the α-ketonitrile oxide would be expected to occur at a lower frequency than the reported absorption at 2300 cm^{-1}.

(9) The production of ketene without the addition of *p*-TSA can be justified since **1a** itself is a fairly strong acid with a $pK_a^{nitro} \sim 5$ and $pK_a^{aci} \sim 2$. See "The Chemistry of Functional Groups—The Chemistry of Nitro and Nitroso Groups," Part 1, H. Feuer, Ed., Interscience, New York, N. Y., 1969, pp 374–376.

SCHEME II



Work by other groups would seem to support the mechanism outlined. Nenitzescu and Isacescu[10a] and Urbanski and Gurzynska[10b] have synthesized stable nitronic acid anhydrides from nitro compounds and ketene similar to the nitronic acid anhydride intermediate **6**. Work by Noland and coworkers[11a] and by Simmons and Kreuz[11b] has shown that certain nitrile oxides similar to intermediate **7** are formed from nitro compounds in acid solution, while synthesis of benzoylnitrile oxide (**7**) by another route has recently been proposed by two independent research groups.[12a,b]

Two pathways are presented in Scheme II for the formation of an intermediate nitronic anhydride **6**. One involves prior formation of α-acetoxy-β-nitrostyrene (**2**) followed by an acyl exchange reaction from the enol oxygen to the nitro group oxygen *via* a six-membered ring transition state. The second pathway involves prior tautomerization to the acinitro compound **5**, which reacts with ketene continously being generated from IPA. The intermediate nitronic anhydride **6** could then eliminate acetic acid to form the nitrile oxide **7**. Although attempts were made to isolate and characterize the nitrile oxide, none were successful. Consequently, Scheme II can only be considered as a reasonable estimate of the reaction sequence.

Little change occurred in the reaction after 48 hr at room temperature; however, upon heating the solution for a few minutes the ir peak at 2260 cm^{-1} disappeared while two new singlets appeared in the nmr spectrum at 2.54 and 6.68 ppm. These singlets represent the methyl group hydrogens and the C-4 proton of the newly formed isoxazole **2a**, respectively. As expected, the two peaks integrated in a 3:1 ratio.

(10) (a) C. D. Nenitzescu and D. A. Isacescu, *Bull. Soc. Chim. Romania*, **14**, 53 (1932); (b) T. Urbanski and W. Gurzynska, *Rocz. Chem.*, **25**, 213 (1951).

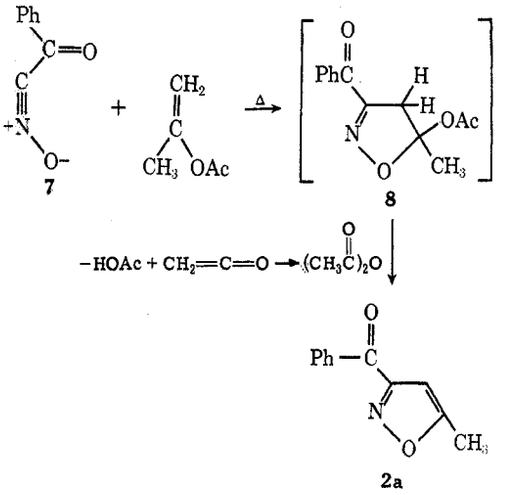
(11) (a) W. E. Noland, J. H. Colley, and P. A. McVeigh, *J. Amer. Chem. Soc.*, **81**, 1209 (1959); (b) T. Simmons and K. L. Kreuz, *J. Org. Chem.*, **33**, 836 (1968).

(12) (a) T. Sasaki, T. Yoshioka, and Y. Suzuki, *Bull. Chem. Soc. Jap.*, **44**, 185 (1971); (b) Y. Otsuji, Y. Tsujii, A. Yoshida, and E. Imoto, *ibid.*, **44**, 223 (1971).

The reaction mixture was then allowed to stand at room temperature for 24 hr. Once again the ir showed an intense absorption peak at 2260 cm^{-1}. The procedure of alternate heating and cooling was continued with the same results as noted before, that is, the loss of absorption in the ir at 2260 cm^{-1} upon heating, with a corresponding increase in formation of the isoxazole as noted by nmr.

