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

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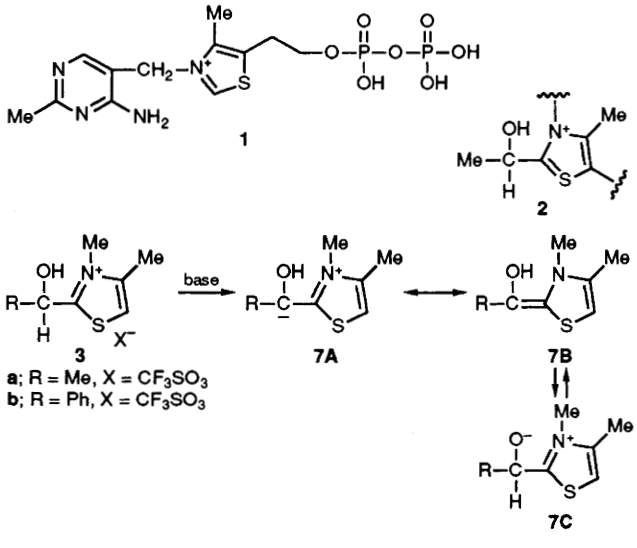
Nitrosobenzene in a basic medium is reduced by 2-(α-hydroxyethyl)- or 2-(α-hydroxybenzyl)-3,4-dimethylthiazolium trifluoromethanesulfonate to yield the intermediate hydroxylamine and 2-acyl-3,4-dimethylthiazolium trifluoromethanesulfonate, with acylation of the former by the latter giving the final products.

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%).

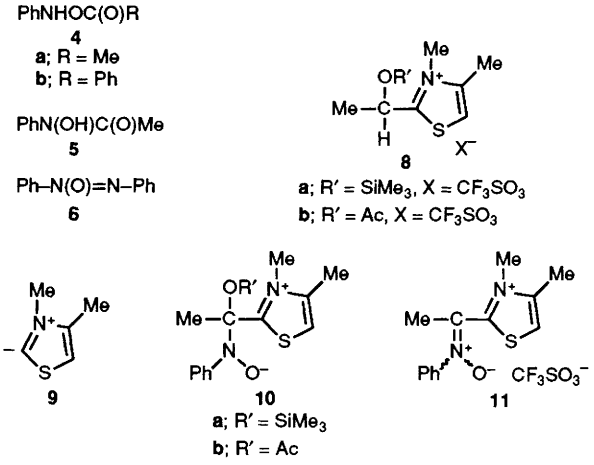
The results can be interpreted as indicating either a fast reduction of the nitroso compound *via* a hydride transfer from **7C** (Scheme 1) or two successive one-electron reductions from




**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; $\delta_H$ ($Me_2SO$) 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; $\delta_H$ ($Me_2SO$) 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.

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‡ Full geometry optimisation for all species was performed, using a reaction cavity radius of 3.20 Å. $\Delta H_f$ (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$^{-1}$.

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