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Reaction of aromatic nitroso compounds with chemical models of 'thiamine active aldehyde'

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ABSTRACT

Aromatic nitroso compounds in the presence of base and 2-(α-hydroxyalkyl)-3,4-dimethylthiazolium trifluoromethanesulfonate and related salts furnish in variable yields *O*- and *N*-acyl-aryl hydroxylamines and 3,4-dimethylthiazolium trifluoromethanesulfonate. A primary kinetic isotope effect of 4.9, obtained for the appropriate 2α-deuterated thiazolium salt, points to the $C_{2\alpha}$–H bond cleavage as the rate determining step. Radical species detected by ESR were unambiguously identified as phenylhydronitroxide, but attempted trapping of the corresponding C–heterocyclic radicals by TEMPO was not successful, and substrates incorporating a potential cyclopropyl radical clock gave products with the cyclopropyl ring intact. Theoretical calculations revealed a large activation energy for such reaction, which thus cannot per se exclude the intervention of such radical species. Evidence for the likely operation of two concurrent mechanisms, a radical and a preponderant ionic pathway, involving the conjugate base of the thiazolium salt, as the chemical model for 'active thiamine', and ArNO is presented for the formation of the products of the reaction.

1. Introduction

Thiamine diphosphate **1** is a coenzyme of importance in mammalian carbohydrate metabolism as it is involved in vital non-oxidative and oxidative processes.[1] The simplest reaction catalysed by this coenzyme in aqueous systems is pyruvate decarboxylation[2] in yeast (Scheme 1). According to this pathway there are three covalent intermediates between the coenzyme/conjugate base and the substrate/product: the direct adduct **2**, the 2-α carbanion **3** in equilibrium with the corresponding enamine ('active aldehyde') and the 2-(α-hydroxy)-ethyl derivatives **4**. Final decomposition of **4** yields the ylide derivative of **1** and acetaldehyde. Alternatively, as in the enzyme pyruvate oxidase found in lacto bacteria,[3] **4** may suffer oxidation leading to the reactive 2-acetylthiazolium species **5**, which reacts with inorganic phosphate producing acetyl phosphate and regenerating the ylide. Much work has been done in studying properties of species such as **4** and its structurally simplified analogues.[4]

The ability of thiamine-dependent enzymes to convert aromatic nitroso compounds into hydroxamic acids has been investigated by Corbett et al.,[5a,b] and more recently Ying et al.[5c] also used nitrosobenzene as the electrophile in the reaction with the homoenolate equivalent to the enamine **3**. Earlier work from our laboratory[5d] also showed (Scheme 2) that the thiazolium salts **6a**, modelled on the thiamine diphosphate coenzyme, reacted with nitrosobenzene (**7a**) in the presence of Et_3N to give a mixture of a model procarcinogen *O*-acetylphenylhydroxylamine[6] (**8a**), phenylacetohydroxamic acid (**8b**), thiazolium salt **9** and azoxybenzene **10**.

2. Results and discussion

Various possibilities that may be considered for their formation are summarised as follows (Scheme 3): that PhNHOAc and PhN(OH)Ac could originate by a hydride ion transfer from **6a′** to PhNO to produce initially the phenylhydroxylamine anion **11a**/**11b** and 2-acetylthiazolium salt **12**. Alternatively the latter two substances could be produced from **13b** and PhNO by a process involving electron transfer and protonation. Subsequent reaction between the ambident nucleophile **11a**/**11b** and ketone **12** would furnish products **8a** and **8b** resulting from oxygen and nitrogen attack, respectively. Either an isomerisation of **8a** or a condensation

