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On the Synthesis of 6-Methoxy-2-benzoxazolinone[1]

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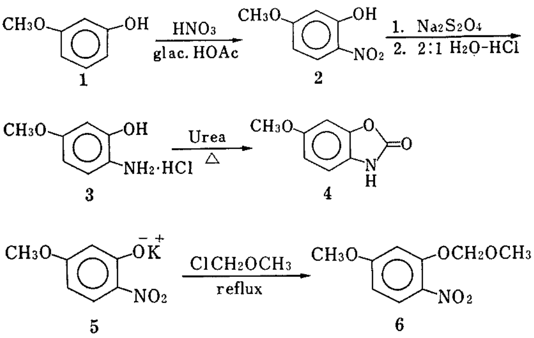
6-Methoxy-2-benzoxazolinone has been synthesized by a simplified, improved procedure, the formation and reduction of 5-methoxy-2-nitrophenol and subsequent fusion of the corresponding amine hydrochloride with urea. In related work, 4-methoxy-2-(methoxymethoxy)-nitrobenzene was prepared.

6-Methoxy-2-benzoxazolinone (MBOA) (**4**) is obtained from the breakdown of 2,4-dihydroxy-7-methoxy-2*H*-1,4-benzoxazin-3(4*H*)-one (DIMBOA) in aqueous solution.[3,4] DIMBOA occurs at its 2-*O*-*β*-D-glucopyranoside in various cereal plants, including corn and wheat, and has been studied in relation to disease and insect resistance of these plants.[4~6]

Allen and Laird[7] reported a preparation of MBOA (overall yield ~17%), which commenced with conversion of 3-methoxyphenol to 5-methoxy-2-nitrosophenol in 87~93% yield. The synthesis continued with reduction of the nitroso compound to the corresponding amine using sodium dithionite (hydrosulfite), formation of the amine hydrochloride using hydrogen chloride gas, and its subsequent fusion with urea. In their procedure, neutralization and ether extraction of the reducing solution, formation of the amine hydrochloride, and the subsequent fusion were accomplished in the dark or under photographic-safety lights. Separatory funnels and flasks were flushed with nitrogen, and water was avoided during preparation of the amine hydrochloride and the subsequent fusion.

For some time prior to Allen and Laird's report, MBOA had been prepared in this laboratory in 16% yield by a procedure not involving any of the above-mentioned precautions.[8] The method involves preparation of 5-methoxy-2-nitrophenol (**2**) in 26% yield and subsequent reduction to the corresponding amine. Urea fusion was effected with both the amine hydrochloride (**3**) and hydrogen acetate salts, prepared in aqueous media, under atmospheric conditions and normal light. Yields were not noticeably affected when the reduction of **2**, the formation of **3**, and the urea fusion were effected in the dark, under nitrogen gas, and in the absence of water. The yield of MBOA based on **2** was 61%. This synthesis produced a lower yield in the first step of the synthesis, but a higher yield in the subsequent steps, than did the synthesis of Allen and Laird.[7]



Use of the nitrosophenol was investigated but was rejected due to its extreme instability in light and the inability to produce it, even in the dark, in pure form except in low yields. Paper chromatography, using benzene as the irrigant, of newly prepared benzene solutions of nitrosophenol yielded chromatograms with one spot; after exposure of solutions to room lighting for three and five minutes, chromatograms exhibited two and three spots, respectively. The decomposition seemed to stabilize after three to four days, when four components were found on chromatograms, one being a small residue of the nitrosophenol. The nitrophenol (**2**) was stable in light and at room temperature.

The preparation of **2** from 3-methoxyphenol (**1**) was accomplished by a modification of the procedure of Hodgson and Clay,[9] who steam-distilled the nitration mixture. We found that **2** partially precipitated and that steam distillation of the precipitated **2** suspended in water reduced by approximately one-half the total time required to steam distill it. Proper ventilation during distillation of **2** is required because of its physiological effects.[10]

Fusion of **3** with urea was accomplished using various ratios of reagents to determine the optimum ratio for MBOA yield with respect to urea. Specifically, various amounts of **3** were fused with identical quantities of urea, 0.60 g. Urea was vaporized in the fusion, as was expected at the fusion temperature, 180°C, but evolution of carbon dioxide was not detected. As is common in small-quantity reactions, which are necessary for preparation of ^{14}C-labeled MBOA, the yields of MBOA fluctuated greatly between repetitions of the reaction. Over a range of mole/mole ratios of 0.5:1 to 1.09:1 of **3**:urea, no maximization of yield occurred; the system behaved somewhat like an equilibrium. When an apparent equilibrium constant (K_{ap}) for the fusion reaction was defined as

$$K_{\mathrm{ap}} = [\mathrm{MBOA}] / [\mathbf{3}]\,[\mathrm{urea}],$$

mole percent was used for the concentration unit, and values of mole percent were evaluated from the experimental weights of the reactants and product, a mean value of 130 (std. dev. 12.5) was calculated for the K_{ap} over the range of mole ratios studied. Hence, under the experimental conditions, since K_{ap} [urea]=constant=[MBOA]/[**3**], the yield of MBOA from urea cannot be maximized by increasing the quantity of **3** used within practical limits. The largest yield was obtained and the variation in the yield of the fusion reaction seemed to become less as the **3**: urea ratios became larger, so a 1.09: 1.0 mole/mole (1.90 g: 0.60 g) ratio of reactants was chosen for small-quantity fusions, for which the yield with respect to urea averaged 27%.

