Reduction of Nitrosobenzene by 2-(α-Hydroxyethyl)-3,4-dimethylthiazolium Salts

Luisa M. Ferreira,[a] Humberto T. Chaves,[a] Ana M. Lobo, *[a] Sundaresan Prabhakar*[a] and Henry S. Rzepa[b]

[a] Secção de Química Orgânica Aplicada, Departamento de Química, and SINTOR-UNINOVA, Campus FCT-UNL, Quinta da Torre, 2825 Monte da Caparica and Centro de Química Estrutural, Complexo I, INIC, Av. Rovisco Pais, 1096 Lisboa Codex, Portugal

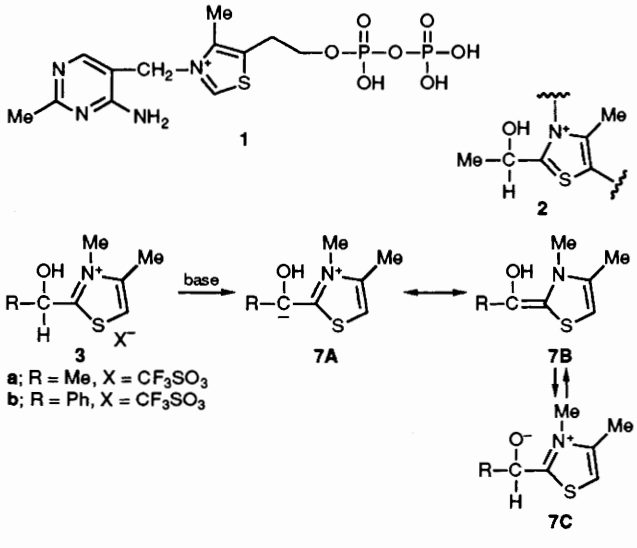
[b] Department of Chemistry, Imperial College of Science Technology and Medicine, London SW7 2AY, UK

Nitrosobenzene in a basic medium is reduced by 2-(α-hydroxyethyl)- or 2-(α-hydroxybenzyl)-3,4-dimethylthiazolium trifluoromethanesulfonate to yield the intermediate hydroxylamine and 2-acyl-3,4-dimethylthiazolium trifluoromethanesulfonate, with acylation of the former by the latter giving the final products.

Thiamine diphosphate **1** is a coenzyme for the decarboxylation of α-keto acids, the formation of α-ketols and transketolase reactions,[1] and exists *in vivo* largely as the 2-(α-hydroxyethyl)thiamine derivative **2**.[2] Aromatic nitroso compounds, on the other hand, are xenobiotics which can arise from reduction of aromatic nitro compounds resulting from a variety of combustion processes.[3]

We report in this paper that when nitrosobenzene reacts with **3a**† in CH_2Cl_2 at room temperature, in the presence of an equivalent amount of Et_3N or 1,4-diazabicyclo[2.2.2]octane (DABCO), a rapid reaction takes place, which was found to be completed after *ca.* 90 min, leading to a major compound **4a** in 44% yield.[4] These types of compounds are thought to be involved in cancer induction by carcinogenic aromatic amines and aromatic nitro compounds.[3] Other compounds found in the reaction mixture were the hydroxamic acid **5** (3%), the azoxy **6** (22%), acetic acid (54%) and the 3,4-dimethylthiazolium trifluoromethanesulfonate (70%). In the absence of base no reaction was observed. With **3b**† the *O*-acyl compound isolated was **4b**[5] (54%) together with the azoxy **6** (22%).

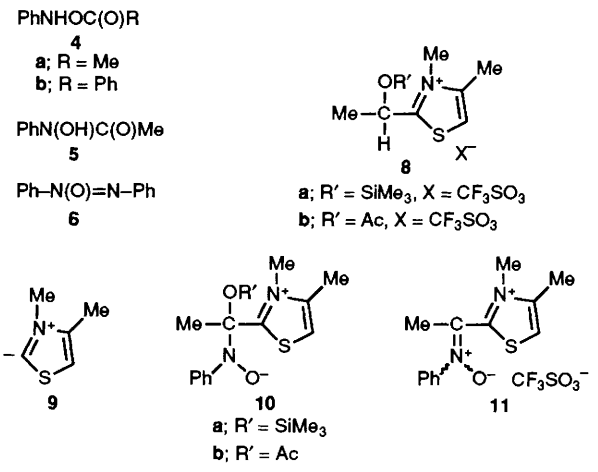
The results can be interpreted as indicating either a fast reduction of the nitroso compound *via* a hydride transfer from **7C** (Scheme 1) or two successive one-electron reductions from



Scheme 1

† *^1H NMR data* for **3a**: [obtained by *N*-methylation of 2-(α-hydroxyethyl)-4-methylthiazole[11] with methyl trifluoromethanesulfonate]: m.p. 83–85 °C; δ_H (Me_2SO) 7.573 (s, 1H, 5-H), 5.336 [m, 1H, C(OH)*H*], 4.897 [d, 1H, C(O*H*)H], 3.827 (s, 3H, N-Me), 2.459 (s, 3H, 4-Me), 1.567 [d, 3H, *J* 6.6 Hz, CH*Me*].

