An Unusual Oxazole Formation

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The reaction of 2-propargyloxybenzamide with strong base has been shown to lead to formation of an oxazole and not a benzoxazepinone as reported. The structure has been confirmed by synthesis.

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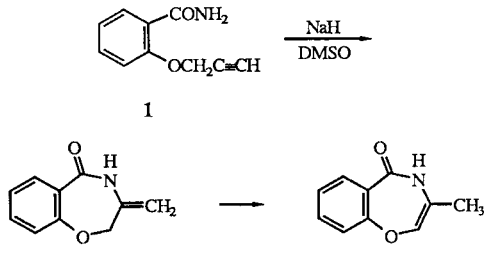
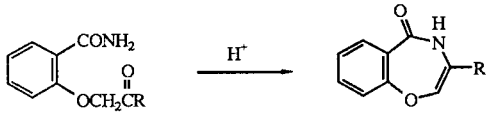
For subsequent chemical transformations we required the benzoxazepinone **3a** reported [1] as being prepared according to Scheme I. It was stated that **1** was converted to **2** which then isomerized to **3a**. Two compounds were isolated and characterized from spectral data.

Scheme I



We adopted the more convenient method of Schenker [2] which had been used to prepare the corresponding 3-phenyl analog **3b** (Scheme II).

Scheme II



4a, R = CH_3
b, R = C_6H_5

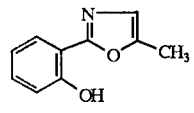
3a, R = CH_3
b, R = C_6H_5

Thus, refluxing **4a** with toluenesulfonic acid in toluene gave **3a** in good yield. However, **3a** as prepared by Scheme I was reported to have a melting point of 44-45° [1]; our sample had a melting point of 161-163°. Spectral data for the two compounds were quite different but an exchangeable proton and an allylic methyl group were indicated for both. The NOE experiments support the benzoxazepinone structure for **3a** as prepared by Scheme II. When the methyl group was irradiated an NOE was observed to both the exchangeable proton and the vinyl proton indicating a spatial proximity consistent with this structure.

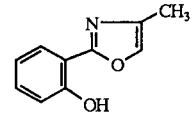
In order to ascertain the identity of the compound obtained by Scheme I, we prepared **1** and subjected it to the reported [1] conditions (sodium hydride-dimethyl sulfoxide, room temperature) and isolated two substances with physical and spectral properties agreeing with those described. Neither was **3a** as prepared according to Scheme II. Our spectral studies, including NOE experiments, support the structural assignment for **2**.

Results and Discussion.

The compound reported [1] to be **3a** gave a positive ferric chloride test for phenols and, in consideration of the analytical and spectral data, was therefore suspected to be oxazole **5** or **6**.



5



6

Pathways which could lead to these oxazoles are outlined in Scheme III.

Treatment of *N*-propargylamides with basic reagents has been shown to produce 5-methyloxazoles [3]. An allene is a likely intermediate [3,4].

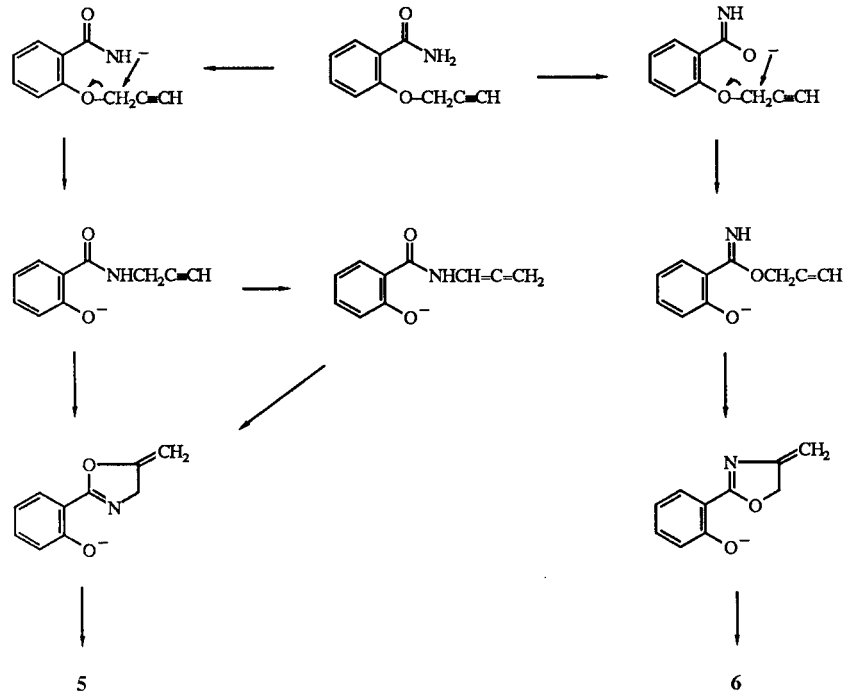
An acylazirene has been suggested as an intermediate in the photolytic rearrangement of 2,5-diphenyloxazole to 2,4-diphenyloxazole [5], but is unlikely in this case.