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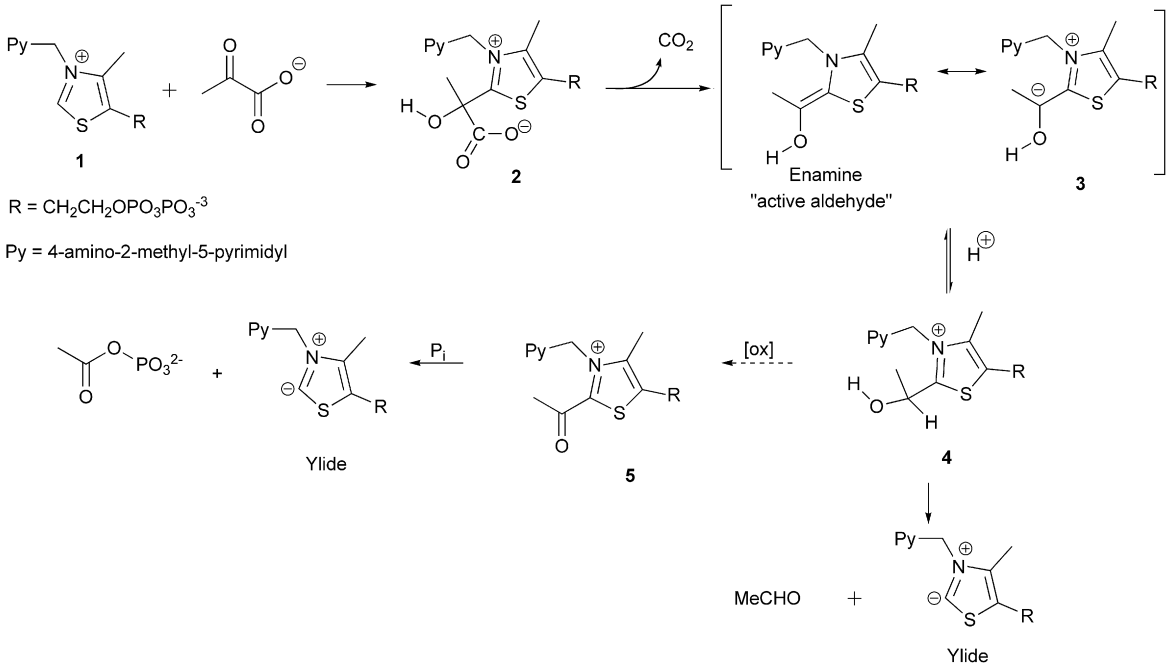
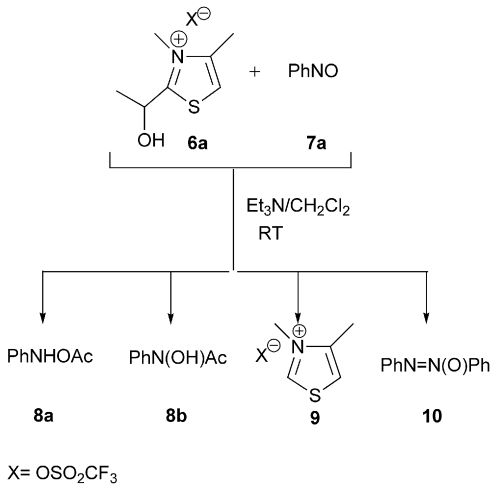
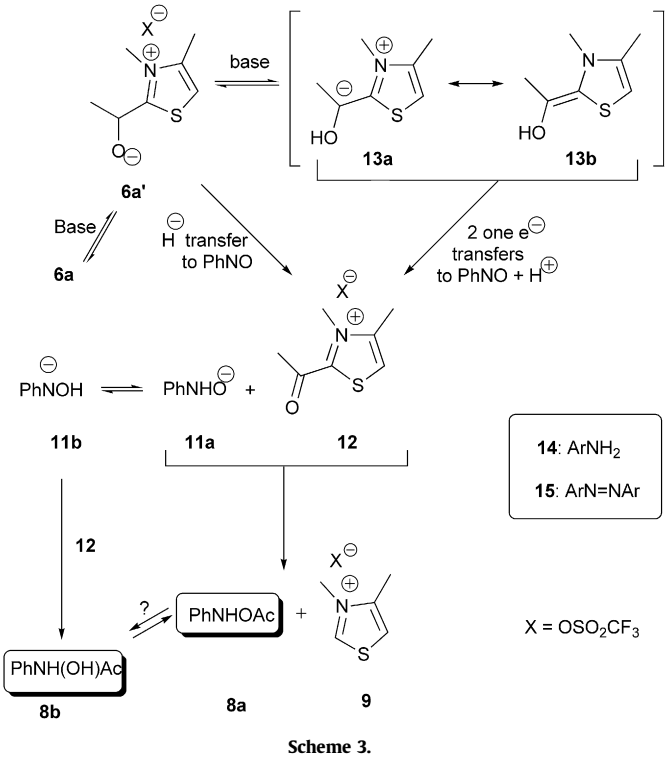


Scheme 1.



