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The Preparation and Reactions of Benzoylnitrile Oxide from Dimethylphenacylsulfonium Bromide[1)]

Yoshio Otsuji, Yasuhiro Tsujii, Akihiko Yoshida, and Eiji Imoto
Department of Applied Chemistry, College of Engineering, University of Osaka Prefecture, Sakai-shi, Osaka
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The nitrosation of dimethylphenacylsulfonium bromide (I) with sodium nitrite and hydrochloric acid in water gave 3,4-dibenzoyl-1,2,5-oxadiazole 2-oxide (II) in a 76% yield. The nitrosation of I in a similar manner in 1 : 1 dioxane-water afforded ω-chloro-ω-isonitrosoacetophenone (III) in an 80% yield. The treatment of III with triethylamine produced II through benzoylnitrile oxide (IX). 1,3-Dipolar cycloadditions of IX generated from III were conducted, using methyl methacrylate, styrene, acrylonitrile, and ethyl chloroformate as dipolarophiles, to yield the expected cycloadducts. The mechanisms of these reactions are discussed.

The α-hydrogen in β-keto sulfonium compounds is extremely acidic and is readily removed by bases such as triethylamine or sodium hydroxide to yield the corresponding sulfonium ylides. The ylides thus formed can be subjected to such electrophilic substitutions as acylation and sulfonation at the α-carbon.[2)] The α-hydrogen in β-keto sulfoxides is of a similar character, and such electrophilic substitutions as alkylation and bromination take place at the α-carbon of the sulfoxides.[3,4)]

In a previous paper,[5)] we have reported that β-keto sulfoxides are nitrosated at the α-position with nitrous acid in hydrochloric acid, and that, at the same time, the sulfoxide group is eliminated; thus, β-keto sulfoxides with no substituent at the α-position are converted to the α-chloro-α-nitroso (or isonitroso) ketones, and α-substituted β-keto sulfoxides, to the α-nitroso ketones.

Recently we found that the nitrosation of dimethylphenacylsulfonium bromide (I) with nitrous acid in hydrochloric acid affords 3,4-dibenzoyl-1,2,5-oxadiazole 2-oxide (II) or ω-chloro-ω-isonitrosoacetophenone (III) in high yields, the yields depending on the reaction conditions employed. In the present paper we will describe the results of a detailed study of this reaction. We will also report on some 1,3-dipolar

1) A part of this investigation was presented at the 19th Symposium on the Organic Reaction Mechanisms, Yamagata, October, 1968.

2) H. Nozaki, *Yuki Gosei Kagaku Kyokai Shi*, **27**, 125 (1965), and the references cited therein.

3) G. A. Russel and G. J. Mikol, *J. Amer. Chem. Soc.*, **88**, 5498 (1966).

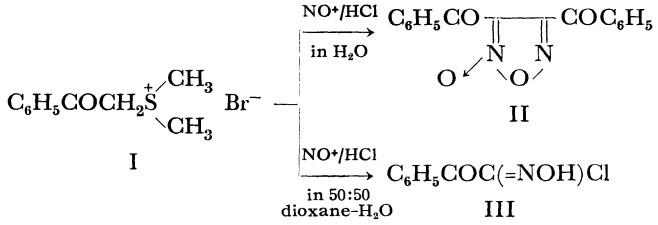
4) G. A. Russel, E. Sabourin, and G. J. Mikol, *J. Org. Chem.*, **31**, 2854 (1966).

5) Y. Otsuji, Y. Tsujii, A. Yoshida, and E. Imoto, This Bulletin, **44**, 219 (1971).

cycloaddition reactions of benzoylnitrile oxide (IX), which is readily derived from III and which would constitute a new type of reactive 1,3-dipole.

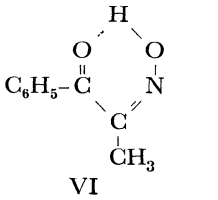
Results and Discussion

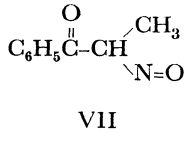
Nitrosation of Dimethylphenacylsulfonium Bromide (I). The treatment of a mixture of I and sodium nitrite in water with hydrochloric acid gave 3,4-dibenzoyl-1,2,5-oxadiazole 2-oxide (II) in a 76% yield, plus a small amount of ω-chloro-ω-isonitrosoacetophenone (III). However, the similar treatment of the same mixture in a 1:1 dioxane-water mixture afforded III in an 80% yield, along with a small amount of II.