The nmr spectral studies indicated the substance isolated *via* Scheme I and reported to be **3a** was more likely oxazole **5**. Thus in the ^{13}C NMR spectrum, peaks were observed at 121.9 and 147.7 ppm, assigned to C-4 and C-5, respectively. Bogdanov *et al.* [6] report the respective carbon absorptions in 2,5-dimethyloxazole at 123.3 and 148.6 ppm; while in 2,4-dimethyloxazole they appear at 137.2 and 134.5 ppm.

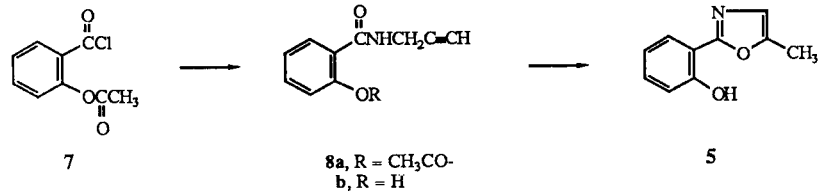
In order to 1) obtain an authentic sample of **5** and 2) ascertain the likelihood of an *N*-propargylamide as an intermediate in the conversion of **1** to **5**, we carried out the sequence of reactions depicted in Scheme IV.

Treatment of **8b**, obtained by hydrolysis of **8a**, with sodium hydride in dimethyl sulfoxide did indeed induce the conversion producing a compound with the same chemical and physical properties claimed for **3a** [1]. However, whereas **1** is rapidly converted to **5** at room temperature, only trace amounts of **5** are formed from **8b** under

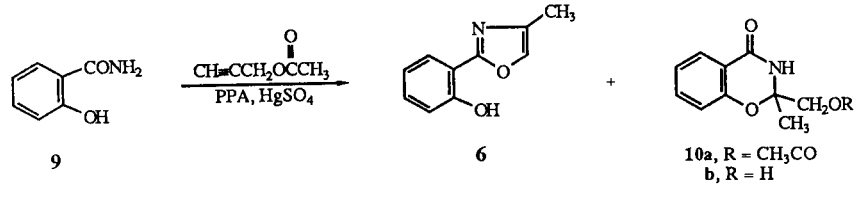
Scheme III



Scheme IV



Scheme V



these conditions and warming is necessary to complete the reaction. Thus, the actual mechanism remains undefined.

To assure ourselves of the absence of the isomeric oxazole, we prepared **6** by the method of Tramier [7], which involves heating an amide and propargyl acetate in polyphosphoric acid containing mercuric sulfate (Scheme V). Oxazole **6** may arise *via* imino ester formations [8,9].

In addition to the desired **6** we isolated benzoxazinones **10a** and **10b**. These compounds are formally condensation products of **9** and hydroxyacetone or its acetate [10,11], which could arise by acid catalyzed hydration of the acetylenic bond of propargyl acetate [12]. As hydroxy ketones can condense with amides to form oxazoles [12-14] it is also possible that a single intermediate generates both the oxazole and benzoxazinones in Scheme V.

