Reaction of β-Keto Ethyleneacetals with Hydroxylamine: A Correction

Vidyadhar M. Paradkar*, Tamara B. Latham and Ashok Krishnaswami

Anaquest Inc., The BOC Group Technical Center, 100 Mountain Avenue,
Murray Hill, NJ 07974

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A reaction of 2-(2-nitrobenzoylmethyl)-1,3-dioxolane (**3**) with hydroxylamine, followed by acid catalyzed cyclization, produced 5-(2-nitrophenyl)isoxazole (**5**) as the only isolable product, whereas 2-(benzoylmethyl)-1,3-dioxolane (**9**) under identical conditions produced a 2.5:1 mixture of 3-phenyl and 5-phenylisoxazoles **10** and **11**. These findings contradict the literature report that β-keto ethyleneacetals on treatment with hydroxylamine produce exclusively 3-substituted isoxazoles. As an additional proof, 3-(2-nitrophenyl)isoxazole (**8**) was prepared by an unambiguous method *via* the nitrile oxide route for comparison. The intermediate obtained on treatment of 2-(2-nitrobenzoylmethyl)-1,3-dioxolane (**3**) with hydroxylamine was found to be an isomeric mixture of 5-hydroxy-5-(2-nitrophenyl)-2-isoxazoline (**4**) and the *syn* and *anti* mono-oximes **19** (at least in solution), either of which could give 5-(2-nitrophenyl)isoxazole (**5**) on acid treatment. A mechanistic rationale is provided to explain the anomalous results.

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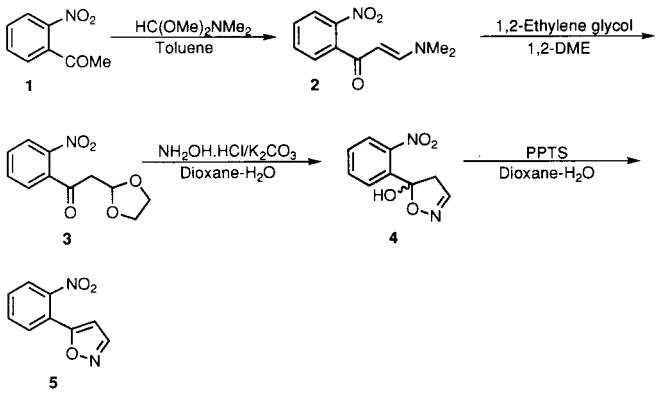
The reaction of β-keto ethyleneacetals with hydroxylamine, followed by cyclization, has been cited in the literature [1-3] as a regioselective method for the preparation of 3-substituted isoxazoles. As part of the program directed towards preparation of various *o*-heterocyclicanilines, we attempted to employ this methodology to prepare 3-(2-nitrophenyl)isoxazole (**8**). The anomalous results obtained during the course of this investigation is the subject of this publication.

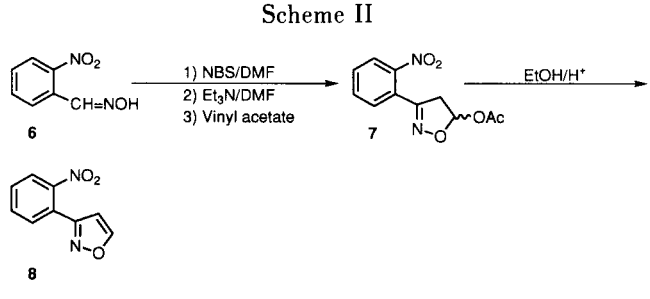
The starting material, 2-(2-nitrobenzoylmethyl)-1,3-dioxolane (**3**), was prepared from 2-nitroacetophenone (**1**) in two steps as depicted in Scheme I. 2-Nitroacetophenone (**1**) was treated with dimethylformamide dimethyl acetal in refluxing toluene to give the enaminone **2** in 76% yield. The enaminone **2** was reacted with a large excess of 1,2-ethylene glycol in 1,2-dimethoxyethane, in the presence of *p*-toluenesulfonic acid, to give 2-(2-nitrobenzoylmethyl)-1,3-dioxolane (**3**) in 39% yield. Although 1,4-additions of various nucleophiles to enaminones are well documented [4], to our knowledge, this is the first examples of addition of a 1,2-diol to an enaminone to give a β-keto ethyleneacetal. In spite of the moderate yields, this method is more convenient than other methods for the preparation of β-keto ethyleneacetals, such as, addition of the anion generated from a cyanohydrin to 2-(bromomethyl)-1,3-dioxolane [5] or an addition of 1,2-ethylene glycol to chlorovinylketones [6] or the palladium catalyzed addition of 1,2-ethylene glycol to vinylketones [7].

