Study of the Ring Opening Reactions of 4-Bromo-3,4-disubstituted-2-isoxazolin-5-ones with Aqueous Sodium Hydroxide[1]

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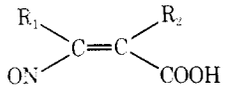
Received August 31, 1978

Because of the success in regioselective ring opening reactions of 3,4-disubstuted-4-halopyrazolones with aqueous alkali to obtain trisubstituted α,β-unsaturated acids,[2] an investigation was undertaken to ascertain if 4-bromo-3,4-disubstituted-2-isoxazolin-5-ones would analogously yield the unknown (*E*)- and (*Z*)-β-nitroso-α,β-alkenoic acids **1**.



1, R_1, R_2 = alkyl or aryl

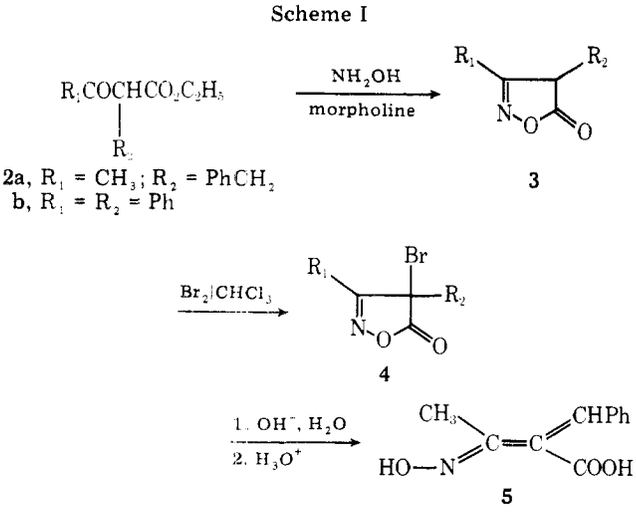
Nitroso olefins in which the nitroso substituent is attached to a sp^2 carbon are not well known[3] although perfluoronitrosoethylene has been reported from the reaction between trifluoroiodoethylene and nitric oxide.[4] Cleavage reactions with 4-substituted-isoxazolin-5-ones and hydrazine have been studied by Mustafa[5] and co-workers but a good leaving group at the 4-position of the isoxazolone ring was not present.

The first step in the synthesis (Scheme I) was accomplished by a modification of Couturier's method[6] and utilized ethyl α-benzylacetoacetate to give the isoxazolone **3a**. Spectral data showed that the compound is over 90% in the enol or enamine tautomeric forms.

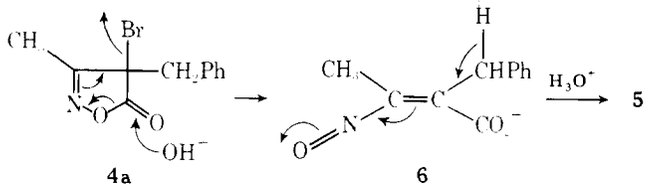
Compound **3a** was converted to 3-methyl-4-benzyl-4-bromo-2-isoxazolin-5-one (**4a**) by bromination. The presence of the 4,4-disubstituted product **4a** was supported by the strong infrared absorption of the carbonyl group at 1800 cm^{-1} and the ^1H NMR data showing the methylene hydrogens split into doublets. The halogenation reaction can be explained by electrophilic bromination of the tautomeric forms of **3a** with proton loss to give **4a**.

Treatment of the 4-bromoisoxazolone with aqueous NaOH followed by acidification gave a bromine-free acidic product in 90% yield. The ^1H NMR showed a singlet at 2.5 ppm for the methyl group, a complex multiplet at 7.4 ppm with an area of five hydrogens characteristic of a monosubstituted phenyl group, and a singlet corresponding to one hydrogen at 6.8 ppm and two acidic hydrogens in the area of 11.5 ppm. These data indicate the structure to be the oximino acid **5**.

Scheme I



The formation of **5** involves ring opening by base and loss of HBr; these steps can occur as indicated in **4a** → **6**, or by initial elimination of HBr followed by ring opening.



