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A novel one-pot synthesis of isomeric naphtho[1,2-*d*]isoxazole 2-oxide and naphtho[1,8-*de*][1,2]oxazine ring systems. A case of simultaneous *o*- and *peri*-cyclisation in naphthalene

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Abstract

2-Hydroxy-1-naphthaldehyde oxime **1** undergoes a one-pot *o*- and *peri*-oxidative cyclisation with lead(IV) acetate to give the isomeric naphtho[1,2-*d*]isoxazole 2-oxide **2** and naphtho[1,8-*de*][1,2]oxazine **3**. A common *o*-nitroso quinonemethide intermediate is invoked for both isomers.

Keywords: naphthalenes; oximes; lead and compounds; oxidation; *N*-oxides; hydroxylation.

Isoxazoles and their benzo derivatives have numerous applications in medicine and agriculture.[1] 1,2-Oxazine derivatives on the other hand are mainly used as intermediates in organic synthesis.[2] Oxidative cyclisation of suitably *o*-disubstituted aromatics with lead(IV) acetate (LTA) is a particularly effective route to a variety of nitrogen heterocycles.[3] This approach has been applied to the synthesis of 1,2-benzisoxazole 2-oxides.[4] To date, no oxidative reaction has been used in the preparation of 1,2-oxazines. In particular, *peri*-annelated naphtho-1,2-oxazines are synthesised by *peri*-cyclisation of 8-acyl-1-naphthols.[5] A recent review covers the synthesis of *peri*-naphthalene heterocycles.[6]

During our studies on heterocyclic mesomeric betaines we have observed that reaction of **1** with LTA affords a mixture of the isomers **2** and **3** (Scheme 1).[7a] After separation by column chromatography the products were obtained in 35 and 42% yield, respectively. Evidently this reaction provides easy access to two diverse isomeric ring systems. Confirmation of the structure of **3** was provided by ring opening to 2,8-dihydroxy-1-naphthonitrile **4**[7b] followed by methylation to 2,8-dimethoxy-1-naphthonitrile **5**. The latter has been prepared independently from 2,8-dihydroxy-1-naphthaldehyde.[8] Compounds **2**–**4**[9] were characterised by satisfactory elemental analyses, and from their mass, ^{13}C and ^{1}H NMR spectra.

In Criegee's[10] work on the oxidation of hydroxy compounds by LTA, it was proposed that an organolead intermediate is formed via either a cyclic or an acyclic transition state. It is, therefore,

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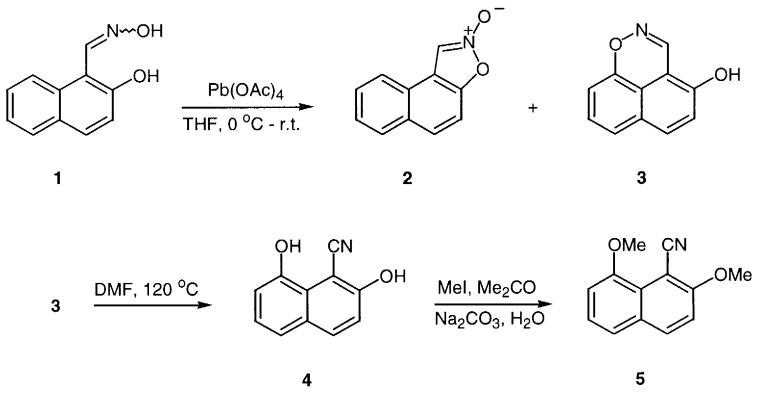
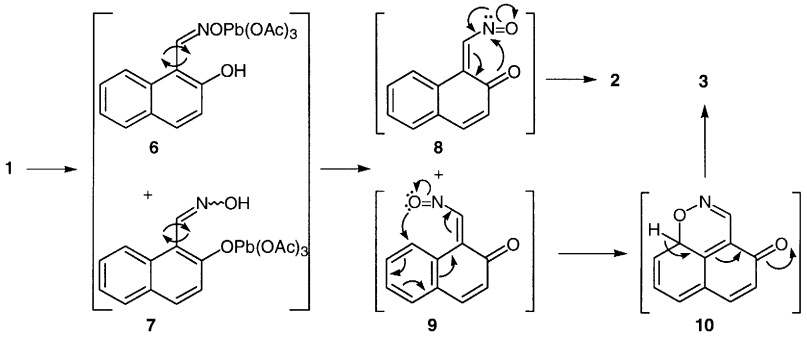


Scheme 1.

reasonable here to assume an analogous intermediate originating from the reaction of **1** with LTA. This intermediate (Scheme 2) may be either **6** or **7**. Both of these, through rotation of the complexed **6** or free oxime **7** side-chains, can decompose to *o*-nitroso quinonemethides **8** and **9**. Intermediate **8** then undergoes an *o*-cyclisation to its heterocyclic valence isomer **2**, while intermediate **9** undergoes a *peri*-ring closure involving the nitroso group to give intermediate **10** that aromatises to **3**. The *peri*-cyclisation is an intramolecular nucleophilic substitution triggered by the quinonoid structure. This implies that the *o*-hydroxy group in **1** is a prerequisite for the formation of **3**.