EXPERIMENTAL

Melting points were determined in open capillaries on a Thomas Hoover apparatus and arc uncorrected. Nuclear magnetic resonance spectra were recorded on a Varian VXR 300 spectrometer. Chemical shifts are recorded in parts per million from tetramethylsilane as an internal standard. Infrared spectra

were recorded on a Perkin Elmer Model 1800 FT IR spectrometer. The spectra were obtained as potassium bromide pellets. Ultraviolet spectra were recorded on a Perkin Elmer Model Lambda 4C spectrometer in ethanol. Mass spectra were recorded on a Finnegan MAT Model 4600.

2-(2-Oxopropoxy)benzamide (**4a**).

A mixture of 137 g (1 *M*) of salicylamide, 150 g (1.1 *M*) of potassium carbonate and 1 ℓ of dimethyl sulfoxide was heated to 55° and 106 g (1.15 moles) of freshly distilled chloroacetone was added dropwise at such a rate that the internal temperature was maintained at about 55° without external heating. After addition was complete, this temperature was maintained by means of an oil bath for 5 hours. The mixture was then poured into 3.5 ℓ of cold water, seeded, and allowed to stand whereupon precipitation slowly occurred. The solids were filtered and dried to give 156 g (80%) mp 170-173°. A sample recrystallized from acetonitrile had mp 172-174°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.18 (s, 3H), 5.03 (s, 2H), 7.03-7.09 (m, 2H), 7.43-7.50 (m, 1H), 7.65 (broad s, 1H, exchangeable), 7.89-7.93 (m, 1H), 8.14 (broad s, 1H exchangeable); ^{13}C nmr (dimethyl sulfoxide-d_6): 26.0, 72.9, 113.2, 121.0, 122.2, 131.2, 155.8, 165.8, 203.3 ppm; ir: 3392, 1729 (C=O), 1668 (C=O) cm^{-1}.

Anal. Calcd. for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.74; N, 7.25. Found: C, 62.23; H, 5.7; N, 7.11.

3-Methyl-1,4-Benzoxazepin-5(4*H*)-one (**3a**).

A mixture of 145 g (0.74 mole) of **4a**, 2.2 g (0.01 mole) of *p*-toluenesulfonic acid monohydrate and 2.6 ℓ of toluene was refluxed with a water separator for 3.5 hours. The hot mixture was filtered through Celite and refrigerated to give 98 g (75%) mp 157-161°. A sample recrystallized from ethyl acetate had mp 161-163°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.69 (d, 3H, J = 1.1 Hz), 6.25 (broad s, 1H), 7.05 (d, 1H, J = 8.2 Hz), 7.24 (t, 1H, J = 7.6 Hz), 7.51-7.56 (m, 1H), 7.73 (dd, 1H, J = 7.8, 1.7 Hz), 9.39 (broad s, 0.9H, exchangeable); ^{13}C nmr (dimethyl sulfoxide-d_6): 15.1, 120.0, 124.5, 124.7, 126.2, 131.5, 134.0, 160.2, 166.4 ppm; ir: 1646 (C=O) cm^{-1}; uv: λ max 272 nm (ε 3000); ms: (EI @ 70 EV) m/e 175 (M$^+$).

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.44, H, 5.21; N, 7.72.

2-Acetyloxy-*N*-(2-propynyl)benzamide (**8a**).

A solution of 6.38 g (0.12 mole) of propargylamine in 75 ml of methylene chloride was stirred in an ice bath and 11.5 g (0.06 mole) of 2-acetyloxybenzoyl chloride [15] in 25 ml of methylene chloride was added dropwise. After 0.5 hour, the precipitated solids were filtered and rinsed with methylene chloride. The solvent was removed from the combined filtrates and the solid residue was heated in cyclohexane. Decanting from insoluble material and cooling gave 9.1 g (72%) mp 80-87°. A sample recrystallized from cyclohexane had mp 86-88°; ^{1}H nmr (deuteriochloroform): 2.29 (t, 1H, J = 2.6 Hz), 2.37 (s, 3H), 4.22 (dd, 2H, J = 5.2, 2.6 Hz), 6.53 (broad s, 1H, exchangable), 7.13 (dd, 1H, J = 8.1, 1.2 Hz), 7.32 (ddd, 1H, J = 7.6, 7.6, 1.2 Hz), 7.46-7.52 (m, 1H), 7.82 (dd, 1H, J = 7.8, 1.7 Hz); ir: 2116, 1770 (C=O), 1637 (C=O) cm^{-1}.

