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A Facile Access to Substituted 2-Nitrosophenols and 2-Nitrophenols via Regioselective Nitrosation of Resorcinol Monoethers

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SYNTHETIC COMMUNICATIONS, 25(15), 2327-2335 (1995)

A FACILE ACCESS TO SUBSTITUTED 2-NITROSOPHENOLS AND 2-NITROPHENOLS *VIA* REGIOSELECTIVE NITROSATION OF RESORCINOL MONOETHERS

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ABSTRACT: Solid sodium nitrite in anhydrous propionic acid is an effective system for regioselective nitrosation of the subject compounds. High yields of pure 2-nitroso products are obtained rapidly and efficiently. Attack at the 4-position becomes competitive if water is present in the medium. The 5-alkoxy (but not the 3,5-dialkoxy)-2-nitrosphenols can be easily oxidized with nitric acid to yield the corresponding 2-nitro compounds.

Several 2-nitroso- and 2-nitrophenols are intermediates for syntheses of important industrial and natural products. Thus, we have described syntheses for 6-methoxybenzoxazolin-2(3*H*)-one (MBOA)[1,2] and 2,4-dihydroxy-7-methoxy-2*H*-1,4-benzoxazin-3(4*H*)-one (DIMBOA)[3,4] (both bioactive constituents of

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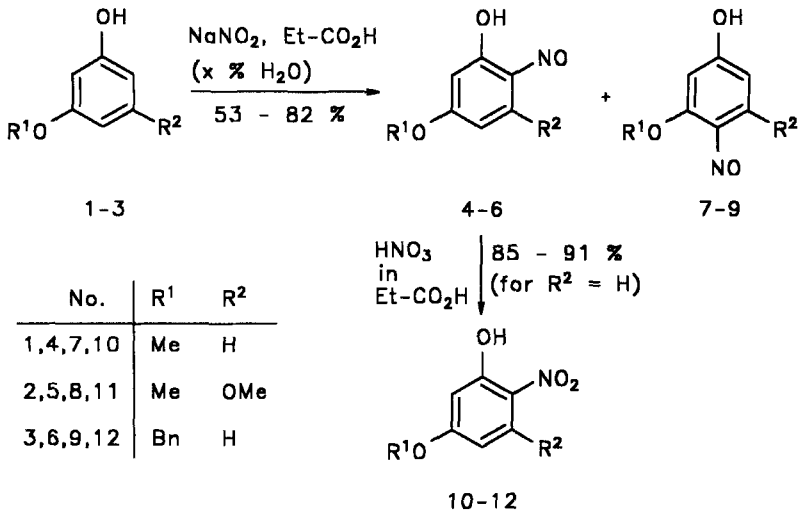
gramineous plants)[5,6] starting with 5-methoxy-2-nitrophenol **10**, and for the naturally occurring cyclic hydroxamic acid 2,4,7-trihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one (TRIBOA)[7] starting with 5-benzyloxy-2-nitrophenol **12**. In addition, a series of commercially important photochromic spiroindolines have been prepared[8] from 3,5-dimethoxy-2-nitrosophenol **5**. All of these syntheses have been hampered by the lack of a regioselective method for the introduction of the nitroso group (which can be oxidized to the nitro derivative if needed) into compounds **1-3**. For instance, in the synthesis of the commercial photochromic compounds, which requires pure **5**, conventional aqueous nitrosation of **2** produces a mixture of **5** and **8** in a ratio of 3:2[9] and special purification methods[10] are required.

Based upon an investigation of the conditions for the nitrosation reaction, we report here a new regioselective approach to these nitroso compounds. Recently, one of us has reported an improved synthesis of **10**[11] via nitrosation of **1** followed by nitric acid oxidation of the nitroso intermediate **4**. The method is entirely aqueous, and requires a recrystallization of **10** from methanol as a final step. It is now known that the success of this procedure relies not upon a selective nitrosation, but rather upon the selective removal of a reaction by-product during the purification step. Reinvestigation of this procedure showed that the nitrosation product consists of a 3:1 mixture of 5-methoxy-2-nitrosophenol **4** and its regioisomer 3-methoxy-4-nitrosophenol **7**. Nitric acid oxidation of this mixture gives a crude 4:1 mixture of **10** and 5-methoxy-2,4-dinitrophenol, from which a 60% yield of pure **10** is obtained after recrystallization. Hence, a nitration competitive with the oxidation, and not a double nitrosation as previously speculated[11], caused the formation of the dinitrophenol by-product.

