Pergamon

Tetrahedron 54 (1998) 7843–7848

TETRAHEDRON

# THE NITRATION OF ELECTRON-RICH AROMATICS

C. L. Dwyer and C. W. Holzapfel *

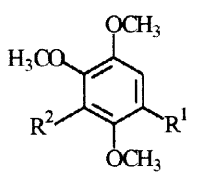
Department of Chemistry and Biochemistry, Rand Afrikaans University,
P.O. Box 524, Auckland Park, 2006, SOUTH AFRICA

Received 20 February 1998; accepted 30 April 1998

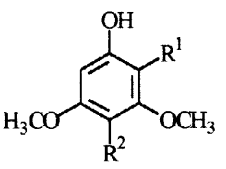
ABSTRACT: The successful mononitration of a variety of electron-rich aromatic substrates is reported, employing either nitronium tetrafluoroborate or "claycop" as the nitrating agent. Dinitration of four of the substrates was achieved when employing nitronium tetrafluoroborate. Several of the products have previously been prepared only by indirect methods. 

Recent developments in areas such as DOM methodology[1] have sparked a renaissance in the field of aromatic chemistry, due to the demand for multifunctional aromatic substrates and the inadequacies of existing techniques. In particular, the nitration of aromatic rings has received considerable attention of late, due to unsolved problems pertaining to regioselectivity, overnitration and competitive oxidation of substrates.[2]

During research directed towards the synthesis of streptonigrin and related heterocyclic compounds[3] we identified dinitro compounds **1c** and **2c** as possible key intermediates. A literature search revealed only an indirect six step route to **1c** starting from guaiacol,[4] despite the fact that both 1,2,4-trimethoxybenzene (**1a**) and 3,5-dimethoxyphenol (**2a**) are commercially available.




**1**



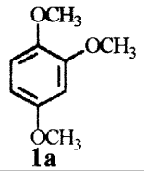
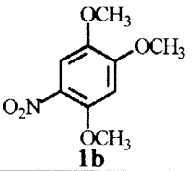
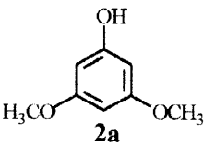
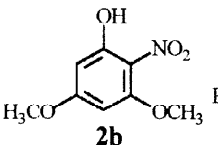
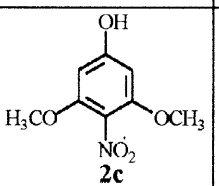
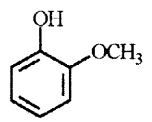
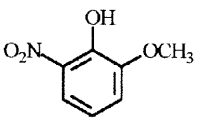
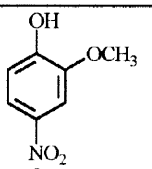
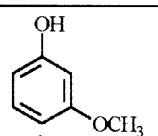
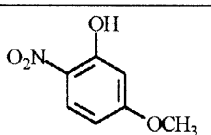
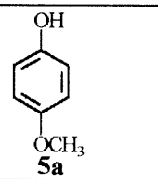
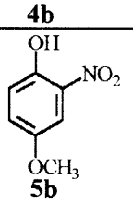
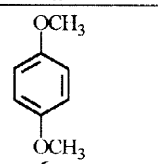
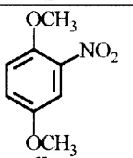
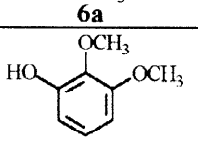
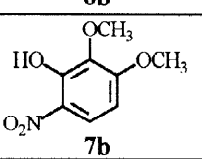
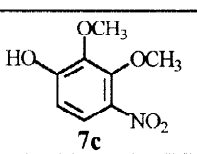
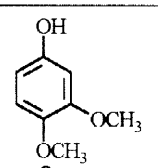
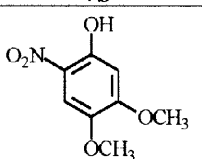
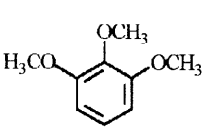
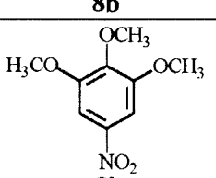