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.11; N, 6.45. Found: C, 66.26; H, 5.10; N, 6.31.

2-Hydroxy-*N*-(2-propynyl)benzamide (**8b**).

A mixture of 7.8 g (0.036 mole) of **8a**, 15 ml of ethanol and 150 ml of water containing 2.1 g of sodium hydroxide was stirred at room temperature for 10 minutes. After filtering through Celite, the filtrate was acidified with cold dilute hydrochloric acid. The solids (5.6 g) which precipitated were chromatographed on silica gel and the product eluted with chloroform. Recrystallization from cyclohexane gave 4.6 g (73%), mp 97-99°; ^{1}H nmr (deuteriochloroform): δ 2.32 (t, 1H, J = 2.6 Hz), 4.25 (dd, 2H, J = 5.2, 2.6 Hz), 6.51 (broad s, 1H, exchangeable), 6.82-7.45 (m, 4H), 12.01 (s, 0.9H, exchangeable); ^{13}C nmr (deuteriochloroform): 29.4, 72.4, 78.8, 113.7, 118.7, 118.8, 125.4, 134.6, 161.5, 169.7 ppm; ir: 2122, 1644 (C=O) cm^{-1}.

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.53; H, 5.22; N, 7.94.

2-(5-Methyl-2-oxazolyl)phenol (**5**).

A mixture of 0.62 g (150 mmoles) of 60% sodium hydride/oil suspension and 15 ml of dimethyl sulfoxide was heated in an oil bath at 55° until a clear solution formed. The solution was cooled to room temperature and 1.31 g (75 mmoles) of **8b** was added. After 2 hours at room temperature, thin layer chromatography indicated only a trace amount of **5**. On heating to 55° the reaction was complete in 0.5 hour. After cooling, the mixture was poured into dilute ammonium chloride and the product extracted into cyclohexane. The solvent was removed, the residue dissolved in a small amount of pentane and the solution refrigerated. The precipitated solids were filtered to give 0.92 g (70%), mp 43-45°. Sublimation at 60°/0.2 mm did not change the mp; ^{1}H nmr (deuteriochloroform): δ 2.22 (d, 3H, J = 1.3 Hz), 6.93 (ddd, 1H, J = 7.8, 7.4, 1.2 Hz), 7.05 (dd, 1H, J = 8.3, 1.2 Hz), 7.05 (dd, 1H, J = 8.3, 1.2 Hz), 7.33 (ddd, 1H, J = 8.3, 7.3, 1.7 Hz), 7.38 (q, 1H, J = 1.3 Hz), 7.79 (dd, 1H, J = 7.8, 1.6 Hz), 11.30 (s, 1H, exchangeable); ^{13}C nmr (deuteriochloroform): 10.8, 111.3, 117.0, 119.2, 125.5, 132.7, 147.7, 157.0, 160.5 ppm; ir: 3422, 1626, 1588, 1488, 1256, 1134, 1006, 832, 754, 720 cm^{-1}; uv: λ max 266 nm (ε 14,200), 278 nm (ε 12,000), 307 nm (ε 9700); ms: (EI @ 70 EV) m/e 175 (M$^+$), (CI-CH_4) m/e 176 (MH$^+$).

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.77; H, 5.26; N, 7.90.

2-(4-Methyl-2-oxazolyl)phenol (**6**).

A mixture of 13.7 g (0.1 mole) of salicylamide, 10.4 g (0.106 mole) of propargyl acetate [16], 0.5 g trichloroacetic acid and 20 g of polyphosphoric acid was heated at 90° in an oil bath and 2.3 g of mercuric sulfate was added in small portions. The temperature was raised to 120° for 0.5 hour, the reaction mixture then cooled and decomposed with cold water. Products were extracted into ethyl acetate and the solvent removed from the extracts. The residue was dissolved in toluene and allowed to stand at room temperature. The solids which formed on standing overnight were filtered (see below).