On the other hand, one of us reported an efficient synthesis of **10**[12a] also starting with **1**, and also employing the nitrosation-oxidation strategy. In this case, propionic acid was used as the solvent for both the nitrosation and the oxidation, and a concentrated aqueous solution of sodium nitrite was used as the source of the nitrosating agent. This method proved to be surprisingly selective[12b] for the preparation of **4**. To further improve the regioselectivity in the nitrosation of resorcinol monoethers, a reexamination of the propionic acid-sodium nitrite system was undertaken.



No.	R^1	R^2
1,4,7,10	Me	H
2,5,8,11	Me	OMe
3,6,9,12	Bn	H

It quickly became obvious that the concentration of water plays a critical role in the success of the procedure. The experiments summarized in the Table were conducted by slowly adding solid sodium nitrite to **1-3** dissolved in solutions of propionic acid and water of varying concentrations. Clearly the water concentration should be minimized to achieve the highest level of regioselectivity in the preparation of **4-6**. To ensure anhydrous conditions, the reaction is best run in propionic acid which contains a small amount of propionic anhydride. It is a distinct advantage of this method that the entirely organic medium ensures complete dissolution of highly hydrophobic compounds like **3**, which could not be nitrosated at all in aqueous media due to its limited solubility.

The system of sodium nitrite in anhydrous propionic acid clearly exhibits unique nitrosating properties. The observed regioselectivity may be related to the apparent presence of an acyl nitrite whose *in situ* formation in solutions of sodium nitrite in anhydrous carboxylic acids is known.[13] Mesomeric structures of propionyl nitrite show the O-NO bond as a polarized covalent bond with the NO unit having a partially positive charge.[14] Our observations, therefore, could be a result of the weaker electrophilicity (and thus the improved selectivity) of propionyl nitrite compared with the free nitrosonium cation present in acidic aqueous solutions.

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Table. Nitrosation of **1-3** in Solutions of Propionic Acid and Water

Substrate	Solvent Composition		2-nitroso : 4-nitroso[a]		Yield[b]
	% H_2O	% Et-CO_2H	Before Isolation	After Isolation	
1	0.7	99.3[c]	93: 7	>99:<1	81
1	25	75	65:35	85:15	72
1	50	50	65:35	72:28	83
1	90	10	61:39	65:35	84
2	0.7	99.3[c]	>99:<1	>99.9:<0.1	82
2	25	75	70:30	75:25	85
2	50	50	60:40	62:38	89
3	0.7	99.3[c]	95:5	>99.9:<0.1	53

[a] All ratios of **4**:**7** and **5**:**8** were determined by HPLC using pure reference compounds[15] to determine response factors. Since the product precipitates during the reaction, the ratios prior to isolation may be inaccurate due to sampling errors. The ratio **6**:**9** was estimated by the ^1H NMR spectrum of the crude product indicating only traces of **9**. TLC proved the isolated, recystallized **6** to be pure.

[b] Yield of isolated products (sum of 2- and 4-nitroso isomers). For **4**+**7** and **5**+**8**, quantitative analysis was done by HPLC using pure reference compounds.[15]

[c] Propionic acid was used as received and contained 0.7 % water.

The pure 2-nitrosophenol derivatives **4** and **6** can be efficiently oxidized to the corresponding 2-nitrophenols **10** and **12** by means of two equivalents of fuming nitric acid in propionic acid, as previously shown.[12a] This method failed in the case of substrate **5**, for which over-nitration was competitive with oxidation of the nitroso group. Hence, 3,5-dimethoxy-2-nitrophenol **11** was not obtained.

The above results show that the addition of solid sodium nitrite to anhydrous propionic acid generates an effective system for the regioselective nitrosation of resorcinol monoethers to afford their 2-nitroso derivatives which, in the case of the simple unsubstituted monoethers, are easily oxidized to the 2-nitro analogues.