**2**

a) $R^1 = R^2 = H$
b) $R^1 = NO_2$, $R^2 = H$
c) $R^1 = R^2 = NO_2$

Preliminary work indicated that the omissions in the literature were for good reasons, as mononitration of these, and a selection of other electron-rich, highly oxygenated substrates proved difficult using a variety of standard nitration techniques. In all cases, competitive oxidation led to the formation of an array of highly coloured oxidation products, with very low or no yields of the desired nitration products. The difficulties involved in nitration of electron-rich aromatics are well documented, but a general solution to the problem has not been reported.[5] In the case of phenols, protection of the hydroxyl group reduces electron density on the ring and may allow successful nitration,[4] but it increases the steric bulk and reduces the *ortho*-directing ability

0040-4020/98/$19.00 
*PII:* S0040-4020(98)00418-9

TABLE 1: MONONITRATION OF ELECTRON-RICH AROMATICS

| STARTING MATERIALS | MAIN PRODUCTS ISOLATED | | YIELDS METHOD A | YIELDS METHOD B |
|---|---|---|---|---|
|  **1a** |  **1b** | **1b** | 81% | 79% |
|  **2a** |  **2b**  **2c** | **2b**<br>**2c** | 79%<br>11% | 71%<br>8% |
|  **3a** |  **3b**  **3c** | **3b**<br>**3c** | 31%<br>39% | 29%<br>36% |
|  **4a** |  **4b** | **4b** | 78% | 79% |
|  **5a** |  **5b** | **5b** | 62% | 67% |
|  **6a** |  **6b** | **6b** | 65% | 89% |
|  **7a** |  **7b**  **7c** | **7b**<br>**7c** | 55%<br>32% | 49%<br>31% |
|  **8a** |  **8b** | **8b** | 65% | 52% |
|  **9a** |  **9b** | **9b** | 46% | 44% |

of the hydroxy group, which may result in regioselectivity problems. Nitrosation followed by oxidation has been successfully employed in some cases by Maleski and co-workers,[7] but the method is indirect and oxidation is not always successful, as evidenced by their failure to prepare **2b** from the corresponding nitroso compound.[7b] Other methods have been employed, but appear to be limited in application.[8]

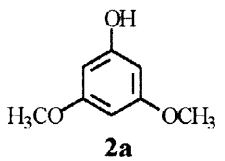
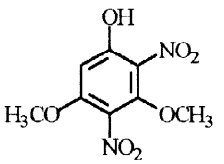
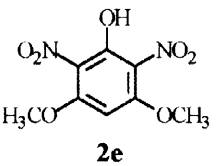
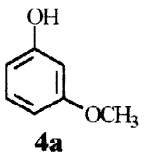
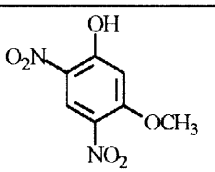
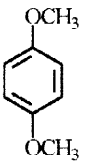
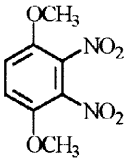
In light of the above, the consistently good results we have obtained for nitration of electron-rich substrates using nitronium tetrafluoroborate ($NO_2^+BF_4^-$)[9] and "claycop"[10] was unexpected. These reagents have been investigated extensively in recent years, but it appears that their potential for the nitration of highly oxygenated aromatics has been largely overlooked. The reactions with both reagents appeared to be highly temperature and solvent dependent, proceeding better at low temperatures and in the absence of chlorinated solvents. With $NO_2^+BF_4^-$, optimal results were obtained when the reactions were carried out in DME at -50°C (Method A, Table 1). The more traditional solvent for reactions with $NO_2^+BF_4^-$, sulfolane,[9a] proved to be of limited use since it is a solid at room temperature, precluding reactions at very low temperatures. Acetonitrile, which has also been used as a solvent for reactions with $NO_2^+BF_4^-$,[9a] proved inferior to DME. Claycop was prepared and used for nitration following the method of Cornélis and Laszlo,[11] except that ether was employed as the solvent for nitration rather than hexane or dichloromethane (Method B, Table 1).

The nitration of four disubstituted and five trisubstituted oxygen-rich aromatics was investigated. As can be seen in Table 1, mononitration of the substrates afforded reasonable to excellent yields of nitration products in all cases, with little discrimination between the two methods. The reactions proceeded rapidly, and were generally complete within minutes. In most cases, substitution occurred preferentially *ortho* to the main directing group (-OH or $-OCH_3$). However, substrate **2a** afforded trace amounts of the *para* isomer **2c**, while substrates **3a** and **7a** afforded comparable amounts of both *ortho* and *para* isomers, with a slight preference for the *ortho* isomer.