4a **6**

Although the β-nitroso unsaturated acid was not formed as originally hoped, it seemed that this goal could be accomplished if no acidic hydrogens were present at the 3- and 4-positions of the haloisoxazolone of **4a**. Accordingly, the synthesis of 4-bromo-3,4-diphenyl-2-isoxazolin-5-one (**4b**) was attempted. However, the reaction of **4b** with aqueous hydroxide resulted in the formation of benzil, **12**. An authentic sample of benzil gave identical spectra as the product and a mixed melting point showed no depression. A possible path leading to the formation of benzil is given in Scheme II.

The first two steps involved hydroxide ion adding across the carbonyl group and intramolecular displacement of bromine followed by ring opening of the epoxide and decarboxylation (CO_2 was found as a product). Other mechanisms involving the intermediate benzil monoxime[7] were eliminated from consideration because this compound was found to be stable under the experimental conditions.

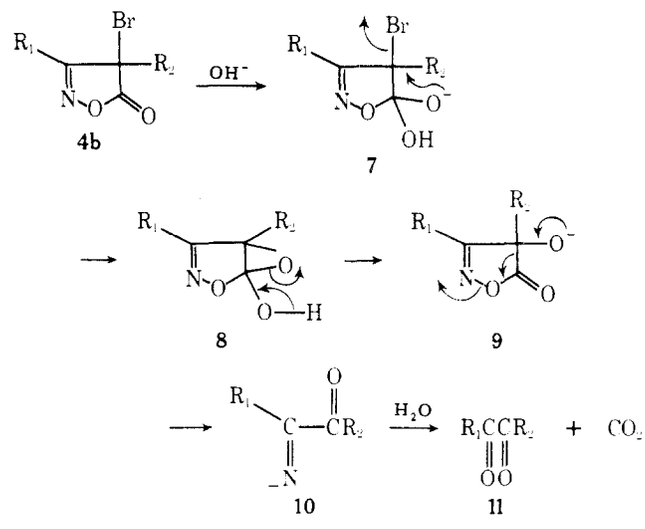
Additional studies testing the generality of ring opening reactions of 3,4-disubstituted-4-halo-2-isoxazolones with no acidic hydrogens at positions 3 and 4 to give 1,2 diketones, and synthesizing highly hindered 3,4-disubstituted-4-haloisoxazolones where ring opening involving an intramolecular displacement reaction would be difficult, are anticipated.

Experimental Section

All melting and boiling points are uncorrected. IR spectra were determined with a Perkin-Elmer Model 621 double-beam spectrophotometer and were calibrated vs. polystyrene. NMR spectra were recorded on a Perkin-Elmer 60 MHz R20A or Varian EM-360 spectrometer with tetramethylsilane as an internal standard. Ultraviolet spectra were obtained on a Cary 14R recording spectrometer. Mass spectra were obtained on a Hitachi RMU-6E spectrometer. Analyses were done by Galbraith Laboratories, Inc., Knoxville, Tenn.

3-Methyl-4-benzyl-2-isoxazolin-5-one (3a). To 22 g (0.1 mol) of ethyl α-benzylacetoacetate was added 9.57 g (0.11 mol) of morpholine in a 12-mL flask fitted with a reflux condenser and stirrer. The mixture was heated to 143 °C for 0.5 h and was allowed to stand overnight at room temperature. To this mixture was added 12.8 g (0.17 mole) of hydroxylamine hydrochloride in ethyl alcohol–water. After

Scheme II



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being stirred until all the material dissolved, HCl was added to the mixture to a pH of 1.5. Ethanol was evaporated leaving an oily product in aqueous solution. A small amount of cold water was added and a solid precipitated on scratching. The solid was collected and yielded after drying 17.9 g (92%) of **3a**: mp 105–6 °C (lit.[8] mp 106 °C); IR (KBr) 3485 cm^{-1}, 1590; NMR ($CDCl_3$) δ 1.9 (s, 3 H), 3.5 (s, 2 H), 7.2 (m, 5 H), 11.2 (s, 1 H, disappeared with D_2O).