Scheme 2.

Independent reaction of **2** with LTA gave only starting material suggesting that a route to **3** via rearrangement of **2** can be ruled out. Another route involving acetoxylation of intermediate **9** followed by acyl rearrangement and, finally, ring closure[11] to **3** can also be ruled out, since reaction of **1** with LTA in the presence of potassium carbonate also led to products **2** and **3**. The route proposed for the formation of **3** (Scheme 2) introduces a new approach to *peri*-fused naphtho-1,2-oxazines. On the other hand, the cyclisation to **3** and ring opening to **4** is in fact a novel overall intramolecular nuclear hydroxylation. Oxidation, and in particular hydroxylation and oxygenation, is an important biological process[12] for which the photochemistry of heterocyclic *N*-oxides has served as a model.[13] Its potential in enzyme-catalysed reactions has been pursued and recognised in the last decade.[14]

In summary, we have presented a novel reaction for the simultaneous formation of naphtho[1,2-*d*]isoxazole 2-oxide and naphtho[1,8-*de*][1,2]oxazine ring systems through the concept of a common intermediate.

Currently, investigations are in progress with regard to the scope and limitations of this reaction. Efforts in unraveling the interesting chemistry of the products are also underway and will be reported soon.

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References

1. Sutharchanadevi, M.; Murugan, R. *Comp. Heterocycl. Chem., 2nd edn*. **1996**, *3*, 221.
2. Gilchrist, T. L.; Wood, J. E. *Comp. Heterocycl. Chem., 2nd edn*. **1996**, *6*, 279.
3. (a) Butler, R. N. *Chem. Rev*. **1984**, *84*, 246. (b) Ellis, G. P. In *Chemistry of Heterocyclic Compounds: Synthesis of Fused Heterocycles, Part 1*; Wiley Interscience: Chichester, 1987. (c) Ellis, G. P. In *Chemistry of Heterocyclic Compounds: Synthesis of Fused Heterocycles, Part 2*; Wiley Interscience: Chichester, 1992.
4. (a) Boulton, A. J.; Tsoungas, P. G. *J. Chem. Soc., Chem. Commun.* **1980**, 421. (b) Boulton, A. J.; Tsoungas, P. G.; Tsiamis, C. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1665.
5. Balu, M. P.; Pooranhand, D.; Ila, H.; Junjappa, H. *Tetrahedron Lett*. **1988**, *29*, 501.
6. Mezheritskii, V. V.; Tkachenko, V. V. *Adv. Heterocycl. Chem*. **1990**, *51*, 1.
7. Experimental procedures: (a) A stirred solution of 2-hydroxy-1-naphthaldehyde oxime **1** (5 g, 26.7 mmol) in tetrahydrofuran (60 mL) under argon was cooled to −5°C. LTA (23.7 g, 53.4 mmol) was added slowly over a period of 45 min. The mixture was allowed to reach room temperature and then filtered. The solid was washed with tetrahydrofuran and the filtrate was evaporated in vacuo. The residue was purified by flash chromatography (25%, 50% dichloromethane/hexane, 30% ethyl acetate/hexane) to give **2** (1.7 g, 35%) and **3** (2.1 g, 42%). (b) A solution of **3** (0.22 g, 1.16 mmol) in *N*,*N*-dimethylformamide (5 mL) was heated at 120°C for 30 min. Water (20 mL) was added and the mixture was extracted with diethyl ether (3×10 mL). The combined extracts were dried (Na_2SO_4) and the solvent was removed in vacuo. The residue was purified by flash chromatography (50%, ethyl acetate/hexane) to give **4** (0.15 g, 70%).