Scheme I

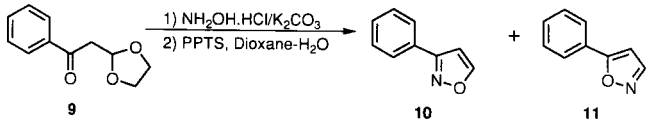


When 2-(2-nitrobenzoylmethyl)-1,3-dioxolane (**3**) was treated with hydroxylamine hydrochloride, which had been pre-neutralized with potassium carbonate, and the resulting hydroxyisoxazoline **4** was treated with pyridinium *p*-toluenesulfonate (PPTS), the only product obtained was 5-(2-nitrophenyl)isoxazole (**5**), not 3-(2-nitrophenyl)-isoxazole (**8**) as previously reported in the literature [3]. We confirmed the regiochemistry of the product of this reaction by an unambiguous synthesis of 3-(2-nitrophenyl)-isoxazole (**8**) by the nitrile oxide route (see Scheme II). In order to verify the literature report [3] that 2-(benzoylmethyl)-1,3-dioxolane (**9**) on treatment with hydroxylamine in dioxane-water, followed by cyclization gave exclusively 3-phenylisoxazole (**10**), we repeated this reaction under the literature conditions (Scheme III). The intermediate obtained on treatment of 2-(benzoylmethyl)-1,3-dioxolane (**9**) with hydroxylamine failed to cyclize to isoxazole on heating in dioxane-water at 100°. However, cyclization could be affected in the presence of pyridinium *p*-toluenesulfonate to give a mixture of 3-phenylisoxazole (**10**) and 5-phenylisoxazole (**11**) in a ratio 2.5:1 as determined by the relative integration of the signals due to the isoxazole protons

Scheme II



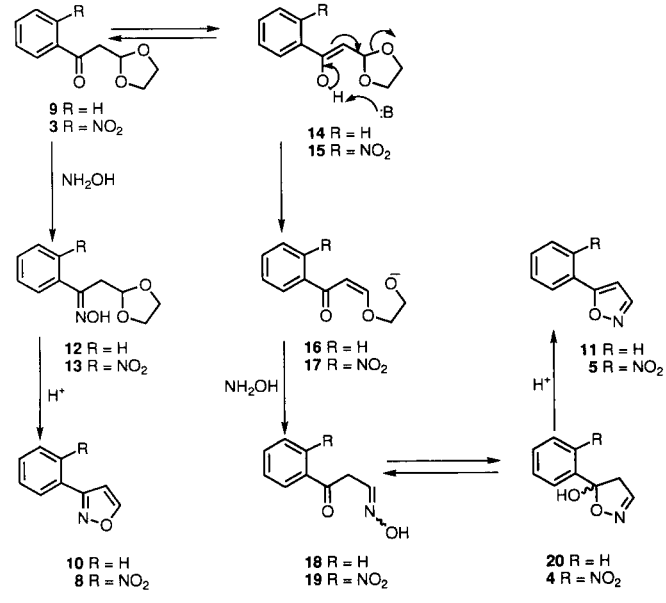
Scheme III



at 8.42 and 8.26 ppm, respectively, in the proton nmr spectrum of the mixture. The major product was indeed 3-phenylisoxazole (**10**) as proved by an unambiguous synthesis of this isomer by the nitrile oxide route [8]. Thus, it was clear that the regioselectivity of this reaction depended on the nature of the *ortho* substituent on the aromatic ring.

