2-Acyl Thiazolium Salts as Selective Agents for the *O*-Acylation of Aromatic Hydroxylamines

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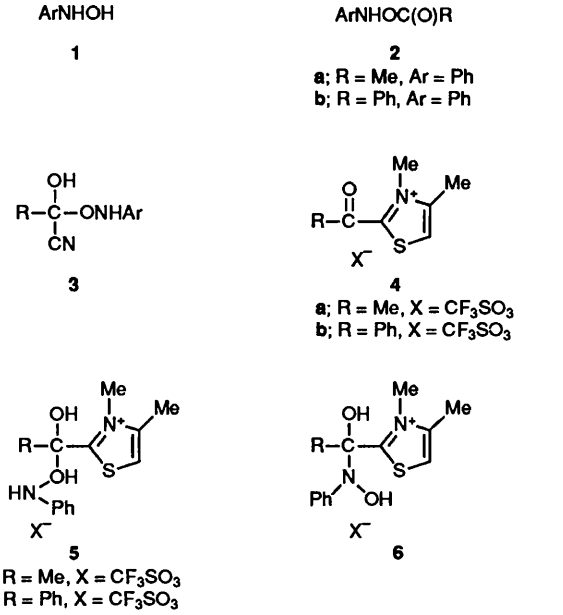
2-Acyl-3,4-dimethylthiazolium triflates, modelled upon the biologically important 2-acyl thiamine derivatives, react in neutral media specifically with the oxygen atom of *N*-aryl hydroxylamines to give rise to tetrahedral intermediates, which collapse to the *O*-acyl derivatives under mildly basic conditions.

The *O*-acylation of aromatic hydroxylamines **1** to yield **2** appears to be a key step in the onset of the lesion provoked by carcinogenic aromatic amines.[1] Direct *O*-acylation of **1** to **2** can be easily achieved *in vitro* by using acyl cyanides,[2] the corresponding tetrahedral precursors[3] **3** being easily detected by low temperature NMR spectroscopy and converted into **2** by treatment with base. Since acyl cyanides are substances that are unlikely to occur in any appreciable amount in biosystems, we undertook a systematic study of potential acyl transfer agents that are biologically more plausible.

We report here that the aromatic hydroxylamine **1** (Ar = C_6H_5) reacts with a solution of 2-acetyl-3,4-dimethylthiazolium trifluoromethanesulphonate (triflate) **4a** in CH_2Cl_2 at room temperature to give the tetrahedral intermediate **5a** which was isolated as a remarkably stable[4] white solid.† An NMR spectrum of **5a** was found to be solvent dependent. Whereas in CD_3CN (ε 37.5) a solution of **5a** reverted immediately to starting materials, in solvents of higher dielectric constant such as D_2O (ε 80.1) or dimethyl sulphoxide (DMSO) (ε 46.6), a detectable amount of the tetrahed-



† **5a**: m.p. 89–90 °C; IR (KBr) ν/cm^{-1} 3400–3200 no carbonyl; δH (DMSO) 2.493 (s, 3H, 4-Me), 4.084 (s, 3H, *N*-Me), 1.864 [s, 3H, C(OH)*Me*], 7.954 (s, 1H, 5-H); δC (DMSO) 99.6 [*C*(OH)Me]; fast atom bombardment mass spectroscopy (glycerol matrix with H_2SO_4) 265 (M^+), 248 (M^+-17), 174 (M^+-PhN), 156 ($M^+-PhNHOH$). **4a** (easily obtained by *N*-methylation of 2-acetyl-4-methylthiazole with methyl triflate); m.p. 96–98 °C; IR (KBr) ν/cm^{-1} 1710 (C=O); δH (DMSO) 2.578 (s, 3H, 4-Me), 2.735 (s, 3H, MeCO), 4.112 (s, 3H, *N*-Me), 8.260 (s, 1H, 5-H); δ_C (DMSO) 185.6 (CO), 161.4 (CN), 150.5 (N-*C*=C), 123.2 (C=*C*-S), 39.4 (*N*-Me), 30.4 (CH_3-CO), 13.9 (CH_3-C=C). **4b**: m.p. 135–137 °C; IR (KBr) ν/cm^{-1} 1670; δH (CD_3CN) 2.615 (s, 3H, 4-Me), 4.093 (s, 3H, *N*-Me), 8.039 (s, 1H, 5-H), 7.623–8.234 (m, 5H, ArH); δC (DMSO) 181.1 (CO), 161.1 (CN), 149.4 (N-*C*=C), 135.2, 134.8 (*ipso*/*para*), 130.1, 128.7 (*meta*/*ortho*), 123.1 (C=*C*-S), 39.0 (CH_3-*N*), 13.1 (CH_3-C=C).