3b: [Obtained by *N*-methylation of 2-(α-hydroxybenzyl)-4-methylthiazole[12] with methyl trifluoromethanesulfonate]: m.p. 86–89 °C; δ_H (Me_2SO) 7.962 (s, 1H, 5-H), 7.574 [d, *J* 4.5 Hz, 1H, C(O*H*)H], 7.474 (s, 5H, ArH), 6.413 [d, *J* 4.5 Hz, C(OH)*H*], 3.774 (s, 3H, N-Me), 2.490 (s, 3H, 4-Me).



7B, to yield the phenylhydroxylamine and the 2-acetylthiazolium derivative. These two species then react in a known manner[6] to give the *O*-acylated products **4**. Compound **4a** can also couple with the parent nitroso to give rise to the azoxy derivative **6**[7] together with the expulsion of acetic acid. Alternatively the water liberated in the formation of **6** from nitrosobenzene and phenylhydroxylamine can compete with the free hydroxylamine for reaction with the 2-acetylthiazolium to generate also acetic acid. The formation of the hydroxamic acid **5** is likely to have its origin in a base-catalysed transacetylation from oxygen to nitrogen,[8] although direct attack of **7B** (Scheme 1) at the nitrogen of the nitroso function[9] cannot be excluded. Self-consistent reaction field calculations of the relative energy **7B**/**7C** were performed to assess the potential identity of the reduction agent. In the gas phase ($\varepsilon = 1$), **7B** is clearly more stable by 45.7 (PM3) or 39.4 (AM1) kcal mol^{-1} (1 cal = 4.184 J), but this decreases to 28.8/18.7 ($\varepsilon = 8$) and 20.0/10.8 ($\varepsilon = 79$).‡ Since the semi-empirical methods do neglect specific solvation due to hydrogen bonding, as well as quadrupole and higher moment terms in the continuum solvation model,[10] it appears possible that **7C** could be the active reducing agent. Where ionization of the hydroxy at the α-carbon in **8a** is blocked by a trimethylsilyl group and carbanion formation occurs at the α-carbon, reaction with nitrosobenzene in the presence of base affords **5** in nearly quantitative yield, after ejection of the ylide **9** from **10a**, and rapid desilylation on aqueous work-up. The acetate group in the plausible precursor **10b**, resulting from the attack of **8b** on nitrosobenzene, proves to be a better leaving group than **9**, and so **11** precipitates in quantitative yield.

We thank Calouste Gulbenkian Foundation, Junta nacional de Investigação Científica e Tecnológica and Instituto Nacional de Investigação Científica (Lisbon) for partial financial support.

Received, 2nd October 1992; Com. 2/05312H

‡ Full geometry optimisation for all species was performed, using a reaction cavity radius of 3.20 Å. ΔH_f (PM3) **7C** 25.4 ($\varepsilon = 1$), 6.5 ($\varepsilon = 8$), 2.6 ($\varepsilon = 79$), H_f (AM1) **7C** 28.9 ($\varepsilon = 1$), 7.2 ($\varepsilon = 8$), −1.0 ($\varepsilon = 79$) kcal mol^{-1}.

References

1 R. Kluger, *Chem. Rev.*, 1990, **90**, 1151; 1987, **87**, 863.
2 A. Ferhst, *Enzyme Structure and Mechanism*, Freeman, New York, 1985, p. 75.
3 F. A. Beland anf F. F. Kadlubar, in *Handbook of Experimental Pharmacology*, ed. C. S. Cooper and P. L. Grover, Springer-Verlag, New York, 1990, vol. 94/I, p. 267.
4 A. M. Lobo, M. M. Marques, S. Prabhakar and H. S. Rzepa, *J. Org. Chem.*, 1987, **52**, 2925.
5 S. Prabhakar, A. M. Lobo and M. M. Marques, *Tetrahedron Lett.*, 1982, 1391.
6 L. M. Ferreira, A. M. Lobo, S. Prabhakar, M. J. M. Curto, H. S. Rzepa and M. Y. Yi, *J. Chem. Soc., Chem. Commun.*, 1991, 1127.
7 M. Novak, K. A. Martin, J. L. Heinrich, K. M. Peet and L. K. Mohler, *J. Org. Chem.*, 1990, **50**, 3023.
8 G. Boche, F. Bosold and S. Schroder, *Angew. Chem., Int. Ed. Engl.*, 1989, **27**, 973.
9 M. D. Corbett and B. R. Chipko, *Bioorg. Chem.*, 1980, **9**, 273.
10 H. S. Rzepa and M. Y. Yi, *J. Chem. Soc., Perkin Trans. 2*, 1991, 531.
11 R. Breslow and E. McNelis, *J. Am. Chem. Soc.*, 1959, **81**, 3080.
12 H. Erlenmeyer, H. Baumann and E. Sorkin, *Helv. Chim. Acta*, 1948, **31**, 1978.