Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Improved Procedures for the Preparation of 2-Nitro-5-methoxyphenol and 6-Methoxy-2(3H)-benzoxazolone from 3-Methoxyphenol

Robert J. Maleski [a]

[a] Tennessee Eastman Division, Eastman Chemicals Company , Kingsport, TN 37662-5231

Published online: 23 Sep 2006.

To cite this article: Robert J. Maleski (1993) Improved Procedures for the Preparation of 2-Nitro-5-methoxyphenol and 6-Methoxy-2(3H)-benzoxazolone from 3-Methoxyphenol, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 23:3, 343-348, DOI: 10.1080/00397919308009786

To link to this article: http://dx.doi.org/10.1080/00397919308009786

SYNTHETIC COMMUNICATIONS, 23(3), 343-348 (1993)

IMPROVED PROCEDURES FOR THE PREPARATION OF 2-NITRO-5-METHOXYPHENOL AND 6-METHOXY-2(3H)-BENZOXAZOLONE FROM 3-METHOXYPHENOL

Robert J. Maleski

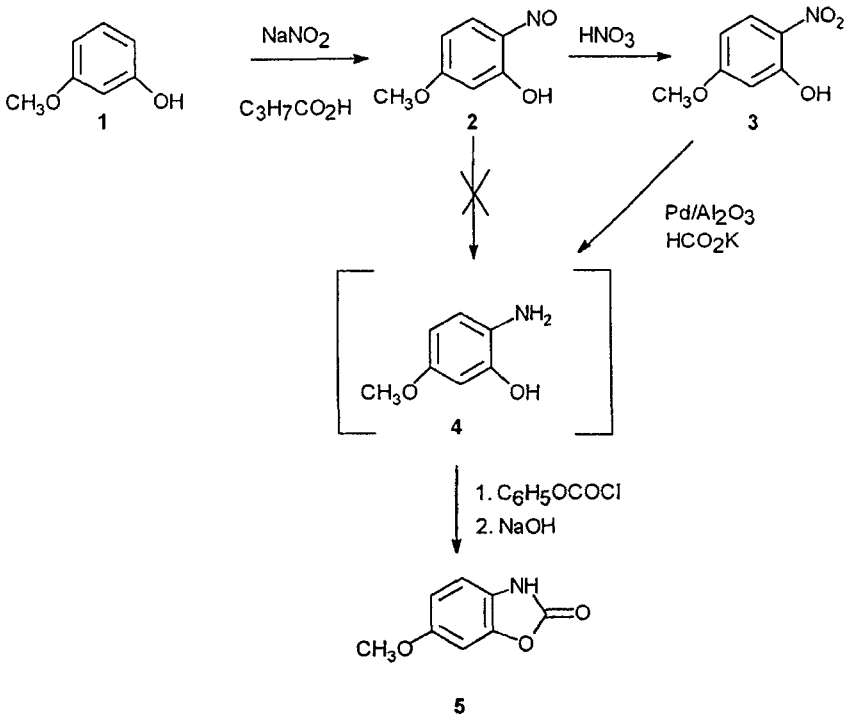
Tennessee Eastman Division, Eastman Chemicals Company, Kingsport, TN 37662-5231

ABSTRACT 3-Methoxyphenol can be selectively nitrosated in propionic acid, and the resulting slurry of 2-nitroso-5-methoxyphenol can be cleanly oxidized by nitric acid to the nitro compound. An improved procedure for the preparation of 6-Methoxy-2(3H)-benzoxazolone from this nitro compound is also presented.

Several excellent procedures[1-3] for converting 2-amino-5-methoxyphenol (**4**) to 6-methoxy-2(3H)-benzoxazolone (**5**), a compound of significant agricultural interest,[4] have recently been published. Amine **4** should be easily accessible from 3-methoxyphenol via the nitro precursor **3**, but convenient procedures for the preparation of **3**, suitable for multi-gram scale-up, have not been disclosed.

Direct nitration of **1** results in so many oxidation products and regioisomers that **3** can only be isolated (in 25-35% yield) by steam distillation.[5,6] A report[7] of a successful direct nitration could not be duplicated in this laboratory.