The structure of II was established by the elemental analysis, by a molecular-weight determination (302, calcd 294), and by a study of its spectra data. The IR spectrum (KBr) showed two carbonyl absorptions around 1660 cm^{-1} as a doublet. The NMR spectrum ($CDCl_3$) showed only multiplet absorptions due to aromatic protons at τ 1.75—2.35. The assigned structure for II was also supported by the fact that II could be obtained by the treatment of III with bases, as will be discussed later. The structure of III was confirmed by comparing it with the sample prepared in the previous paper,[4] they were identical in every respect.

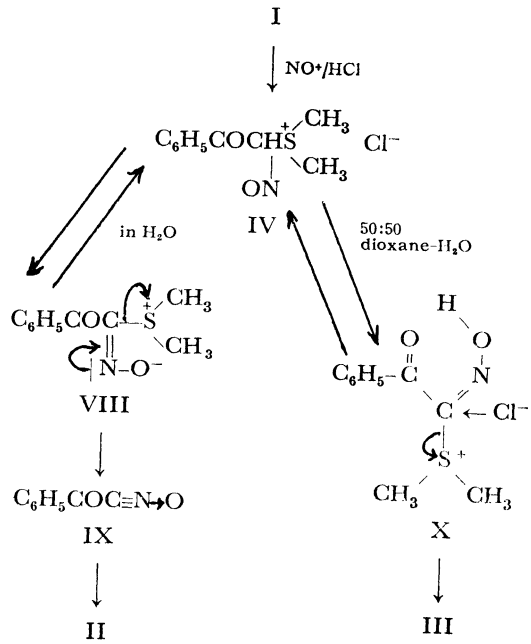
One of the most significant features of the nitrosation of the sulfonium salt is its remarkable solvent effect on the proportions of the products formed. How can this solvent effect be explained?. The first step of the reaction, both in water and an aqueous dioxane, is no doubt an attack of the nitrosonium ion at the α-carbon of the sulfonium salt to produce the nitroso sulfonium bromide (IV), which might be unstable under the reaction conditions.[6] We assumed that the configurations of IV in the solvents determined the proportions of the products, and we chose α-nitrosopropiophenone (V) as a model compound of IV. Its configurations were then studied in the mixed solvents of dioxane and water. The UV spectrum of V in dioxane and in dioxane-water (1:1) showed, respectively, absorption maxima at 250 mμ ($\varepsilon=1.1\times10^4$) and 255 mμ ($\varepsilon=1.2\times10^4$); these values are very close to that of benzene in the same solvent (255 mμ). On the other hand, the spectrum of V in water showed a maximum at 280 mμ ($\varepsilon=9\times10^3$), a value which is very close to that of benzaldehyde in the same solvent. These results suggest that V exists predominantly in the form of VI in dioxane-water and in the form of VII in water. In VI the keto and hydroxyimino groups form a stabilized, six-membered ring system by means of intramolecular hydrogen bonding; hence, the conjugation between the benzene ring and carbonyl group would be considerably reduced by the loss of the coplanarity between them. Thus, the UV spectrum of VI resembles that of benzene. On the other hand, an intermolecular hydrogen bonding between water and the keto and/or nitroso groups would dominate the intramolecular hydrogen bonding which is realized in VI. Therefore, the keto group conjugates with the benzene ring and the UV spectrum of VII resembles that of benzaldehyde.





On the basis of the above considerations, we propose the tentative mechanisms represented in Scheme 1 for the nitrosation of the sulfonium salt I.

The intermediate IV is stabilized in water by the elimination of a proton to form VIII, which in turn produces benzoylnitrile oxide (IX). The nitrile oxide, IX, then dimerizes to afford II. However, IV is stabilized in an aqueous dioxane by forming an intramolecularly-hydrogen-bonded X, which then produces III.



Scheme 1

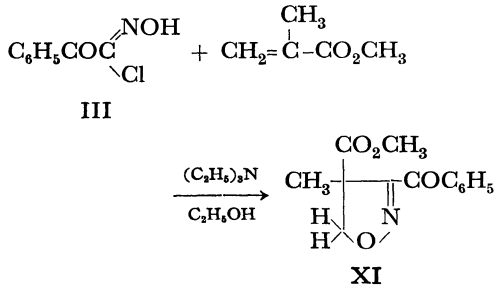
Reaction of ω-Chloro-ω-isonitrosoacetophenone (III) with Bases. The treatment of III with one equiv. of triethylamine in ethanol afforded II in a quantitative yield. The compound, II, thus produced was identical