Scheme III depicts the final steps of the reaction.

SCHEME III



The nitrile oxide **7** can undergo a 1,3-dipolar cycloaddition reaction with the enol acetate to form an intermediate Δ-2 isoxazoline **8** which can then eliminate acetic acid to form the product isoxazole **2a**.

However, no evidence could be found in the nmr spectrum for the Δ^2-isoxazoline intermediate **8**. Apparently, the slow step in the reaction sequence involves formation of the isoxazoline with a fast deacetylation to yield the isoxazole. The proposed sequence does help to explain why α-nitroacetone (**1b**) gives such poor yields, since it is well known that nonaromatic stabilized nitrile oxides spontaneously dimerize to furoxans,[13a] which may undergo further degradation or polymerization.[13b]

Experimental Section

General.—Melting points were taken by capillary using a Thomas-Hoover Uni-Melt instrument and are corrected. Boiling points are uncorrected. Infrared spectra were determined on a Perkin-Elmer 457 spectrophotometer, uv spectra with a Cary II spectrophotometer, and nmr in deuteriochloroform on a Varian A-60A with tetramethylsilane as an internal standard. Vpc analyses were performed on a Varian Model 90-P with thermal detectors or Varian Model 2100-A with flame-ionization detectors. Mass spectra were obtained on an AEI Model MS-902 mass spectrometer. Elemental analyses were performed by Berkeley Microanalytical Laboratories.

α-Nitroacetophenone (1a).—This compound was prepared by the method of Bachman and Hokama[14] in 70% yield, mp 105–106°.

(13) (a) C. Grundman and J. M. Dean, *J. Org. Chem.*, **30**, 2809 (1965); (b) A. Quilico and G. Speroni in "Heterocyclic Compounds—Five- and Six-Membered Compounds with Nitrogen and Oxygen," R. H. Wiley, Ed., Interscience, New York, N. Y., 1962, p 295 ff.

(14) G. B. Bachman and T. Hokama, *J. Amer. Chem. Soc.*, **81**, 4882 (1959).

α-Nitroacetone (1b).—This ketone was prepared by oxidation of 1-nitro-2-propanol[15a] by the method of Brown and Garg,[15b] mp 48–50° (lit.[15c] mp 49–50°).

3-Benzoyl-5-methylisoxazole (2a).—A solution of 14.0 g (0.085 mol) of **1a** and *p*-TSA (140 mg) in IPA (60 ml) was refluxed in an atmosphere of dry nitrogen for 24 hr, during which period acetone was continuously distilled over and collected in a Dean–Stark trap. The clear, dark-brown reaction mixture was cooled and excess IPA was removed by rotary evaporation under reduced pressure. The black residue was taken up in ether (150 ml) and washed with 10% sodium carbonate solution followed by water, filtered through anhydrous sodium sulfate, and dried further over drierite.

Purification by distillation under reduced pressure, bp 102–110° (0.1 mm), followed by recrystallization yielded 9.86 g of white crystals from hexane: mp 43.0–44.5° (lit.[16] mp 50°); ir ν_{max} (KBr) 1665 (C=O), 1600 (C=N ring stretching), 1450 and 1425 (N–O ring stretch), 1270, 1215, and 895 cm^{-1}; nmr ($CDCl_3$) δ 8.2 (m, 2, *o*-aroyl), 7.48 (m, 3, *m*- and *p*-aroyl), 6.42 (s, 1, C-4), 2.44 (s, 3, C-5 Me); λ_{max}^{EtOH} 260 nm (log ϵ 4.40); mass spectrum *m/e* 187 (M^+), (base peak), 105, other major peaks 77, 58, 51, 43, 28; high resolution mass measurement of M^+, 187.0639 (calcd 187.0633).

Anal. Calcd. for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.55; H, 4.86; N, 7.47.