REACTION SCHEME



Various remedies to the problems with direct nitration have been published, but neither protection of the hydroxyl group followed by nitration and deprotection,[8] nor sulfonation followed by nitration,[9] nor continuous extraction of the product during the nitration[10] offer any substantial advantage.

Nitrosation of **1** followed by oxidation of **2** is operationally simple, and two such procedures[5,11] have been published. The first of these still involves steam distillation of a low yield of **3,** and the second (claimed to be a high yield process) failed to provide any usable product in this laboratory. In both cases the fundamental problem is the nitrosation step, which produces 20-30 mole % of the 4-nitroso isomer along with many highly colored impurities.[12] Addition of nitric acid to such a gross mixture results

in so many by-products that extraordinary measures must be taken to purify the product.

In fact, high purity **2** can be obtained in 65% yield by simply using propionic acid as both the solvent and the source of acidity needed to form nitrous acid. When water is limited only to the amount needed to dissolve the sodium nitrite, the selectivity of the nitrosation appears (TLC) to be dramatically improved, and a simple filtration is all that is needed to recover pure product. In contrast to previous reports,[11,12b] **2** is stable for months as a dry solid, even when stored without protection from oxygen and light.

Isolated **2** could not be cleanly converted to **4** by transfer hydrogenation[13] so oxidation of **2** to **3** was necessary. This can be done without isoation of **2**: simply adding 2 equivalents of nitric acid to the reaction slurry of **2** results in clean and rapid formation of **3**. The procedure has been carried out on a 0.4 mole scale in 57% overall yield based on **1**. The entire operation can be carried out in a few hours. Isolated **3** was extremely pure, as evidenced by its sharp melting point and clean ^{1}H NMR spectrum: the aqueous propionic acid from which the product crystallizes and with which it is washed is an excellent solvent for the reaction by-products.

The above procedures are especially well-suited for large scale preparations of **2** and **3** and are presented in detail below. Also included is an improved hydrogen transfer procedure for the preparation of **5** from **3**. This procedure, which avoids the isolation of the air-sensitive **4**, uses potassium formate as the hydrogen donor. This change eliminates the time-consuming evaporation of solvent and ammonia required in the ammonium-formate based procedure.[3]

EXPERIMENTAL

2-Nitroso-5-Methoxyphenol (2) A solution of 12.4 g (0.1 mole) of 3-methoxyphenol (Aldrich) in 100 mL of propionic acid was cooled to -5 to

0° and a solution of 6.9 g (0.1 mole) of sodium nitrite in 15 mL of water was added dropwise over about 0.5 hr, holding the temperature at -5 to 0°. The resulting slurry was stirred 0.5 hr, and 60 mL of water was added dropwise below 5°. The product was filtered and washed with 60 mL of 50% aqueous propionic acid, and then with a large volume of water to give 10.1 g (66%) of product, mp 153-154 (lit[12] mp 154°); IR (KBr): 1041, 1249, 1402, 3440 cm^{-1}; MS: m/z 153 (M^+, 100), 136 (82) , 108 (33); ^1H NMR (360 MHz, DMSO) : δ 3.82 (s, 3H), 6.11 (bs, 1H, H-6), 6.42 (dd, 1H, J=2.5,10 Hz, H-4), 7.06 (d, 1H, J=10 Hz, H-3).

2-Nitro-5-Methoxyphenol (3) A solution of 37.2 g (0.3 mole) of 3-methoxyphenol (Aldrich) in 300 mL of propionic acid was treated at -5 to 0° with a solution of 21 g (0.304 mol) of sodium nitrite dissolved in 50 mL of water. After stirring for 1hr at -5 to 0°, 37.9 g (0.6 mole) of 98% nitric acid was added at this temperature. The addition was accompanied by the evolution of large amounts of nitrogen oxide gases. The slurry was stirred for 1 hr below 0°, and was warmed to room temperature over 2 hr. Water (250 mL) was added dropwise at room temperature, and the solid was filtered and washed with 300 mL of 50% aqueous propionic acid to give 29.4 g (58%) of pure product, mp 92-93° (lit[5] mp 94-95°). No impurities were detected by ^1H NMR or by TLC; IR (KBr): 1283, 1591, 1622 cm^{-1}; MS: m/z 169 (M^+, 100), 139 (39), 111(41); ^1H NMR (360 MHz, DMSO): δ 3.85 (s, 3H); 6.60 (dd, 1H, J=2.7, 9.3 Hz, H-4); 6.64 (d, 1H, J= 2.7 Hz, H-6), 7.98 (d, 1H, J=9.3 Hz, H-3).