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EXPERIMENTAL

General. The starting materials **1** and **2**, all reagents, and all solvents were purchased (Aldrich) and were used as received. HPLC analysis was performed using a 15 cm x 4.6 cm Spheresorb 5 ODS (2) column, and an eluant composed of 25 % acetonitrile and 75 % water (v/v) containing 0.5 weight percent of phosphoric acid. Detector wavelength was set at 300 nm. IR spectra were measured on a Carl Zeiss Jena Specord M80 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Model Gemini-300 spectrometer at frequencies of 75.5 and 300.1 MHz. ^{13}C NMR chemical shifts were assigned using standard 2D NMR techniques. Mass spectra were obtained with a Varian MAT CH6 mass spectrometer at 70 eV (E. I ionization, source temperature 200 °C). Elemental analyses were performed on a Heraeus CHN-O-RAPID analyzer. Melting points were obtained on a Thomas Hoover apparatus in open capillary tubes, and are uncorrected.

3-Benzyloxyphenol (3)

A solution of 14.5 g (0.05 mole) of resorcinol dibenzylether[16] in acetic acid (250 ml) was hydrogenated in an Erlenmeyer flask fitted with a hydrogen side inlet over 10 % Pd/C (150 mg) at normal pressure at 25° C until 1120 ml of hydrogen had been taken up. The catalyst was filtered off and the solvent was removed *in vacuo*. The remaining oil was shaken with water (40 ml) and diethyl ether (30 ml). The ether phase was separated and the aqueous layer was again extracted with ether (40 ml). The combined organic extracts were washed with water (10 ml). **3** was then extracted as sodium salt from the ethereal solution with 10 % NaOH (5 x 10 ml). The combined alkaline extracts were neutralized, maintaining a temperature of 30° C in a water bath, by slow addition of powdered solid carbon dioxide until crude **3** separated as a pale brown oil, which was extracted with diethyl ether (3 x 20 ml). After removal of the solvent, distillation of the residual oil *in vacuo* yielded 8.1 g (81 %) of **3** as pale yellow oil (bp 140-141 °C/0.5 mmHg), which crystallized on standing (mp 49-50 °C; lit[17] mp 50-51 °C).

This new two step procedure for **3** by selective monodebenzylation of resorcinol dibenzylether obtainable from resorcinol in 85 % yield[16] proved to be superior to the preparation of **3** by monobenzylation of resorcinol (36 % yield only).

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General Procedure for the Synthesis of the 2-Nitrosophenol Derivatives 4-6

CAUTION! *Since propionyl nitrite, a thermally unstable material,*[13] *may be an intermediate in the following reactions, any scale-up work must involve a thorough understanding of the behaviour of the reaction mass to thermal or mechanical stresses.*

A solution of the corresponding resorcinol monoether **1-3** (0.04 mole) in propionic acid (50 ml) containing 1 weight percent of propionic anhydride was cooled to -5° C and was treated with 2.90g (0.042 mole) of sodium nitrite, which was added with stirring over 15-30 min, holding the temperature at -5 to 0° C. After 1 hr, 50 ml of water was added, and the mixture was filtered, washed well with water, and dried to give the 2-nitrosophenols **4-6**.

5-Methoxy-2-nitrosophenol (4)

Starting from 3-methoxyphenol **1** 4.94 g (81%) of **4**, mp 155-156 °C (lit[12a] mp 154 °C) were obtained. ^{1}H NMR has been reported;[12a]; ^{13}C NMR ($CDCl_3$): δ 56.8 (OCH_3), 101.0 (C-6), 118.2 (C-4), 135.9 (C-3), 151.4 (C-2), 170.4 (C-1), 171.9 (C-5). HPLC analysis indicated product of >99 % purity, with <0.5 % of the isomer **7**.