The overall results can be explained by the mechanistic pathway shown in Scheme IV. In case of simple 2-(benzoylmethyl)-1,3-dioxolane (**9**) there are two distinct reaction pathways leading to the formation of either 3- or 5-phenylisoxazoles **10** or **11**. In the first pathway hydroxylamine would react with the ketone function to give oximeacetal **12** which on heating with an aqueous acid would open up the dioxolane ring followed by cyclization to give 3-phenylisoxazole (**10**). In the second pathway an abstraction of a proton from the enol **14** by a base (in the present case hydroxylamine) would trigger the opening of the 1,3-dioxolane ring to produce the alkoxymethylene ketone **16**. This species would preferentially undergo a 1,4-addition by hydroxylamine, followed by elimination of ethylene glycol, leading to the formation of mono-oxime **18** or its isomeric

Scheme IV



isoxazoline **20**. The mono-oxime **18** (or isoxazoline **20**) on treatment with aqueous acid would lead to the formation of 5-phenylisoxazole (**11**). When 2-(2-nitrobenzoylmethyl)-1,3-dioxolane (**3**) is used as the starting material the latter pathway is exclusively followed. Such behavior can be explained based on the higher acidity of the enol **15** of 2-(2-

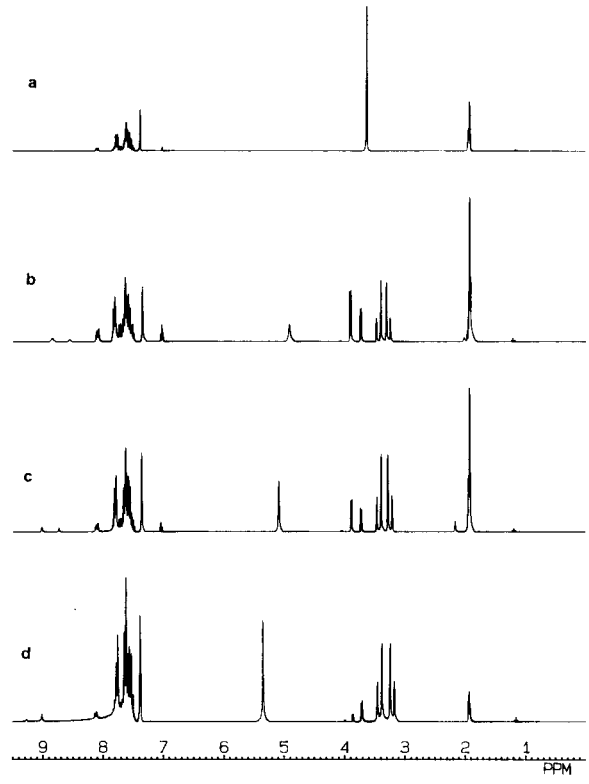


Figure. a) 270 MHz pmr spectrum of **4** in acetonitrile-d_3 after deuterium oxide exchange; b) 270 MHz pmr spectrum of **4** in acetonitrile-d_3 at 65°; c) same as in b except at 25°; d) same as in b except at −35°.

nitrobenzoylmethyl)-1,3-dioxolane (**3**) compared to the enol **14** of 2-benzoylmethyl-1,3-dioxolane (**9**), making the proton abstraction by a weak base, such as hydroxylamine, and the subsequent opening of the dioxolane ring more facile in the former case. The hydroxyisoxazoline **4** was isolated in the case of 2-(2-nitrobenzoylmethyl)-1,3-dioxolane (**3**) and was found to be in equilibrium with isomeric mono-oxime **19** by the proton nmr studies in deuterated acetonitrile solution (see Figure). The two doublets centered at 3.88 ppm and 3.72 ppm were assigned to the methylene protons of *syn* and *anti* isomers of **19** (although not necessarily in that order), and the doublet of quartet (ABX) centered at 3.31 ppm was assigned to the diastereotopic protons at C_4 in the hydroxyisoxazoline **4**. Spectra recorded at −35°, 25° and 65° showed a change in isoxazoline **4** to mono-oxime **19** ratio from 8:1 to 3.5:1 to 2:1, respectively, as measured by the relative integrals of the methylene signals. In addition to variable temperature dynamic equilibrium studies, deuterium exchange studies reinforced the presence of a dynamic equilibrium between hydroxyisoxazoline **4** and mono-oxime **19**. The deuterium exchange spectrum of **4** showed the collapse of the multiplet due to the methylene protons of both the hydroxyisoxazoline **4** and the mono-oxime **19**. Castells and Colombo have demonstrated such a dynamic equilibrium between a