Scheme 2.



Scheme 3.

of enamine **13b** and PhNO was mentioned as a possible route to **8b**. Azoxybenzene (**10**) was thought to arise from PhNHOAc and PhNO.

Given the biological importance of such reaction, and the presence of nitroso aromatics as xenobiotics in the environment, the study of the reaction was extended to other nitroso aromatics and related thiazolium salts (Table 1). These substances also gave largely similar results except that in certain cases anilines (**14**) and/or azobenzenes (**15**) were obtained (entries 3, 5, 6 and 8; Table 1).

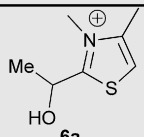
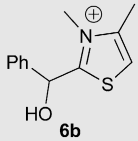
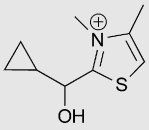
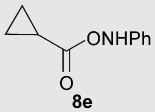
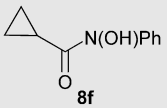
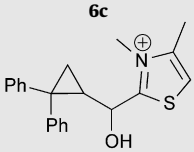
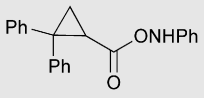
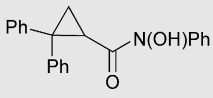
2.1. Solvent/base

Although the reaction was found to occur in solvents of different polarities (dimethoxyethane, dioxane, dichloromethane, chloroform, dichloroethane, acetonitrile) the eventual choice of CH_2Cl_2 was dictated by solubility considerations and acceptable rates of the reactions. Of the three organic bases Et_3N, Hunig's base and DABCO, the first two were found to be more satisfactory than the last. NaH was also used as a base for the reaction.

2.2. Preparation of starting materials: thiazolium carbinols 6

All thiazolyl ketones, except **18d**, were secured from the appropriate ester **16** and 2-lithium-4-methylthiazole **17** (1: 1.1 molar ratio), as described earlier[7a] (Scheme 4).

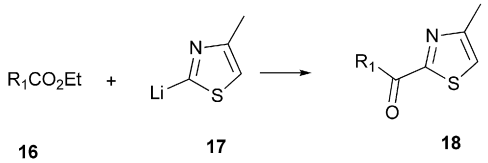
Table 1
Reaction of aromatic nitroso with thiazolium salts and base

Entry	R–C_6H_4N=O	Thiazolium salt[a]	*O*-Acyl hydroxylamines[b] (%)	Hydroxamic acids (%)	ArN(O)=NAr (%)	ArN=NAr (%)	$ArNH_2$ (%)
		 **6a**	ArNHOAc **8a**	ArN(OH)Ac **8b**			
1	**7a**, R=H	**6a**	45	14	22	—	—
2	**7b**, R=4-Br	**6a**	14	21	59	—	—
3	**7c**, R=4-NO_2	**6a**	13[c]	—	48	23	—
4	**7d**, R=4-Cl	**6a**	5	15	30	—	—
5	**7e**, R=3-Me	**6a**	11	19	43	—	6
6	**7f**, 2,4,6-tri-*tert*-butyl nitrosobenzene	**6a**	—	—	—	—	28
		 **6b**	ArNHOCOPh **8c**	ArN(OH)COPh **8d**			
7	**7b**	**6b**	21	25	46	—	—
8	**7c**	**6b**	46[d]	—	29	12	—
9	**7d**	**6b**	24	17	31	—	—
10	**7e**	**6b**	28	23	43	—	—
		 **6c**	 **8e**	 **8f**			
11	**7a**	**6c**	50	ca. 1	19	—	—
		 **6d**	 **27c**	 **27e**			
12	**7a**	**6d**	23	2	—	—	—

[a] Counter ion for all salts, $CF_3SO_3^-$.
[b] *O*-Acyl hydroxylamines are, in general, labile substances and hence they were characterised and quantified, unless stated otherwise, as stable *N*-acyloxy-4-nitrobenzamides (see Section 4).
[c] Characterised as the corresponding *N*-benzamide.
[d] Characterised as the corresponding *N*-acetamide.