In related work, the 1-methoxymethoxy derivative (**6**) of **2** was prepared by adapting the method of Honkanen and Virtanen[11] for the preparation of 2-(methoxymethoxy)-nitrobenzene. The low-melting solid, **6**, a new compound, decomposes to **2** upon standing at room temperature for two weeks; the compound is stable, however, when stored in the dark at −20°C. The acetal is easily removed by hydrolysis in acidic (HCl) methanol.

EXPERIMENTAL

Melting points were determined in open capillary tubes, using a calibrated Fisher Johns Melting Point Apparatus, but were not corrected. Mass spectra were obtained using a CEC Model 21–104 instrument; IR spectra were obtained in a Beckman IR–10 instrument using KBr pellets. Elemental analyses were performed by the Alfred Bernhardt Microanalytical Laboratory, Engelskirchen, West Germany, and by Galbraith Laboratories, Inc., Knoxville, Tennessee.

5-Methoxy-2-nitrophenol (2)

3-Methoxyphenol (**1**) (51.0 g, 0.411 mole) was dissolved in glacial acetic acid (51 g) and nitrated at 0°C by the gradual addition of 35 ml (51 g, 0.81 mole) of nitric acid in 150 g of glacial acetic acid. The clear, brownish mixture reacted vigorously upon warming to room temperature and evolved nitrous oxide. The dark solution was allowed to stand overnight. Then the precipitated crystals were removed by filtration, suspended in water, and subsequently steam distilled in an apparatus placed in a hood (produced 13.6 g **2** in 4.5 hr). The filtrate was added and distillation was continued (produced 4.6 g **2** in 7.8 hr). The product (**2**) (18.2 g, 26%) crystallized from ethanol as yellow needles: mp 93~94°C [lit.[9] 95°C].

2-Amino-5-methoxyphenol hydrochloride (3)

To **2** (2.76 g, 0.016 mole) in 100 ml of water, solid anhydrous sodium dithionite (6.0 g, 0.034 mole) was added gradually with stirring. As the mixture was heated, an additional 6 g of the reducing agent was added. The suspension became a clear, yellow solution which, after cooling, was neutralized with solid sodium bicarbonate. The solution was then extracted with six, 80-ml portions of ether. Evaporation of the ether extract left a white, crystalline solid, which became colored red after 1~2 days in light. The white solid was identified as a primary amine by IR absorption at 3320 cm^{-1} and 3270 cm^{-1} (N–H stretch). The amine dissolved when treated with 30 ml of a 4 M hydrochloric acid solution and immediately formed a dark-purple solution. The formation of Wurster's salts$^{12)}$ reported by Allen and Laird$^{7)}$ was never observed after reduction of the nitro compound. The light-blue solid, the amine hydrochloride (**3**) (2.76 g, 94%), was used without purification.

6-Methoxy-2-benzoxazolinone (**4**)

Fusion of the amine hydrochloride (2.76g, 0.016 mole) with urea (2.76 g, 0.046 mole) was done according to the procedure of Smissman, LaPidus, and Beck.$^{13)}$ The product was extracted from the fusion residue with eight, 20 ml portions of 4 M hydrochloric acid solution. The residue was triturated with a glass stirring rod with each addition of the dilute acid. The purple, acidic solution was extracted with ten, 50-ml portions of ether. After evaporation of the ether, the resulting residue (**4**) was extracted in the evaporation flask into six, 25 ml portions of hot water (~95°C). The combined hot-water extracts were filtered to remove any insoluble material and the partially purified product precipitated (1.64 g, 63% based on **3**, 16% based on **1**) and was then recrystallized first from water, then from methylene chloride as slightly reddish needles: mp 153~154°C [lit.$^{13)}$ mp 154~155°C]; *Anal.* Calcd. for $C_8H_7NO_3$: C, 58.18; H, 4.21; N, 8.48; O, 29.06. Found: C, 57.83; H, 4.19; N, 8.61; O, 29.22. Mass spectrum M^+ 165 (expected 165).

The acetyl derivative of MBOA was prepared: mp 148~150°C [lit.$^{14)}$ mp 150°C]; mass spectrum M^+ 207 (expected 207).

4-Methoxy-2-(methoxymethoxy)nitrobenzene (**6**)

Potassium 5-methoxy-2-nitrophenolate (**5**) was prepared by dissolving 4.0 g (0.024 mole) of **2** in ethanol and treating it with 1.4 g (0.022 mole) of potassium hydroxide pellets (86% purity) which had been dissolved in a minimum amount of water. Upon evaporation of the bright-orange solution to dryness, orange flakes of **5** formed. The potassium salt (3.0 g, 0.014 mole, dried 18 hr at 50°C) was suspended in 100 ml of benzene (dried with anhydrous sodium sulfate), and 1.0 ml (0.013 mole) of chloromethyl methyl ether was added. After it was refluxed for 6.5 hr, the mixture was filtered, and filtrate was extracted with four portions of dilute, aqueous sodium hydroxide. The benzene solution was dried with anhydrous sodium sulfate and evaporated, leaving a yellow oil which solidified overnight. The crude product was dissolved in a minimum quantity of ethanol and precipitated by addition of ligroin (60~90°C petroleum-distillate fraction). Then it was recrystallized twice from ethanol to yield a cream-colored product which gave only one spot by TLC (2.69 g, 53%); mp 47.5~48.0°C: MS *m/e*: 213 (M^+), Calcd. for $C_9H_{11}NO_5$ 213. *Anal.* Calcd. for $C_9H_{11}NO_5$: C, 50.70; H, 5.20; N, 6.57; O, 37.52. Found: C, 50.90; H, 5.38; N, 6.27; O, 37.36.

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