These successes led us to investigate dinitration of the substrates. However, attempts at dinitration with "claycop"[10b] were unsuccessful, while only substrates **2a**, **4a** and **6a** could be successfully dinitrated using two equivalents of $NO_2^+BF_4^-$ under the same conditions that were employed for mononitration (Method C, Table 2). Dinitration of **6a** provided an interesting, if unexpected, result. On the basis of the *meta*-directing effect of the first nitro group introduced, in conjunction with steric constraints, we expected to obtain 1,4-dimethoxy-2,6-dinitrobenzene. However, as has previously been reported for nitration using $HNO_3$/AcOH ,[12] the main product of dinitration is 1,4-dimethoxy-2,3-dinitrobenzene (**6c**). In the case of substrate **2a**, two dinitro regioisomers were isolated, compound **2d** being the major product. Clearly the dinitration of electron-rich compounds still presents a formidable problem and is only partially solved by employing $NO_2^+BF_4^-$.

With both mono- and dinitrations, it appears that the substitution pattern of the starting materials is crucial in determining the outcome of the reaction. In all cases, all-*meta*-substituted substrates reacted at a slower rate and afforded better results than the corresponding *ortho*- or *para*-substituted compounds (e.g. **4a** versus **3a** and **5a**; **2a** versus **7a** and **8a**). This is understandable if one considers the inherent preference for formation of *ortho*- and *para*-quinones from the corresponding diols or dialkoxy compounds. In addition, the presence of a phenolic group appears to exacerbate the formation of byproducts (e.g. **5a** versus **6a**, **8a** versus **1a**).

TABLE 2 : DINITRATION USING METHOD C ($NO_2^+BF_4^-$)

| STARTING MATERIALS | MAIN PRODUCTS ISOLATED | | YIELDS |
|---|---|---|---|
|  **2a** |  **2d**  **2e** | **2d** **2e** | 65% 22% |
|  **4a** |  **4c** | **4c** | 78% |
|  **6a** |  **6c** | **6c** | 76% |

These results clearly indicate that the direct nitration of highly oxygenated aromatics can be achieved by employing $NO_2^+BF_4^-$ or "claycop" as the nitrating agent. In addition, successful dinitration of selected substrates can also be achieved when employing two equivalents of $NO_2^+BF_4^-$. Direct access to compounds **2b** and **4b** solves reported problems in this regard.[7] While these methods do not address the issues pertaining to regioselectivity, in many cases they do appear to limit the problem of competitive oxidation, which is prevalent when using other nitration methods.

## EXPERIMENTAL

All reactions were performed under a positive nitrogen pressure in dry solvents, using flamed out glass apparatus. Room temperature refers to *ca.* 20-25°C. NMR spectra were recorded on a Varian Gemini-300 spectrometer. Electron impact and high resolution electron impact mass spectra were recorded on a Finnigan-MAT 8200 spectrometer at 70 eV. Melting points were determined on a Reichert Kofler hot-stage apparatus, and are uncorrected.

### METHOD A: MONONITRATION USING NITRONIUM TETRAFLUOROBORATE

A well stirred solution of the substrate (5.0 mmol) in DME (10 ml) was cooled to -50°C. $NO_2^+BF_4^-$ (5.1 mmol) was added to the solution in one portion and the reaction was monitored by TLC until consumption of the starting material was indicated. The entire reaction mixture was filtered through a silica column, the solvent

was removed *in vacuo*, and the crude products were purified *via* column chromatography on silica gel using the appropriate solvent.

**METHOD B: MONONITRATION USING "CLAYCOP"**

The aromatic substrate (5.0 mmol) was added to a well stirred suspension of claycop (2.5 g) and acetic anhydride (50.0 mmol) in diethyl ether (25 ml) at room temperature. The reaction was monitored by TLC until consumption of the starting material was indicated. The reaction mixture was then filtered under reduced pressure, and the filter cake was washed with additional ether (2 x 25 ml portions). The solvent was removed *in vacuo* and the products were purified *via* column chromatography on silica gel using the appropriate solvent.