6-Methoxy-2(3) Benzoxazolone A solution of potassium formate was prepared in a nitrogen atmosphere by adding 6.28 g of 88% formic acid (0.12 mole) dissolved in 15 mL of water to 7.68 g of potassium hydroxide pellets (87% assay, 0.12 mole) dissolved in 60 mL of absolute alcohol. Catalyst (0.15 g of 5% palladium on charcoal) and 2-nitro-5-methoxyphenol (6.12 g, 0.04 mole) were then added and the resulting slurry was warmed to 70° and held for 3 hr. Analysis by TLC (Silica Gel 60 plates, 40% ethyl acetate in heptane) indicated a complete reaction. The reaction mass was cooled to 25° and 40 mL of degassed water was then added followed by dropwise addition of 6.26 g (0.04 mole) of phenyl

chloroformate (FOAM) holding the temperature at 25-30° during the addition. The resulting slurry was stirred at 25° for 0.5 hr and treated with a solution of 1.6 g (0.04 mole) of sodium hydroxide dissolved in 30 mL of water. The solution was warmed to 45-50° and held for 1hr. The catalyst was removed by filtration through a pad of diatomaceous earth. The filter pad was washed with 20 mL of 50 % alcohol and the product was precipitated by the addition of 10 % HCl to a pH of 5-6. After filtration and water washing 5.26 g (80%) of product, mp 153-154° (lit[8] mp 153-154°) was obtained. All spectra were in accord with those previously reported[1]; no impurities were detected by NMR or TLC.

Acknowledgements: The author would like to thank C. E. Osborne for collecting the NMR spectra, S. M. Cline for collecting the mass spectra, Y. W. Alsmeyer for collecting the IR spectra, K. S. Chamberlin for helpful discussions, and Eastman Chemical Company for permission to publish this work.

REFERENCES:

1. Nachman, R. J., J. Heterocyclic Chem., 1982, 19, 1545.

2. Sicker, D., Synthesis, 1989, 875.

3. Maleski, R. J., Osborne, C. E., and Cline, S. M., J. Heterocyclic Chem., 1991, 28, 1937.

4. Sam, J. and Valentine, F. L., J. Pharm. Sci., 1969, 58, 1043.

5. Hodgson, H. H. and Dyson, R. J., J. Chem. Soc., 1929, 2777 .

6. Richey, J. D., Scism, A. J., Caskey, A. L., and BeMiller, J. N., Agric. Biol. Chem., 1975, 39, 683.

7. Kinugawa, J., Ochiai, M., and Yamamoto, H., Yakugaku Zasshi, 1959, 79, 931; C.A. 1960, 54, 497.

8. Smissman, E. E., LaPidus, J. B., and Beck, S. D., J. Org. Chem., 1957, 22, 220.

9. Hodgson, H. H. and Clay, J., J. Chem. Soc., 1935, 946.

10. Richey, J. D., Caskey, A. L., and BeMiller, J. N., Agric. Biol.Chem., 1976, 40, 2413.

11. Jahelka, J., Sterba,V., and Valter, K., Collect. Czech. Chem. Commun., 1973, 38, 877.

12. This is also true in the other published procedures for the preparation of **2**: a) Henrich, F. and Rhodius, O., Chem. Ber., 1902 35, 1475; b) Allen, E. H. and Laird, S. K., J. Org. Chem., 1971, 14, 2004.

13. Grieger, R. and Nestrick, T., Chem. Rev, 1974, 74, 567.

(Received in USA 18 August, 1992)