4-Bromo-3-methyl-4-benzyl-2-isoxazolin-5-one (4a). To 9.45 g (0.05 mol) of **3a** in 100 mL of chloroform was added 8.0 g (6.05 mol) of bromine in 50 mL of chloroform. The resulting mixture was warmed for 0.5 h at 50 °C and evolution of HBr was observed. The chloroform was evaporated leaving an oil which, on cooling in an ice bath and addition of small portions of ligroin, solidified. The product obtained in 85% yield had a mp of 60–65 °C and on recrystallization from benzene–petroleum ether melted at 76–78 °C: IR (KBr) 1800 cm^{-1}, 1585 (w); NMR ($CDCl_3$) δ 2.2 (s, 3 H), 3.32 (1 H, d, J = 14.0 Hz), 3.71 (1 H, d, J = 14.0 Hz), 7.20 (m, 5 H).

Anal. Calcd for $C_{10}H_{10}NO_2Br$: C, 49.25; H, 3.73; N, 5.22; Br, 29.85. Found: C, 49.32; H, 3.75; N, 5.16; Br, 30.05.

Formation of 2-Benzal-3-hydroxyiminobutanoic Acid (5). To a solution of sodium hydroxide (4.60 g, 0.115 mol) in 150 mL of H_2O was added with cooling and stirring 6.70 g (0.025 mole) of **4a**. After 0.5 h, the ice bath was removed and stirring was continued for 6 h. Acidification was carried out at −3 °C with 3 N HCl and the resulting product (4.92 g, 96% yield) was filtered and dried and had mp 174–76 °C dec: IR (KBr) 1576 cm^{-1}, 1620, 1715, 3300; NMR (Me_2SO) δ 2.5 (s, 3 H), 6.8 (s, 1 H), 7.4 (m, 5 H), 11.5 (s, 2 H, disappeared with D_2O); UV (95% C_2H_5OH) 278 nm (4.44 log ϵ).

Anal. Calcd for $C_{11}H_{11}O_3N$: C, 64.39; H, 5.37; N, 6.83. Found: C, 64.52, H, 5.48; N, 6.75.

Ethyl α-Phenylbenzoylacetate (2b). This compound was prepared in 65% yield utilizing the method of Howk and McElvain[9] and using cyanodesoxybenzoin[10] as the starting material.

3,4-Diphenyl-2-isoxazolin-5-one (3b). Ethyl α-phenylbenzoylacetate (30 g, 0.11 mol) was placed in 300 mL of absolute alcohol in a 1-L flask and 36 g (0.51 mol) of hydroxylamine hydrochloride was added; the mixture was refluxed for 2 h. After standing overnight, most of the product precipitated. The remaining product was precipitated by diluting the solution with water. After drying, the product was boiled with anhydrous ether, filtered, and obtained in 78% yield, mp 150–52 °C (lit.[10] 146–49 °C).

4-Bromo-3,4-diphenyl-2-isoxazolin-5-one (4b). Finely powdered **3b** (15 g, 0.040 mol) was suspended in 600 mL of anhydrous CCl_4 and the mixture was treated with 10 g (0.045 mol) of anhydrous bromine. The mixture was shaken periodically and the isoxazolone dissolved with the evolution of white fumes. After all the isoxazolone had been dissolved, the CCl_4 was removed by rotary evaporator and the product **4b** was recrystallized from CH_3OH in 75% yield, mp 68–70 °C (lit.[10] mp 72 °C).

Attempted Synthesis of 2,3-Diphenyl-3-nitrosopropenoic Acid Formation of Benzil 11. To 150 mL of aqueous NaOH (94.60 g, 0.11 mol) cooled in an ice bath was added 7.3 g (0.024 mol) of **4b** at 0 °C. After 0.5 h the ice bath was removed and stirring was continued for 6 h. The resulting yellow solution was acidified with 6 N HCl and the solid product formed was recrystallized from benzene and then from acetone and was obtained in 72% yield, mp 95–6 °C: Anal. (C, 80.0, H, 4.90, no nitrogen); IR (1681 cm^{-1}, 1540, 1445); NMR ($CDCl_3$) δ 7.4 (m, 10 H); mass spectrum (m/e at 210, 105, 77 (1.00)); UV (C_2H_5OH) 259 nm (4.31 log ϵ) gave support to the product as being benzil.