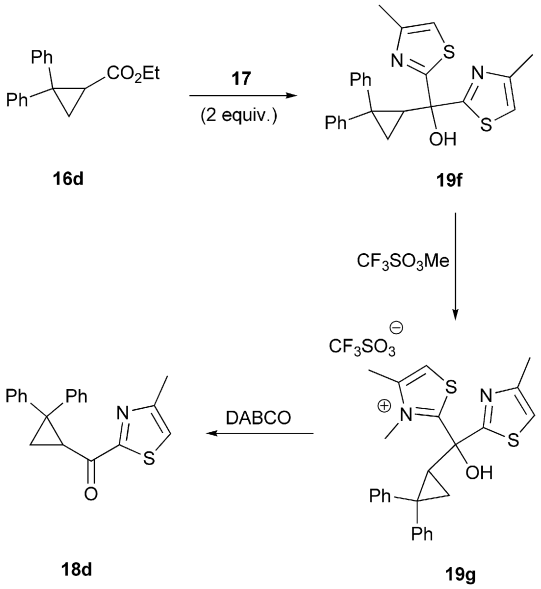
The above procedure, however, did not give acceptable results for ethyl 2′,2′-diphenylcyclopropyl-carboxylate **16d**.[7b] The requisite ketone **18d** was found to be admixed with the bis-addition product **19f** and their separation proved to be difficult. Therefore it was obtained in three steps involving: (i) 2 equiv of the lithium salt per mole of **16d**, (ii) N-monoalkylation of the resulting **19f** to **19g** and (iii) DABCO induced fragmentation of **19g** to **18d** in 50% overall yield (Scheme 5).

Reduction of ketones **18** with $NaBH_4$ furnished the corresponding secondary alcohols **19**. These were alkylated with CF_3SO_3Me to yield respective the *N*-quaternised carbinol **6** (Scheme 6).

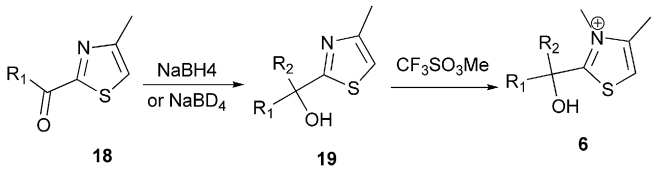


a R_1= Me
b R_1= Ph
c R_1= cyclopropyl
d R_1 = 2',2'-diphenylcyclopropyl

Scheme 4.



Scheme 5.



Scheme 6.