hydroxyisoxazoline and a mono-oxime in the case of the hydroxylamine addition product of benzoylacetaldehyde [9]. The same hydroxyisoxazoline **4** was formed when the enaminone **2** was reacted with hydroxylamine hydrochloride in dioxane-water at room temperature, presumably by 1,4-addition of the hydroxylamine followed by the elimination of dimethylamine [10].

In summary, the regioselectivity of the reaction of 2-(benzoylmethyl)-1,3-dioxolane with hydroxylamine seems to be dependent upon the nature of the substituent on the phenyl ring and is not a method of choice for the preparation of 3-aryl substituted isoxazoles.

EXPERIMENTAL

All reagents and solvents were reagent grade or were purified by standard methods before use and the reactions were routinely carried out under an inert atmosphere. Melting points were taken in open capillaries on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were taken on a Bio-Rad FTS60 spectrophotometer equipped with a MCT liquid nitrogen cold detector or on a Shimadzu IR-460 infrared spectrophotometer. The pmr spectra were determined at 300 MHz using a Bruker AC300 in deuteriochloroform, unless specified otherwise. The variable temperature and deuterium exchange studies were performed at 270 MHz on a JEOL GSX270 spectrometer in deuterated acetonitrile solution. The ^{13}C nmr were recorded at 75.4 MHz using a Bruker AC300 in deuteriochloroform, unless specified otherwise. All chemical shifts are reported in parts per millions (δ) relative to tetramethylsilane. Microanalyses were performed by Robertson Microlit Laboratories Inc., Madison, NJ. Silica gel 60 (70-230 mesh ASTM) used for column chromatography was supplied by E. Merck. Analytical thin-layer chromatography (tlc) was performed on silica gel with fluorescent indicator coated on 2.5 x 7.5 cm glass plates in 0.2 mm thickness. Bulb-to-bulb distillations were carried out by using a kugelrohr distillation apparatus (Aldrich Chemical Co.).

3-(Dimethylamino)-1-(2-nitrophenyl)-2-propene-1-one (**2**).

A solution of 2-nitroacetophenone (10.00 g, 60.55 mmoles) and *N,N*-dimethylformamide dimethyl acetal (12.80 g, 66.95 mmoles) in 250 ml of toluene was heated at reflux for 16 hours under nitrogen. The reaction mixture was cooled in the refrigerator overnight and the crystals obtained were filtered to yield 10.20 g (76%) of **2**, mp 127-130°; ir (potassium bromide): 1638 (CO), 1576 cm^{-1}; pmr: δ 7.93 (d, 1H, *J* = 8.2 Hz, Ar *H*), 7.70-7.10 (m, 4H, Ar *H* and vinyl *H*), 5.29 (d, 1H, J = 12.6 Hz, vinyl *H*), 3.09 (s, 3H, NCH_3), 2.87 (s, 3H, NCH_3).

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.92; H, 5.31; N, 12.81.

2-(2-Nitrobenzoylmethyl)-1,3-dioxolane (**3**).