Acknowledgments. We would like to express our gratitude to the National Science Foundation and the Central Awards Committee, State University of New York, Faculty Grants for the Improvement of Undergraduate Instruction for partial support of this work. We would also like to thank the organic chemistry class who participated in project-oriented laboratories and accomplished some of the preliminary work.

Registry No.—**2a**, 620-79-1; **2b**, 58929-02-5; **3a**, 68708-06-5; **3b**, 68708-07-6; **4a**, 68708-08-7; **4b**, 68708-09-8; **5**, 68708-10-1; **11**, R_1 = R_2 = Ph, 134-81-6.

References and Notes

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Potassium Permanganate Oxidation of Methadone and Its Convenient Transformation to Metabolites

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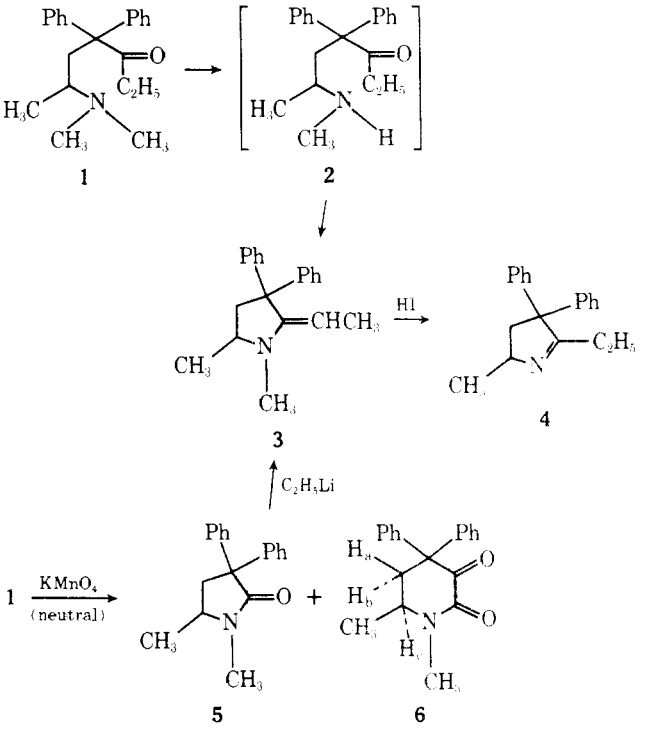
Received September 19, 1978

The major metabolite of the important drug methadone 1 in humans and in rats has been identified as 1,5-dimethyl-3,3-diphenyl-2-ethylidenepyrrolidine (3) together with its



N-demethylated analogue 4 and their aryl hydroxylation products as minor metabolites.[1-5] Formation of these metabolites, in vivo, is considered to proceed via hitherto unknown *N*-demethylmethadone 2.[1,2] Attempts to prepare the major metabolite 3 by treatment of 1 with either cyanogen bromide[6] or chloroformate esters[7] were not fruitful, and were reported in both cases to give 3,3-diphenyl-2-ethylidene-5-methyltetrahydrofuran. While inert to oxidation with mercuric acetate, methadone was cleaved to benzophenone with alkaline potassium permanganate.[8,9] To our knowledge in vitro chemical transformation of methadone to its metabolites has not been accomplished so far. The metabolites, however, have been prepared in overall poor yields involving long synthetic sequences.[2,4] We have reinvestigated[10] the demethylation problem and found that treatment of 1 with potassium permanganate[11] under neutral conditions cleanly affords 1,5-dimethyl-3,3-diphenyl-2-pyrrolidone (5),[12] a precursor

0022-3263/79/1944-0874$01.00/0