6) M. Mukaiyama, N. Takei, and K. Saigo (Abstract of the papers presented at the 23rd Meeting of the Chemical Society of Japan, III, Tokyo (1970) p. 1516) have found that the nitrosation of I with isopropyl nitrite in methylene dichloride gives ω-bromo-ω-isonitrosoacetophenone in a 77% yield. They could not isolate a plausible intermediate, IV, because of its unstability, even in an organic medium.

with the sample obtained in the previous paragraph. The similar treatment of III with a sodium hydroxide solution also yielded II, but in a low yield. Considering that the formation of a 1,2,5-oxadiazole 2-oxide ring system (furoxan) is characteristic of the nitrile oxides,[7] it is apparent that the nitrile oxide, IX, is an intermediate of the above reactions; the reaction can feasibly be regarded as a 1,3-dipolar cycloaddition of one molecule of the nitrile oxide onto the CN bond of the other.

1,3-Dipolar Cycloadditions of Benzoylnitrile Oxide (IX). Since the above results indicated that IX can be liberated from III, the 1,3-dipolar cycloadditions of IX were studied using four unsaturated compounds as dipolarophiles. During the studies it was found that, in order to avoid the interfering dimerization of the reactive nitrile oxide, IX, to the furoxan II, the reaction must be carried out with low stationary concentrations of IX. The slow addition of a dilute solution of triethylamine to an alcoholic solution of III and a dipolarophile at a low temperature (−5—0°C) favored the cycloaddition.

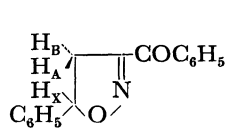
The treatment of III with an equiv. of methyl methacrylate in this manner afforded 3-benzoyl-4-methyl-4-methoxycarbonyl-Δ^2-isoxazoline (XI) in a 91% yield.



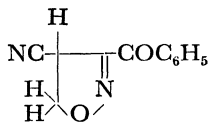
III

XI

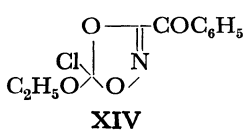
Similar treatments of III with styrene, acrylonitrile, and ethyl chloroformate produced 3-benzoyl-5-phenyl-Δ^2-isoxazoline (XII), 3-benzoyl-4-cyano-Δ^2-isoxazoline (XIII), and 3-benzoyl-5-chloro-5-ethoxy-1,4,2-dioxazole (XIV) in yields of 61%, 51%, and 26% respectively.



XII



XIII



XIV

The structures of XI, XII, XIII, and XIV were derived from their analytical and spectral data. The results of the elemental analyses, the molecular-weight determinations, and the IR spectra for these compounds were consistent with the assigned structures, as will be described in the "Experimental" section. However, the structures of these compounds were finally established by their NMR spectra. The NMR spectrum of XI in carbon tetrachloride exhibited a multiplet at τ 1.75—2.25 (5H, C_6H_5CO), two singlets at τ 6.22 (3H, $COOCH_3$) and 8.36 (3H, CH_3 at 4-C), and an AB quartet at τ 6.85 (2H, J=17 Hz, 5-CH_2). These signals, especially the chemical shift and the spectral pattern of the AB quartet, support the assigned structure for XI. The NMR spectrum of XII in carbon tetrachloride showed a multiplet at τ 1.70—2.72 (10H, C_6H_5CO at 3-C and C_6H_5 at 5-C) and an ABX pattern due to H_A, H_B, and H_X protons. The signals of this ABX system appeared at τ 6.27 and 6.76 (2H, H_A and H_B of 4-C) and at τ 4.35 (1H, H_X of 5-C). The coupling constants were as follows: J_{AB}=17.8 Hz, J_{AX}=11.2 Hz and J_{BX}=9.7 Hz. These data strongly support the assigned structure for XII. The NMR spectrum of XIII in carbon tetrachloride was relatively simple in its pattern as compared with that of XII. The spectrum showed a multiplet at τ 1.69—2.72 (5H, C_6H_5-CO), a triplet at τ 4.60 (1H, J=9.0 Hz, 4-CH), and a doublet at τ 6.25 (2H, J=9.0 Hz, 5-CH_2). The chemical shifts of the triplet and doublet signals indicate that the assigned structure for XIII is correct and that no other structures can be derived from these spectral data. Finally, the NMR spectrum of XIV in carbon tetrachloride showed a multiplet at τ 1.78—2.55 (5H, C_6H_5CO), a quartet at τ 5.36 (2H, J=7.5 Hz, $O\mathbf{CH_2}CH_3$), and a triplet at τ 8.59 (3H, J=7.5 Hz, $OCH_2\mathbf{CH_3}$). These data are again in agreement with the assigned structure for XIV.