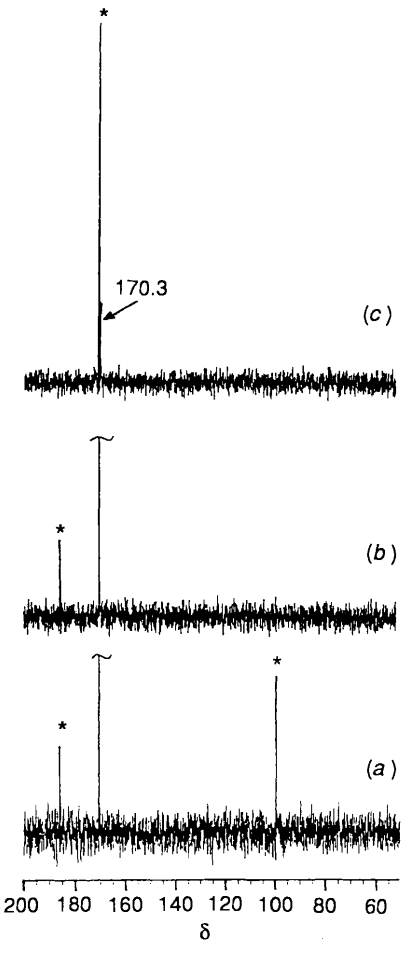


Fig. 1 ^{13}C NMR spectra (300 MHz, 20°C) of ^{13}C enriched **5a** after dissolving in DMSO and waiting (*a*) 2 min; (*b*) 15 min; (*c*) dissolving **5a** in the presence of an equimolar amount of DABCO. Peaks marked with an asterisk are referred to in the text. The peak at δ 170.3 corresponds to $Me^{13}CO_2Et$ added as an internal reference.

ral species is found even after 10 min, as shown by the presence of a singlet at δ_H 1.864 attributed to the methyl attached to the tetrahedral carbon‡ (Fig. 1) (δ_C 99.6) replacing the resonance at δ_H 2.578 of the acetyl methyl of **4a** (δ_C 185.6 for C=O). Addition of a base such as 1,4-diazabicyclo[2.2.2]octane (DABCO) or polymer supported 4-vinylpyridine crosslinked with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (2%) to a solution of **5a** resulted in the immediate formation of **2a** (δ 170.7 for C=O) identical with the compound obtained in the reaction of **1** with acetyl cyanide.[2a,3] Similar results were obtained using the acylating agent **4b**, which yielded **5b** as an unstable oil upon treatment with phenylhydroxylamine. Upon basic treatment **2b** was likewise obtained in high yield (*ca.* 80%), identified by comparison with an authentic sample.[2b] If the acylation reaction is performed in the presence of a base, no tetrahedral intermediate is isolable, the *O*-acylated product **2** being formed directly. *N*-Acylation of **1** to give the corresponding hydroxamic acid was not observed under the conditions described.

If it is assumed that **5** and the *N* isomer **6** are in equilibrium (previously established for the corresponding intermediates derived from acetyl cyanide[3]), the origins of the *O*-specificity can be probed by comparing the relatives energies of these two forms. We used the AM1 and PM3 models at the SCF (gas phase) and the SCRF (self-consistent-reaction field) levels,[5] the latter methodology having been shown to reproduce the relative solution energies of a range of polar heterocyclic tautomers[6] and zwitterionic systems.[7] The difference between the SCF and SCRF energies corresponds to the solvation energy, which for **5** (PM3, 65.8, AM1, 67.0) is greater than for **6** (PM3, 57.9, AM1, 49.0 kcal mol^{-1} 1 cal = 4.184 J), these values being similar to those estimated experimentally[8] for *e.g.* pyridinium cations (≈5.5 kcal mol^{-1}) AM1 predicts **5** to be more stable§ at both the SCF (by 6.3 kcal mol^{-1}) and SCRF levels (by 24.3 kcal mol^{-1}), whereas for PM3 the predicted gas phase preference for **6** (by 1.3 kcal mol^{-1}) is reversed at the SCRF level (−6.6 kcal mol^{-1}), implying the **5** : **6** ratio may be sensitive to solvent polarity.

These results point out that 2-acyl-3,4-dimethylthiazolium salts, modelled upon the biologically significant 2-acetyl thiamine,[4] are selective *O*-acylating reagents of aromatic hydroxylamines under mild conditions. Earlier work by Corbett[9] assumes that the reaction between α-diketoglutarate dehydrogenase and an aromatic nitroso compound proceeds *via* an intermediate hydroxylamine **1** and a thiamine derived acyl species of type **4**, formed by an oxidation–reduction process, followed by *N*-acylation of the hydroxylamine to yield a hydroxamic acid. On the basis of our results, it is very probable that the unsatisfactory mass balance previously observed[9] can be more simply accounted for by the initial formation of the unstable *O*-acyl derivative of **1** and its subsequent decomposition.

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‡ A ^{13}C enriched **4a** and **5a** could be easily obtained by using $Me^{13}CO_2Et$ and BuLi (*cf.* ref. 10) for the synthesis of **4a**.

§ Full geometry optimisation was undertaken for the cationic component of **5** and **6** at the SCF and SCRF levels, using modified[5] MOPAC 5 or AMPAC 2.1 programs, ε = 46.6 and a spherical reaction cavity radius of 3.85 Å estimated for both isomers from the calculated molecular volumes.[7] The gas phase SCF calculated PM3 (AM1) heats of formation (kcal mol^{-1}) are: (**5**, R = Me) 157.7 (153.9), (**6**, R = Me) 156.4 (160.2). The corresponding SCRF energies were (**5**, R = Me) 91.9 (86.9), (**6**, R = Me) 98.5 (111.2).