8. Adams, R.; Greissman, T. A. *J. Am. Chem. Soc.* **1938**, *60*, 2166.
9. ^{1}H and ^{13}C assignments of compounds **2**–**4** were extrapolated from DQF–COSY, HMQC and HMBC spectra obtained using standard pulse sequences. Compound **2**: m.p. 198–200°C; [found: C, 71.39; H, 3.60; N, 7.46. $C_{11}H_7NO_2$ requires: C, 71.33; H, 3.81; N, 7.56%]; ν_{max} (Nujol) 1650, 1635, 1220 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.23 (1H, d, *J*=9 Hz, H-4), 7.56 (1H, t, *J*=8 Hz, H-7), 7.61 (1H, s, H-1), 7.70 (1H, t, *J*=8 Hz, H-8), 7.86 (1H, d, *J*=8 Hz, H-6), 7.95 (1H, d, *J*=9 Hz, H-5), 8.95 (1H, d, *J*=8 Hz, H-9); δ_C (100.6 MHz, $CDCl_3$) 123.05 (C-4), 125.34 (C-7), 125.70 (C-9), 128.70 (C-6), 129.17 (C-8), 129.44 (C-9b), 129.83 (C-5a), 130.61 (C-3a), 130.87 (C-9a), 134.92 (C-5), 148.21 (C-1); *m/z* (EI): 185 (87, M$^+$), 169 (25), 149 (50), 129 (100), 114 (32), 102 (64), 76 (33%); HRMS (EI): M$^+$ found: 185.0486. $C_{11}H_7NO_2$ requires: 185.0477. Compound **3**: m.p. 130–132°C; [found: C, 71.50; H, 3.79; N, 7.42. $C_{11}H_7NO_2$ requires: C, 71.33; H, 3.81; N, 7.56%]; ν_{max} (Nujol) 3390, 1610, 1590 cm^{-1}; δ_H (400 MHz; DMSO-d_6) 6.63 (1H, d, *J*=8 Hz, H-9), 7.08 (1H, d, *J*=9 Hz, H-5), 7.13 (1H, t, *J*=8 Hz, H-8), 7.18 (1H, d, *J*=8 Hz, H-7), 7.67 (1H, d, *J*=9 Hz, H-6), 8.35 (1H, s, H-3), 10.61 (1H, s, br, OH); δ_C (100.6 MHz, DMSO-d_6) 99.76 (C-3a), 104.98 (C-9), 118.94 (C-7), 120.18 (C-5), 121.11 (C-9b), 127.57 (C-8), 127.15 (C-6a), 131.19 (C-6), 144.97 (C-3), 148.44 (C-4), 150.72 (C-9); *m/z* (EI) 185 (100, M$^+$), 163 (11), 151 (10), 129 (7), 113 (10), 85 (3%); HRMS (EI): M$^+$ found: 185.0480. $C_{11}H_7NO_2$ requires: 185.0477. Compound **4**: m.p. 167–168°C; ν_{max} (Nujol) 3500, 3300, 2230, 1530 cm^{-1}; δ_H (400 MHz; DMSO-d_6) 6.91 (1H, d, *J*=7.7 Hz, H-7), 7.20 (1H, t, *J*=7.7 Hz, H-6), 7.22 (1H, d, *J*=9 Hz, H-3), 7.32 (1H, d, *J*=7.7 Hz, H-5), 7.93 (1H, d, *J*=9 Hz, H-4), 10.16 (1H, s, br, OH-2), 11.21 (1H, s, br, OH-8); δ_C (100.6 MHz, DMSO-d_6) 90.11 (C-1), 112.39 (C-7), 117.95 (C-3), 118.62 (CN), 120.89 (C-5), 124.77 (C-8a), 125.90 (C-6), 130.94 (C-4a), 136.13 (C-4), 153.17 (C-8), 163.49 (C-2); *m/z* (EI) 185 (100, M$^+$), 169 (6), 139 (20), 113 (13), 83 (18%); HRMS (EI): M$^+$ found: 185.0482. $C_{11}H_7NO_2$ requires: 185.0477.
10. Criegee, R. *Angew. Chem*. **1958**, *70*, 173, and references cited therein.
11. Mochalov, S. M.; Surikova, T. P.; Shabarov, Y. S. *Chem. Heterocycl. Compd*. (*Engl. Transl.*) **1976**, *12*, 738.
12. (a) Holland, H. L. *Adv. Appl. Microbiol*. **1997**, *44*, 125. (b) Di Gennaro, Galli, E.; Albini, G.; Pelizzoni, F.; Sello, G.; Pestetti, G. *Res. Microbiol*. **1997**, *148*, 355.
13. Albini, A.; Alpegiani, M. *Chem. Rev*. **1984**, *84*, 43.
14. (a) Hudlicky, T.; Endoma, M. A. A.; Butora, G. *Tetrahedron: Asymmetry* **1996**, *7*, 61. (b) Boyd, D. D. R.; Sharma, N. D.; Brannigan, I. N.; Haughey, S. A.; Malone, J. F.; Clarke, D. A.; Dalton, H. *J. Chem. Soc., Chem. Commun*. **1996**, 2361.