A solution of **2** (5.00 g, 22.69 mmoles), 1,2-ethylene glycol (8.20 g, 132.10 mmoles) and *p*-toluenesulfonic acid (4.18 g, 21.97 mmoles) in 116 ml of 1,2-dimethoxyethane was refluxed for 16 hours. After cooling to room temperature the solvent was removed on a rotavapor and the residue was partitioned between water and methylene chloride. The methylene chloride layer was washed with water, followed by brine and the solvent was removed after drying (sodium sulfate) to yield a dark red oil. Chromatography of the oil on silica gel and elution with hexane-ethyl acetate 80:20 provided 2.00 g (39%) of **3** as a pale yellow oil. The analytical sample was prepared by bulb-to bulb distillation (bath temperature 140° at 0.35 mm); ir (film): 3107, 2959, 2890, 1706 (CO), 1529 cm^{-1}; pmr: δ 8.02 (d, 1H, J = 8.4 Hz, Ar *H*), 7.66 (t, 1H, J = 7.5 Hz, Ar *H*), 7.53 (m, 1H, Ar *H*), 7.40 (d, 1H, J = 7.5 Hz, Ar *H*), 5.24 (t, 1H, J = 4.8 Hz, $OCHO$), 4.00-3.60 (m, 4H, OCH_2CH_2O), 3.12 (d, 2H, J = 4.8 Hz, $COCH_2$); ^{13}C nmr: δ 198.7, 137.5, 134.2, 130.6, 129.8, 127.7, 124.0, 100.7, 64.8, 47.1.

Anal. Calcd. for $C_{11}H_{11}NO_5$: C, 55.70; H, 4.67; N, 5.90. Found: C, 55.83; H, 4.75; N, 5.92.

2-(Benzoylmethyl-1,3-dioxolane (**9**).

2-(Benzoylmethyl)-1,3-dioxolane was prepared in 39% yield from 3-(dimethylamino)-1-phenyl-2-propene-1-one [11] by the aforementioned procedure; purification was achieved by bulb-to-bulb distillation (bath temperature 120° at 0.35 mm, lit [6] mp 58-59°); pmr: δ 7.90 (d, 2H, J = 5.4 Hz, Ar *H*), 7.60-7.20 (m, 3H, Ar *H*), 5.39 (t, 1H, J = 5.0 Hz, $OCHO$), 4.10-3.70 (m, 4H, OCH_2CH_2O), 3.29 (d, 2H, J = 5.0 Hz, $COCH_2$).

5-Hydroxy-5-(2-nitrophenyl)-2-isoxazoline (**4**).

A solution of hydroxylamine hydrochloride (0.79 g, 11.36 mmoles) in 2.0 ml of water was neutralized with a solution of potassium carbonate (0.78 g, 5.70 mmoles) in 4 ml of water at ice-bath temperature. A solution of **3** (1.80 g, 0.76 mmoles) in 12 ml of 1,4-dioxane was added dropwise and the reaction mixture was stirred for two days at room temperature. The solvent was removed on a rotavapor and the residue was partitioned between water and methylene chloride. The methylene chloride layer was washed with water, followed by brine and after drying (sodium sulfate) the solvent was removed to yield a dark yellow oil. The oil was purified by chromatography on silica gel and eluted with hexane-ethyl acetate 80:20 to yield 1.30 g (66%) of **4** as a pale yellow oil. A small amount of this oil was crystallized from hexane-ethyl acetate to give a white solid mp 88-90°; ir (potassium bromide): 3335 (OH), 1602 (C=N), 1537 cm^{-1}; pmr (acetonitrile-d_3): δ 9.04 (br s, O*H* oxime) 8.76 (br s, O*H* oxime), 8.15-8.00 (m, Ar *H*), 7.90-7.40 (m, Ar *H*), 7.32 (d, J = 1.65 Hz, C*H*=N isoxazoline), 7.03 (t, J = 5.0 Hz, C*H*=N oxime), 5.0 (s, O*H* isoxazoline), 3.88 (d, J = 5.0 Hz, CH_2C=NOH), 3.72 (d, J = 6.0 Hz, CH_2C=NOH), 3.31 (dq (ABX), J_1 = 18.8 Hz, J_2 = 1.65 Hz, CH_2 isoxazoline); ^{13}C nmr (acetonitrile-d_3): δ 198.8, 150.3, 148.8, 146.3, 145.5, 144.2, 137.2, 135.5, 135.4, 134.8, 132.66, 132.38, 131.0, 129.2, 128.8, 128.8, 125.4, 125.4, 124.8, 118.3, 104.5, 50.9, 43.6, 39.1.