3,5-Dimethoxy-2-nitrosophenol (5)

Starting from 3,5-dimethoxyphenol **2** 6.0 g (82%) of **5**, mp 172-173 °C (lit[18] mp 175-176° C) were obtained; ^{1}H NMR (DMSO-d_6): δ 3.88 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 5.89 (d, 1H, J = 2.2 Hz, H-4), 5.99 (d, 1H, J = 2.2 Hz, H-6); ^{13}C NMR (DMSO-d_6): δ 56.5 (3-OCH_3), 56.9 (5-OCH_3), 94.3 (C-4), 95.2 (C-6), 144.7 (C-2), 159.6 (C-3), 174.0 (C-1), 174.9 (C-5). HPLC analysis indicated product of >99 % purity, with <0.1 % of the isomer **8**.

5-Benzyloxy-2-nitrosophenol (6)

Starting from 3-benzyloxyphenol **3** gave rise to a solid which after recrystallization yielded 4.78 g (53%) of **6** , mp 130-131° C (MeOH); IR (KBr): ν 1640, 1570, 1420, 1245, 1135 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 5.13 (s, 2H, CH_2), 6.17 (d, 1H, J = 2.4 Hz, H-6), 6.63 (dd, 1H, J = 9.6 Hz, J = 2.4 Hz, H-4), 7.41-7.52 (m, 5H, *phenyl*), 7.69 (d, 1H, J = 9.6 Hz, H-3); ^{13}C NMR ($CDCl_3$): δ 72.0 (CH_2), 102.1 (C-6), 118.4 (C-3), 128.3 (C-2′, C-6′), 129.2 (C-4′), 129.4 (C-3′, C-5′), 134.8 (C-

4), 135.9 (C-2), 136.0 (C-1′), 169.7 (C-1), 170.6 (C-5); ms (m/z): 229 (M^+, 15), 212 (27), 124 (39), 91 (100). *Anal.* Calcd. for $C_{13}H_{11}NO_3$: C, 68.12; H, 4.84; N, 6.11. Found: C, 67.91; H, 4.92; N, 6.07.

TLC analysis proved **6** after recrystallization to be pure.

3-Methoxy-4-nitrosophenol (7)

This compound, which appears to exists in DMSO as the keto-oxime tautomer, was prepared by nitrosodemethylation of 1,3-dimethoxybenzene by a published procedure.[15] The red solid was purified by multiple recrystallizations from water to a constant mp of 195-196 °C (lit[19] mp 236 °C). Quantitative analysis by ^1H NMR, using carefully purified 4-methoxyphenol as an internal standard, confirmed the purity of the sample. ^1H NMR (DMSO-d_6): δ 3.79 (s, 3H, OCH_3), 5.82 (d, 1H, J = 1.8 Hz, H-2), 6.27 (dd, 1 H, J = 1.8 Hz, J = 10.2 Hz, H-6), 7.60 (d, 1H, J = 10.2 Hz, H-5); ^{13}C NMR (DMSO-d_6): δ 56.1 (OCH_3), 104.3 (C-2), 123.0 (C-5), 129.8 (C-6), 145.1 (C-4), 163.1 (C-3), 187.6 (C-1).

3,5-Dimethoxy-4-nitrosophenol (8)

This compound, which also appears to exists in DMSO as the keto-oxime tautomer, was prepared by nitrosodemthylation of 1,3,5-trimethoxybenzene,[15] and was purified as above by multiple recrystallizations from 60% aqueous ethanol (v/v) to a constant mp of 223-224 °C (lit[18] mp 222 °C). ^1H NMR (DMSO-d_6): δ 3.72 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 5.62 (d, 1H, J = 1.7 Hz), 5.64 (d, 1H, J = 1.7 Hz); ^{13}C NMR (DMSO-d_6): δ 56.0 (OCH_3), 56.1 (OCH_3), 102.0 (C-2 or C-6), 103.3 (C-2 or C-6), 137.5 (C-4), 157.6 (C-3 or C-5), 161.1 (C-3 or C-5), 185.6 (C-1).

General Procedure for the Synthesis of the 2-Nitrophenol Derivatives 10 and 12

To a precooled (-12 °C) suspension of the corresponding 2-nitrosophenol **4** or **6** (0.025 mole) in propionic acid (40 ml) was added dropwise with stirring 3.15 g (0.05 mole) of 100% nitric acid at a rate maintaining the temperature below -5 °C. After 1 hr, water (40 ml) was slowly added. The solid is filtered off, washed by mixing it with ice-water (80 ml), and again filtered and dried. TLC showed the products **10** and **12** to be pure without recrystallization.