As can be seen from these examples, the nitrile oxide, IX, undergoes 1,3-dipolar cycloadditions onto the C=C and C=O double bonds. It also adds preferentially to the C=C rather than to the C≡N bond in acrylonitrile, as is commonly observed with such aromatic nitrile oxides as benzonitrile oxide.[7] The orientation of the cycloaddition can be interpreted in a manner similar to that proposed for benzonitrile oxide;[7] *i. e.*, the resonance structures of IX would be XV, XVI, and XVII, and its principal polarized formula would be XVII:

VX XVI XVII

Experimental

The melting points are uncorrected. The IR spectra were recorded on a Hitachi EPI-S2 infrared spectrometer. The NMR spectra were obtained on a Hitachi H-60 high-resolution NMR spectrometer, with TMS as the internal standard. The UV spectra were recorded on a Hitachi EPU-2V recording spectrophotometer. The elemental analyses were performed with a Yanagimoto MT-1 CHN Corder. The molecularweight determinations were carried out with a Hitachi-Perkin Elmer 115 molecular-weight apparatus, using benzene as the solvent.

Reagents. A commercial sodium nitrite (97% purity) was used without further purification. The α-isonitropropiophenone was prepared by the method of Hartung and Crossley.[8] The other chemicals were of commercial origin and

7) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 565 (1963).

8) W. H. Hartung and F. Crossley, "Organic Syntheses," Coll. Vol. II, p. 363 (1948).

were used after purification by distillation or recrystallization.

Dimethylphenacylsulfonium Bromide (I)[9]. A solution of 80 g (0.4 mol) of phenacyl bromide and 25 g (0.4 mol) of dimethyl sulfide in 250 m*l* of methanol was refluxed for 10 hr, and then the solvent was evaporated to dryness to give a white solid. Recrystallization from ethanol afforded 73 g (70%) of the pure sulfonium bromide (I); mp 142—143°C.

Nitrosation of I in Water. Into a solution of 10 g (0.04 mol) of I and 3.5 g (0.05 mol) of sodium nitrite in 100 m*l* of water, 100 m*l* of concentrated hydrochloric acid were stirred over a period of 1 hr at room temperature. Stirring was continued for 2 hr to yield a yellow solid, along with a small amount of an orange solid. Both solids were precipitated on the bottom of the flask. The orange solid was picked out from a mixture of the solids by a spatula. The recrystallization of the yellow solid from isopropyl alcohol gave 4.3 g (76%) of 3,4-dibenzoyl-1,2,5-oxadiazole (II) as white crystals; mp 78—80°C.

Found: C, 65.55; H, 3.45; N, 9.81%. Calcd for $C_{16}H_{10}O_4N_2$: C, 65.30; H, 3.43; N, 9.52%.

The orange solid was recrystallized from benzene to yield 120 mg of ω-chloro-ω-isonitrosoacetophenone (III) as white crystals; mp 130—132°C.

Nitrosation of I in an Aqueous Dioxane. Into a solution of 10 g (0.04 mol) of I and 3.5 g (0.05 mol) of sodium nitrite in 50 m*l* of water and 50 m*l* of dioxane, 100 m*l* of concentrated hydrochloric acid were stirred over a period of 1 hr at room temperature. Stirring was continued for 2 hr to produce a white solid, along with a small amount of a yellow solid; these solids were then separated by filtration. The yellow solid was picked out from a mixture of the solids by a spatula. The recrystallization of the white solid from chloroform afforded 6 g (80%) of III as white crystals; mp 130—132°C.

The yellow solid was recrystallized from isopropyl alcohol to yield 60 mg of II as white crystals, the IR spectrum of which was completely identical with that of the authentic sample of II obtained above.

Reaction of ω-Chloro-ω-isonitrosoacetophenone (III) with Bases. A. With Triethylamine. A solution of 2 g (0.02 mol) of triethylamine in 50 m*l* of ethanol was stirred into a solution of 3 g (0.016 mol) of III in 50 m*l* of ethanol under cooling in an ice bath over a period of 30 min. Stirring was continued for 2 hr, and then the solvent was evaporated to dryness. The residue was recrystallized from isopropyl alcohol to yield II as white crystals in an almost quantitative yield; mp 78—80°C. The material thus obtained was identical with the sample prepared above in every respect.