Anal. Calcd. for $C_9H_8N_2O_4$: C, 51.93; H, 3.87; N, 13.46. Found: C, 52.04; H, 3.75; N, 13.41.

5-(2-Nitrophenyl)isoxazole (**5**).

A solution of **4** (1.20 g, 4.76 mmoles) and pyridinium *p*-toluenesulfonate (0.95 g, 3.78 mmoles) in 42 ml of dioxane-water 6:1 was refluxed for 16 hours. The solvent was removed on a rotavapor and the residue was taken up in methylene chloride. The methylene chloride layer was washed with water, followed by brine and the solvent was removed after drying over sodium sulfate. The crude product was purified by chromatography on silica gel and eluted with hexane-ethyl acetate 60:40 to provide 684 mg (74%) of **5**. The analytical sample was crystallized from hexane-ethyl acetate, mp 80-81°; ir (potassium bromide): 3168, 3144, 3026, 2878, 1618, 1585 cm^{-1}; pmr: δ 8.35 (d, 1H, J = 1.9 Hz, *H*-3 isox-

azole), 7.92 (d, 1H, J = 7.9 Hz, Ar *H*), 7.90-7.60 (m, 3H, Ar *H*), 6.52 (d, 1H, J = 1.9 Hz, *H*-4 isoxazole); ^{13}C nmr: δ 164.6, 150.7, 147.9, 132.7, 131.1, 130.6, 124.3, 121.3, 102.9.

Anal. Calcd. for $C_9H_6N_2O_3$: C, 56.85; H, 3.18; N, 14.73. Found: C, 56.81; H, 3.16; 14.54.

3-(2-Nitrophenyl)isoxazole (**8**).

A solution of *N*-bromosuccinimide (45.00 g, 252.82 mmoles) in 50 ml of DMF was added dropwise to a solution of **6** (8.60 g, 51.76 mmoles) in 30 ml of DMF maintaining the temperature below 15°. After the addition was complete, a solution of triethylamine (25.60 g, 252.98 mmoles) in 30 ml of DMF was added dropwise keeping the temperature below 10°. To complete the reaction, stirring was continued for an additional 1 hour. The reaction mixture was poured on ice and was quickly extracted with 2 x 150 ml of methylene chloride. The methylene chloride layer was washed with ice water, dried (sodium sulfate) and filtered quickly into a pre-cooled flask containing vinyl acetate (18.68 g, 216.98 mmoles). The methylene chloride solution containing 2-nitrobenzonitrile oxide and vinyl acetate was refluxed for 16 hours. After cooling to room temperature the solvent was removed and the residue was chromatographed on silica gel and eluted with hexane-ethyl acetate 75:25 to provide 6.5 g of partially pure 5-acetoxy-3-(2-nitrophenyl)-2-isoxazoline which was taken directly to the next step. A solution of the acetoxy compound in 150 ml of ethanol containing 30 ml of concentrated hydrochloric acid was refluxed for 27 hours. The solvent was removed and the residue was partitioned between water and methylene chloride. The methylene chloride layer was washed with water followed by brine and the solvent was removed on a rotavapor after drying (sodium sulfate). The residue was purified by chromatography on silica gel and eluted with hexane-ethyl acetate 85:15 to give 3.96 g (40%) of **8**. The analytical sample was crystallized from hexane-ethyl acetate, mp 84-85°; ir (potassium bromide): 3150, 3128, 2859, 1613, 1578 cm^{-1}; pmr: δ 8.50 (d, 1H, J = 1.6 Hz, *H*-5 isoxazole), 7.98 (d, 1H, J = 8.0 Hz, Ar *H*), 7.80-7.50 (m, 3H, Ar *H*), 6.49 (d, 1H, J = 1.6 Hz, *H*-4 isoxazole); ^{13}C nmr: δ 158.7, 148.5, 132.9, 131.5, 130.6, 124.4, 123.8, 104.7.