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5-Methoxy-2-nitrophenol (10)

Starting from **4**, 3.59 g (85%) of **10**, mp 94-95 °C (lit[11] mp 94-95°C), was obtained.

5-Benzyloxy-2-nitrophenol (12)

Starting from **6** afforded 5.58 g (91%) of **12**, mp 96-97° C. IR (KBr): ν 1620, 1590, 1530, 1270 cm^{-1}; ^1H NMR (DMSO-d_6): δ 5.19 (s, 2H, CH_2), 6.65 (dd, 1H, J = 9.2 Hz, J = 2.6 Hz, H-4), 6.72 (d, 1H, J = 2.6 Hz, H-6), 7.34-7.45 (m, 5H, *phenyl*), 7.97 (d, 1H, H-3), 10.97 (s, 1H, OH); ^{13}C NMR (DMSO-d_6): δ 70.4 (CH_2), 103.5 (C-6), 108.4 (C-4), 127.6 (C-3), 128.1 (C-2′, C-6′), 128.4 (C-4′), 128.8 (C-3′, C-5′), 129.5 (C-2), 136.2 (C-1′), 156.0 (C-1), 164.7 (C-5); ms (m/z): 245 (M^+, 85), 227 (27), 151 (13), 125 (14), 91 (100). *Anal.* Calcd. for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.55; H, 4.78; N, 5.81.

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REFERENCES

1. Sicker, D., *Synthesis* **1989**, 875.
2. Maleski, R.J., Osborne, C.E. and Cline, S.M., *J. Heterocyclic Chem.* **1991**, *28*, 1937.
3. Sicker, D. and Hartenstein, H., *Synthesis* **1993**, 771.
4. Hartenstein, H. and Sicker, D., *Tetrahedron Lett.* **1994**, *35*, 4335.
5. Grambow, H.J., Lückge, J., Klausener, A. and Müller, E., *Z. Naturforsch. [C]*, **1986**, *41*, 684.
6. Niemeyer, H.M., *Phytochemistry* **1988**, *27*, 3349.
7. Kluge, M., Hartenstein, H., Hantschmann, A. and Sicker, D., *J. Heterocyclic Chem.*, submitted.

Downloaded by [York University Libraries] at 19:01 26 June 2014

8. a. Kwak, S.W. and Chen, C.W., *U. S. Patent* 4,816,584 (1989);
b. Kwiatkowski, P.L., *U. S. Patent* 4,936,995 (1990).
9. Hoelscher, C. "Synthesis and Process Development of Spiro(indoline) Photochromic Compounds", 206th American Chemical Society Meeting, Chicago, IL, Aug 22-27 (1993).
10. Manner, J.A., *U. S. Patent* 5,019,659 (1991).
11. Hartenstein, H. and Sicker, D., *J. Prakt. Chem.* **1993**, *335*, 103.
12. a: Maleski, R.J., *Synth. Commun.* **1993**, *23*, 343; b: Maleski, R. J., *U. S. Patent* 5,250,741 (1993).
13. Kozolov,V.V. and Belov, B.I., *Zh. Org. Khim. (Engl. Transl.)* **1991**, *33*, 1898.
14. Behnisch, R., *Carbonsäure-Salpetrigsäure-Anhydride*, in: Methoden der Organischen Chemie (Houben-Weyl), Vol. E16c (Klamann, D., Ed.) , Georg Thieme Verlag, Stuttgart, New York, **1992**, pp 16-20.
15. Shpinel', Y.I., Klimova, I.V. and Belyaev, E.Y., *Zh. Obshch. Khim. (Engl. Transl.)* **1991**, *27*, 1309.
16. Rowe, E.J., Kaufman, K.L. and Piantadosi, C., *J. Org. Chem.* **1958**, *23*, 1622.
17. Fitton, A.O. and Ramage, G.R., *J. Chem. Soc.* **1962**, 4870.
18. Weidel, H. and Pollak, J., *Monatsh. Chem.* **1900**, *21*, 15.
19. Darchem, A. and Peltier, D., *Bull. Soc. Chim. Fr.*, **1972**, 4061.

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