**METHOD C: DINITRATION USING NITRONIUM TETRAFLUOROBORATE**

A well stirred solution of the substrate (5.0 mmol) in DME (10 ml) was cooled to -50°C. $NO_2^+BF_4^-$ (10.2 mmol) was added to the solution in one portion and the reaction was monitored by TLC until consumption of the starting material was indicated. The entire reaction mixture was filtered through a silica column, the solvent was removed *in vacuo*, and the crude products were purified *via* column chromatography on silica gel using the appropriate solvent.

**2-Methoxy-4-nitrophenol (3c)**, **5-methoxy-2-nitrophenol (4b)** and **4-methoxy-2-nitrophenol (5b)**. The products obtained were identical in all respects to authentic samples purchased from Aldrich Chemical Company.

**2-Methoxy-6-nitrophenol (3b)**,[13] **2,5-dimethoxynitrobenzene (6b)**,[5c] **2,4,5-trimethoxynitrobenzene (1b)**,[5a] **3,5-dimethoxy-4-nitrophenol (2c)**,[14] **1,4-dimethoxy-2,3-dinitrobenzene (6c)**,[12] **5-methoxy-2,4-dinitrophenol (4c)**,[15] **3,4,5-trimethoxynitrobenzene (9b)**,[16] and **2,3-dimethoxy-6-nitrophenol (7b)**.[17] The products obtained were identical in all respects to literature reports.

**2,3-Dimethoxy-4-nitrophenol (7c)**. Yellow crystals; mp. 53-56°C; $^1$H NMR ($CDCl_3$) δ 7.65 (d, 1H, $J_{6\text{-}5}$=9.1 Hz, H-6), 6.75 (d, 1H, $J_{5\text{-}6}$=9.1 Hz, H-5), 6.23 (br s, 1H, OH), 3.97 (s, 6H, $OCH_3$); $^{13}$C NMR ($CDCl_3$) δ 154.4, 148.3, 140.6, 137.2, 121.9, 110.0, 61.8, 61.4; EIMS *m/z* (rel. int. %) $[M]^+$ 199 (100), 152 (44); HREIMS *m/z* 199.0480 ($C_8H_9NO_5$ requires 199.0481).

**3,5-Dimethoxy-2-nitrophenol (2b)**. Yellow crystals; mp. 129-131°C (lit.[18] 131°C); $^1$H NMR ($CDCl_3$) δ 11.54 (br s, 1H, OH), 6.13 (s, 1H, $J_{6\text{-}4}$=2.6 Hz, H-6), 6.00 (d, 1H, $J_{4\text{-}6}$=2.6 Hz, H-4), 3.87 (s, 3H, $OCH_3$), 3.82 (s, 3H, $OCH_3$); $^{13}$C NMR ($CDCl_3$) δ 166.0, 159.7, 158.1, 111.8, 93.7, 92.8, 56.7, 55.9; EIMS *m/z* (rel. int. %) $[M]^+$ 199 (100), 169 (36), 152 (56), 141 (39); HREIMS *m/z* 199.0480 ($C_8H_9NO_5$ requires 199.0481).

**4,5-Dimethoxy-2-nitrophenol (8b)**. Yellow crystals; mp. 125-127°C; $^1$H NMR ($CDCl_3$) δ 11.01 (s, 1H, OH), 7.42 (s, 1H, H-6), 6.51 (s, 1H, H-3), 3.93 (s, 3H, $OCH_3$), 3.86 (s, 3H, $OCH_3$); $^{13}$C NMR ($CDCl_3$) δ 158.1, 153.4, 143.3, 125.8, 105.0, 100.6, 56.7, 56.4; EIMS *m/z* (rel. int. %) $[M]^+$ 199 (100), 169 (4), 141 (6); HREIMS *m/z* 199.0481 ($C_8H_9NO_5$ requires 199.0481).

**3,5-Dimethoxy-2,4-dinitrophenol (2d)**. Yellow-brown crystals; mp. 106-109°C; $^1$H NMR ($CDCl_3$) δ 10.60 (br s, 1H, OH), 6.46 (s, 1H, H-6), 3.95 (s, 3H, $OCH_3$), 3.94 (s, 3H, $OCH_3$); $^{13}$C NMR ($CDCl_3$) δ 159.0, 156.9, 150.6, 114.1, 112.9, 97.2, 64.5, 57.2; EIMS *m/z* (rel. int. %) $[M]^+$ 244 (83); 214 (28), 197 (21), 186 (7), 169 (16), 69 (100); **HREIMS** *m/z* 244.0332 ($C_8H_8N_2O_7$ requires 244.0332).