Anal. Calcd. for $C_9H_6N_2O_3$: C, 56.85; H, 3.18; N, 14.73. Found: C, 56.92; H, 2.79; N, 14.75.

3-Phenyl and 5-Phenylisoxazoles **10** and **11**.

A solution of hydroxylamine hydrochloride (0.69 g, 9.90 mmoles) in 1.5 ml of water was neutralized at ice-bath temperature with a solution of potassium carbonate (0.68 g, 4.95 mmoles) in 3.5 ml of water. A solution of **9** (1.26 g, 6.6 mmoles) in 15 ml of dioxane was added dropwise and the reaction mixture was stirred at room temperature for two days. The solvent was removed and the residue was partitioned between water and methylene chloride. The methylene chloride layer was washed with water, dried over sodium sulfate and the solvent was removed on a rotavapor to yield a dark brown oil which was used directly for the next step.

A solution of the aforementioned oil and pyridinium *p*-toluenesulfonate (1.28 g, 5.10 mmoles) in 42 ml of dioxane-water 6:1 was refluxed for 16 hours. The solvent was removed *in vacuo* and the residue was partitioned between water and methylene chloride. The methylene chloride layer was washed with water, followed by brine and after drying (sodium sulfate), the solvent was removed to yield a yellow oil. The oil was purified by chromatography on silica gel and eluted with hexane-ethyl acetate 80:20 to give 330 mg (34%) of 2.5:1 mixture of 3-phenyl and 5-phenylisoxazoles **10** and **11**; pmr: δ 8.42 (d, J = 1.50 Hz, *H*-5 isoxazole), 8.26 (d, J = 1.70 Hz, *H*-3 isoxazole), 7.80-7.60 (m, Ar *H*), 7.60-7.20 (m, Ar *H*), 6.64 (d, J = 1.50 Hz, *H*-4 isoxazole), 6.49 (d, J = 1.70 Hz, *H*-4 isoxazole).

3-Phenylisoxazole (**10**).

3-Phenylisoxazole was prepared by the literature procedure [8] from benzaldoxime and vinyl acetate. The crude product was purified by bulb-to-bulb distillation (bath temperature 75° at 1.0 mm, lit [8] 89-90° at 2.0 mm); pmr: δ 8.46 (1H, J = 1.6 Hz, *H*-5 isoxazole), 8.00-7.70 (m, 2H, Ar *H*), 7.70-7.30 (m, 3H, Ar *H*), 6.67, (d, 1H, J = 1.6 Hz, *H*-4 isoxazole).

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REFERENCES AND NOTES

[1] N. K. Kochetkov and S. D. Sokolov in Advances in Heterocyclic Chemistry, Vol **2**, A. R. Katritzky, A. J. Boultin and J. M. Lagowski, eds, Academic Press, New York, New York, 1963, pp 365-422.

[2] S. S. Lang, Jr. and Y.-i. Lin, in Comprehensive Heterocyclic Chemistry, Vol **6**, K. T. Potts, ed, Pergamon Press, Oxford, 1984, pp 1-130.

[3] N. K. Kochetkov and E. D. Khomutova, *Zh. Obshch. Khim.*, **30**, 954 (1960).

[4] R. F. Abdulla and R. S. Brinkmeyer, *Tetrahedron*, **35**, 1675 (1979).

[5] S. Hünig and G. Wehner, *Synthesis*, 180 (1975).

[6] N. K. Kochetkov, E. E. Nifant'ev and A. N. Nesmeyanov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 949 (1957).

[7] T. Hosokawa, T. Ohta and S. Murahashi, *J. Chem. Soc., Chem., Commun.*, 848 (1983).

[8] R. Paul and S. Tchelitcheff, *Bull. Soc. Chim. France*, 2215 (1962).

[9] J. Castells and A. Colombo, *J. Chem. Soc., Chem. Commun.*, 1062 (1969).

[10] Y.-i. Lin and S. A. Lang, Jr., *J. Heterocyclic Chem.*, **14**, 345 (1977).

[11] A. Bargagna, F. Evangelisti and P. Schenone, *J. Heterocyclic Chem.*, **16**, 93 (1979).