3-Acetyl-5-methylisoxazole (2b).—A solution of 1.03 g (0.01 mol) of **1b** and *p*-TSA (10 mg) in 20.0 g (0.10 mol) of IPA was refluxed under nitrogen for 15 hr, during which period acetone was collected in a Dean–Stark trap. The clear dark-brown reaction mixture was worked up as described for **2a**. Glc analysis of the partially purified reaction mixture on a 10 ft × 0.125 in. Versamid column operated at 100° in a Varian Aerograph Model 90-P showed the presence of a peak (~5% of the mixture) with a retention time of 7.1 min, identical with that of an authentic sample of **2a** synthesized by the method of Schmidt and Widmann.[17] The crude material was partially purified by distillation (10 mm), yield a few drops of a pale yellow liquid which contained ~50% of **2b** as determined by glc analysis. A small sample of the pure isoxazole was obtained by preparative glc and found to be identical with the known compound by comparative ir ν_{max}^{neat} 1701 (C=O), 1600 (C=N ring stretch), 1450 and 1425 (N–O ring stretch), 1355, 1260, 1180, and 950 cm^{-1}; nmr ($CDCl_3$) δ 6.40 (s, 1, C-4), 2.64 (s, 3, OC Me), 2.50 (s, 3, C-5 Me); λ_{max}^{EtOH} 249 nm (log ϵ 3.60); mass spectrum *m/e* 125 (M^+), 43 (base peak), other major peaks 110 (M − 15), 69, 58, 31, and 28.

α-Acetoxystyrene (or 1-Phenylethenol Acetate) (3).—A solution of 50.0 g (0.417 mol) of acetophenone and 4.0 g (0.021 mol) of *p*-TSA in IPA (200 ml) was stirred at reflux temperature under dry nitrogen for 16 hr. Acetone was collected in a Dean–Stark trap as the reaction proceeded. After the reflux period, the reddish-brown solution was poured into distilled water (250 ml) and extracted with three 100-ml portions of ether. The combined extracts were washed with 5% $NaHCO_3$, followed by water, filtered through anhydrous sodium sulfate, and dried further over Drierite. Evaporation of the solvent gave 105.2 g of a dark-brown, foul-smelling liquid which was purified by distillation: yield 47.5 g of clear liquid; bp 100–103° (10 mm); ir ν_{max}^{neat} 1780 (C=O), 1655 (C=C vinyl stretch), 1205 (C–O stretch of enol acetate), 955 and 880 cm^{-1}; nmr ($CDCl_3$) δ 7.31 (m, 5, aromatic), 5.39 (d, 1, J = 2 Hz, vinyl), 4.98 (d, 1, J = 2 Hz, vinyl), 2.19 (s, 3, Me); mass spectrum *m/e* 162 (M^+), 105 (base peak), other major peaks 134 (M − CO), 120 (M − ketene), 91, 77, 51, and 43; high resolution mass measurement of M^+, 162.0669 (calcd, 162.0681).

Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: 73.78; H, 5.98.

3-Benzoyl-5-phenylisoxazole (4a).—A solution of 1.65 g (0.01 mol) of **1a**, *p*-TSA (10 mg), and 4.87 g (0.03 mol) of **3** was heated at 110° in a dry nitrogen atmosphere for 12 hr. The clear dark-brown reaction mixture was cooled, taken up in ether (75 ml), washed successively with 5% $NaHCO_3$ and water, and dried (Drierite). After rotary evaporation of the ether under reduced pressure, the residual liquid was distilled under reduced pressure, yielding 2.4 g of acetophenone as determined by comparative ir with an authentic sample.

Glc analysis of the black distillation residue on a 6 ft × 0.125 in. 3% OV-1 column operated at 130° using a Varian 2100 analyzer showed small amounts of acetophenone and **3** plus other minor impurities, as well as a relatively large peak with a retention time of 8.7 min. Tlc on Eastman silica gel GF chromograms developed in hexane–EtOAc–MeOH (2:2:1) and visualized with uv light showed a bright spot, R_f 0.64, running behind acetophenone, R_f 0.74, and **3**, R_f 0.68.