**3,5-Dimethoxy-2,6-dinitrophenol (2e)**. Yellow-orange crystals; mp. 154-157°C; $^1$H NMR ($CDCl_3$) δ 6.09 (s, 1H, H-4), 4.01 (s, 6H, 2 x $OCH_3$); $^{13}$C NMR ($CDCl_3$) δ ; 158.3 (2C), 151.2, 114.0 (2C), 87.5, 57.1 (2C); EIMS *m/z* (rel. int. %) $[M]^+$ 244 (100), 214 (76), 197 (45), 183 (13), 169 (47); HREIMS *m/z* 244.0332 ($C_8H_8N_2O_7$ requires 244.0332).

## ACKNOWLEDGEMENTS

We thank the FRD (South Africa), AECI and SASOL for funding.

## REFERENCES

1. Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.
2. a) Firouzabadi, H., Iranpoor, N. and Zolfigol, M. A. *Synth. Commun.* **1997**, *27*, 3301. b) Suzuki, H., Takeuchi, T. and Mori, T. *J. Org. Chem.* **1996**, *61*, 5944. c) Riego, J. M., Sedin, Z., Zaldívar, J. M., Marziano, N. C. and Tortato, C. *Tetrahedron Lett.* **1996**, *37*, 513.
3. Holzapfel, C. W. and Dwyer, C. L. *Heterocycles* **1998**, *48*, 215.
4. Kametani, T. and Ogasawara, K. *Yakugaku Zasshi* **1965**, *85*, 985. (*Chem. Abstr.* **1966**, *64*, 6611e.)
5. a) Rathore, R., Bosch, E. and Kochi, J. K. *Tetrahedron* **1994**, *50*, 6727. b) Castedo, L., Borges, J. E., Marcos, C. F. and Tojo, G. *Synth. Commun.* **1995**, *25*, 1717. c) Dhanalekshmi, S., Balasubramanian, K. K. and Venkatachalam, C.S. *Tetrahedron* **1994**, *50*, 6387.
6. Smissman, E. E., LaPidus, J. B. and Beck, S. D. *J. Org. Chem.* **1957**, *22*, 220.
7. a) Maleski, R. J. *Synth. Commun.* **1993**, *23*, 343. b) Maleski, R. J. *Synth. Commun.* **1995**, *25*, 2327.
8. a) Hodgson, H. H. and Clay, J. J. *J. Chem. Soc.* **1935**, 946. b) Richey, J. D., Caskey, A. L. and BeMiller, J. N. *Agric. Biol. Chem.* **1976**, *40*, 2413.
9. a) Kuhn, S. J. and Olah, G. A. *J. Am. Chem. Soc.* **1961**, *83*, 4564. b) Olah, G. A. and Lin, H. C. *J. Am. Chem. Soc.* **1974**, *96*, 549.
10. a) Cornélis, A.and Laszlo, P. *Synthesis* **1985**, 909. b) Gigante, B., Prazeres, A. O., Marcelo-Curto, M. J., Cornélis, A. and Laszlo, P. *J. Org. Chem.* **1995**, *60*, 3445.
11. Cornélis, A., Laszlo, P. *Aldrichimica Acta* **1988**, *21*, 97.
12. Shaik, I. A., Johnson, F. and Grollman, A. P. *J. Med. Chem.* **1986**, *29*, 1329.
13. Chaudhuri, K. and Chawla, H. M. *Ind. J. Chem. Sect. B*, **1985**, *24B*, 1277.
14. Brown, P. E., Lewis, R. A. and Waring, M. A. *J. Chem. Soc. Perkin Trans. 1* **1990**, 2979.
15. Hartenstein, H. and Sicker, D. *J. Prakt. Chem.* **1993**, *335*, 103.
16. a) Hughes, G. K., Neill, K. G. and Ritchie, E. *Aust. J. Sci. Res., Ser. A* **1950**, *3*, 497. b) Will, W. *Ber. Dtsch. Chem. Ges.* **1888**, *21*, 602.
17. Nachman, R. J. *J. Heterocycl. Chem.* **1982**, *19*, 1545.
18. Kampouris, E. M. *J. Chem. Soc.(C)* **1967**, 2568.