B. With Sodium Hydroxide. Into a suspension of 2 g of III in 40 m*l* of benzene, we stirred, drop by drop, 12 m*l* of a 14% aqueous sodium hydroxide solution at 0°C. After stirring for 1 hr, the benzene layer was separated, dried over calcium chloride, and then evaporated to yield a white solid. The recrystallization of the solid from isopropyl alcohol gave about 200 mg of II; mp 78—80°C.

Formation of 3-Benzoyl-4-methyl-4-methoxycarbonyl-Δ²-isoxazoline (XI). Into a solution of 3 g (0.016 mol) of III and 1.6 g (0.016 mol) of methyl methacrylate in 50 m*l* of absolute ethanol, we stirred, at −5—0°C, a solution of 2 g (0.02 mol) of triethylamine in 50 m*l* of absolute ethanol over a period of 2 hr. The mixture, which soon turned yellow, was stirred for 3 more hr at the same temperature, concentrated to half its volume under reduced pressure, and then poured onto 100 m*l* of water. The aqueous mixture was extracted several times with methylene dichloride. The organic layer was washed with water and dried over sodium sulfate, and the solvent was evaporated. The distillation of the residue afforded 3.6 g (91%) of XI as a pale yellow oil; bp 190—191°C/7 mmHg.

Found: C, 62.84; H, 5.05; N, 5.87%. Calcd for $C_{13}H_{13}O_4N$: C, 63.15; H, 5.30; N, 5.67%.

Molecular weight: 252 (calcd 247). IR (KBr): 1740, 1655 cm^{-1} (C=O).

Formation of 3-Benzoyl-5-phenyl-Δ²-isoxazoline (XII). A solution of 3 g (0.016 mol) of III and 1.7 g (0.016 mol) of styrene in 50 m*l* of absolute ethanol was treated with a solution of 2.02 g (0.02 mol) of triethylamine in 50 m*l* of absolute ethanol as has been described above. After stirring for 3 hr under cooling in an ice bath, the reaction mixture was concentrated to half its volume under reduced pressure and then poured onto 100 m*l* of water. The aqueous mixture was extracted several times with methylene dichloride. The organic layer was washed with water and dried over sodium sulfate, and then the solvent was evaporated. The distillation of the residue gave 2.5 g (61%) of XII as a yellow oil; bp 185°C/3.5 mmHg.

Found: C, 75.87; H, 5.33; N, 5.93%. Calcd for $C_{16}H_{13}O_2N$, C, 76.47; H, 5.22; N, 5.57%.

Molecular weight: 250 (calcd 246). IR ($CHCl_3$): 1700, 1660 cm^{-1} (C=O).

Formation of 3-Benzoyl-4-cyano-Δ²-isoxazoline (XIII). A solution of 3 g (0.016 mol) of III and 0.85 g (0.016 mol) of acrylonitrile in 50 m*l* of absolute ethanol was treated with 2.02 g (0.02 mol) of triethylamine in 50 m*l* of absolute ethanol as has been described above. A similar work-up of the reaction mixture produced a brown oil after the evaporation of the methylene dichloride. The oil solidified upon cooling in a dry ice-acetone mixture. The solid was separated by filtration and recrystallized from water-ethanol to afford 1.7 g (52%) of XIII as pale yellow crystals; mp 70—71°C.

Found: C, 66.40; H, 4.13; N, 14.09%. Calcd for $C_{11}H_8O_2N_2$: C, 66.02; H, 4.03; N, 13.99%.

Molecular weight: 203 (calcd 200). IR (KBr): 1770 cm^{-1} (C=O).

Formation of 3-benzoyl-5-chloro-5-ethoxy-1,4,2-dioxazole (XIV). A solution of 3 g (0.016 mol) of III and 1.7 g (0.016 mol) of ethyl chloroformate in 50 m*l* of absolute ethanol was treated with 2.02 g (0.02 mol) of triethylamine in 50 m*l* of absolute ethanol as has been described above. A similar work-up of the reaction mixture and evaporation of the solvent (methylene dichloride) produced a brown oil which solidified upon cooling in a dry ice-acetone mixture. The solid was separated by filtration and recrystallized from ethanol to yield 1 g (26%) of a white solid; mp 56—59°C.

Found: C, 51.96; H, 4.08; N, 5.61%. Calcd for $C_{11}H_{10}O_4NCl$: C, 51.66; H, 3.91; N, 5.48%.

Molecular weight: 256 (calcd 256). IR (KBr): 1800, 1680 cm^{-1}.

9) K. W. Ratts and A. Yao, *J. Org. Chem.*, **31**, 1185 (1966).