The toluene filtrate was applied to a silica gel column and elution carried out with toluene to give 2.28 g (13%) of an oil which solidified. Recrystallization from pentane and sublimation at 60°/0.2 mm gave 1.73 g of **6**, mp 52-54°; ^{1}H nmr (deuteriochloroform): δ 2.40 (d, 3H, J = 1.3 Hz), 6.83 (q, 1H, J = 1.3 H), 6.93 (ddd, 1H, J = 7.8, 7.2, 1.2 Hz), 7.05 (dd, 1H, J = 8.3, 1.2 Hz), 7.33 (ddd, 1H, J = 7.3, 8.3, 1.7 Hz), 7.79 (dd, 1H, J = 7.8, 1.7 Hz), 11.28 (s, 1H, exchangeable); ^{13}C nmr (deuteriochloroform): 11.3, 111.3, 117.1, 119.3, 125.8, 132.1, 133.0, 135.9, 157.2, 161.0 ppm;

ir: 3247, 1651, 1596, 1488, 1303, 1256, 1135, 1006, 832, 753, 720 cm^{-1}; uv: λ max 265 nm (ε 15,200), 278 nm (ε 13,700), 307 nm (ε 10,600); ms: (EI @ 70 EV) m/e 175 (M^+), (CI-CH_3) m/e 176 (MH^+).

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.34; H, 5.18; N, 7.85.

2-Acetyloxy-2,3-dihydro-2-methyl-4*H*-1,3-benzoxazin-4-one (**10a**).

Further elution of the above column with ether gave an oil which was purified by Kugelrohr distillation at 145-150°/0.2 mm and recrystallization from cyclohexane to give 2.44 g (10%), mp 83-85°; ^1H nmr (deuteriochloroform): δ 1.70 (s, 3H), 2.02 (s, 3H), 4.26 (s, 2H), 6.91 (d, 1H, J = 8.4 Hz), 7.03-7.10 (m, 1H, exchangeable); ^{13}C nmr (deuteriochloroform): 20.6, 23.9, 66.6, 87.1, 116.6, 116.9, 122.2, 127.6, 134.8, 155.8, 162.7, 170.3 ppm; ir: 1746 (C=O), 1682 (C=O) cm^{-1}; ms: (EI @ 70 EV) m/e 235 (M^+).

Anal. Calcd. for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.25; H, 5.60; N, 5.87.

2,3-Dihydro-2-hydroxymethyl-2-methyl-4*H*-1,3-benzoxazin-4-one (**10b**).

The solids which had precipitated from toluene (see above) were recrystallized from toluene to give 1.27 g (7%), mp 177-180°. A sample recrystallized from acetonitrile had mp 178-180°; ^1H nmr (dimethyl sulfoxide-d_6): 1.48 (s, 3H), 3.37 (dd, 1H, J = 11.6, 5.9 Hz), 3.54 (dd, 1H, J = 11.6, 5.9 Hz), 5.22 (t, 1H, J = 6.1 Hz, exchangeable), 6.94 (dd, 1H, J = 8.3 Hz), 7.05 (td, 1H, J = 7.5, 0.9 Hz), 7.44-7.50 (m, 1H), 7.72 (dd, 1H, J = 7.7, 1.7 Hz), 8.50 (s, 1H, exchangeable); ^{13}C nmr (dimethyl sulfoxide-d_6): 22.8, 65.1, 89.1, 116.7, 117.2, 121.4, 126.8, 134.2, 155.5, 161.0 ppm; ir: 3420, 1660 (C=O) cm^{-1}; ms: (EI @ 70 EV) m/e 193 (M^+), (CI-CH_4) m/e 194 (MH^+).

Anal. Calcd. for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.74; N, 7.25. Found: C, 62.11; H, 5.78; N, 7.39.

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