The residue was chromatographed on a 20-g silica gel column (E. Merck, 30–70 mesh) using hexane–EtOAc (9:1) as eluent. Fractions (10 ml) were collected using an ISCO Model 327 automatic collector. Glc analysis showed that fractions 7–16 were primarily the desired product. Two recrystallizations of the crude material from hexane gave 590 mg of white solid: mp 85.0–86.5° (lit.[18] mp 89°); ir ν_{max}^{KBr} 1665 (C=O), 1590 (C=N ring stretch), 1460 and 1430 (N–O ring stretch), 1240 and 895 cm^{-1}; nmr ($CDCl_3$) δ 8.49 (m, 2, ortho aroyl), 7.94 (m, 2, ortho aryl), 7.62 (m, 6, meta and para aroyl and aryl), and 7.15 (s, 1, C-4); λ_{max}^{EtOH} 264 nm (log ϵ 4.55); mass spectrum *m/e* 249 (M^+), 105 (base peak), other major peaks 189, 146, 116, 111, 89, 77, 63, 51, and 28.

3-Acetyl-5-phenylisoxazole (4b).—A solution of 1.03 g (0.01 mol) of **1b**, *p*-TSA (10 mg), and 4.87 g (0.03 mol) of **3** was heated at 70° in a dry nitrogen atmosphere for 4 hr. The resulting black, tarry reaction mixture was worked up and distilled to remove acetophenone as described for **4a**.

Glc analysis of the distillation residue on a 6 ft × 0.125 in. 3% OV-1 column operated at 125° using a Varian Aerograph Model 2100 with flame ionization detectors showed the residue to consist largely of unreacted **3**, approximately 10% of **4b** with a retention time of 8.3 min, and many minor unresolved products.

The isoxazole **4b** was isolated by column chromatography on a 15-g silica gel G column (E. Merck, 100 mesh) using hexane–ether (9:1) as eluent. Fractions (10 ml) were collected using an ISCO Model 327 automatic collector. Glc analysis showed that fractions 9–12 were primarily the desired product. Three recrystallizations of the crude material from hexane gave 56 mg of pure **4b**, mp 98–99° (lit.[19] mp 105° and 98–99°). Comparative ir, nmr, and a mixture melting point showed the product to be identical with that isolated by fractional recrystallization from the reaction mixture produced in the synthesis outlined by Ajello and Cusmano:[2a,b] ir ν_{max}^{KBr} 1701 (C=O), 1580 (C=N ring stretch), 1440 and 1430 (N–O ring stretch), 1355, 1220, and 940 cm^{-1}; nmr ($CDCl_3$) δ 7.71 (m, 2, ortho aryl), 7.40 (m, 3, meta and para aryl), 6.80 (s, 1, C-4), 2.65 (s, 3, O=C—CH_3); λ_{max}^{EtOH} 250 nm (log ϵ 4.18); mass spectrum *m/e* 187 (M^+), 43 (base peak), other major peaks 172 (M − 15), 145 (M − 42), 105, 77, 51, and 28.

Registry No.—**1a**, 614-21-1; **1b**, 10230-68-9; **2a**, 34671-15-3; **2b**, 24068-54-0; **3**, 2206-94-2; **4a**, 3672-49-9; **4b**, 7063-98-1; isopropenyl acetate, 108-22-5.

(15) (a) C. A. Sprang and E. F. Degering, *J. Amer. Chem. Soc.*, **64**, 1063 (1942); (b) H. C. Brown and C. P. Garg, *ibid.*, **83**, 2952 (1961); (c) C. Harries, *Justus Liebigs Ann. Chem.*, **319**, 251 (1901).

(16) The melting point reported by Ajello and Cusmano[4a,b] is in error.

(17) J. Schmidt and K. T. Widmann, *Ber.*, **42**, 1875 (1909).

(18) T. Ajello, *Gazz. Chim. Ital.*, **67**, 728 (1937).

(19) The melting point reported by Ajello and Cusmano[2a,c] is in error. Our corrected melting point agrees with that of Kano and coworkers: H. Kano, I. Adachi, R. Kido, and K. Hirose, *J. Med. Chem.*, **10**, 417 (1967).