2.3. Carbanion chemistry of some derivatives of 2α-hydroxyethyl thiazolium salts

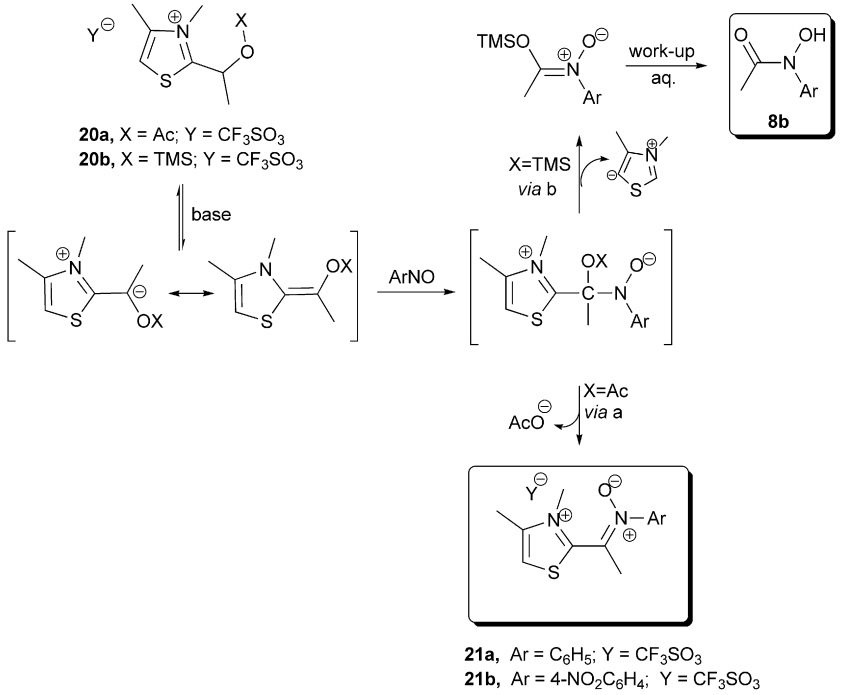
When the OH group of **6a** was protected either as an acetyl **20a** or as a silyl derivative **20b**, their reactions with ArNO, in the presence of a base, afforded the nitrones **21a**,**b** (pathway a) and the hydroxamic acid **8b** (Ar=Ph) (pathway b), respectively. These reactions undoubtedly proceed via the derived carbanion or enamine as shown below (Scheme 7).

However, in the absence of such protection, the deprotonation of **6a** could generate the corresponding alkoxide **6a**′ and/or the carbanion **13a** in resonance with enamine **13b**, and any one of them could be implicated in the formation of **8a** and **8b** (cf. Scheme 3). The pK_a of the $C_{2\alpha}$–H in thiamine is estimated to be between 17 and 19,[8,9] a value close to that of a typical secondary alcohol.

Based on the chemistry reported for the active aldehyde with electrophiles, both ionic[1a] and radical pathways can be envisioned for the reaction **6a**→**8a**+**8b** (Scheme 2). We first consider in some detail the latter process since PhNO is a good electron acceptor and thiazolium salts in basic medium have been shown to undergo easy oxidation to form relatively stable heterocyclic radicals.[10]

2.4. Detection and identification of phenylhydronitroxide radical (PhNH–O˙)

1. When the reaction of **6a** and **7a** was studied by ESR it was found that in the absence of base a mixture of **6a** and **7a**, in equimolar proportions in CH_2Cl_2, was indefinitely stable and did not generate any radical species detectable by ESR spectroscopy.
2. Addition of an equivalent of Et_3N to the above solution resulted in the appearance of strong ESR signals (bandwidth 44 G), as shown in the spectrum of Figure 1a.
3. An identical spectrum was recorded with *N*,*N*-diisopropylamine, or when the solvent was changed to CD_2Cl_2, indicating



Scheme 7.

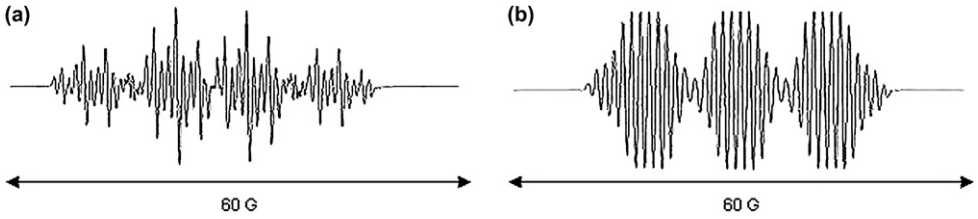
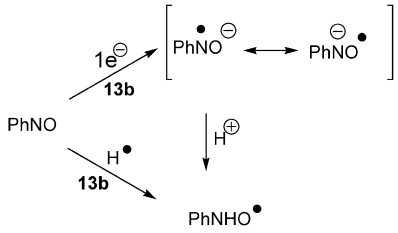


Figure 1. (a) Observed ESR spectrum for the reaction involving equimolar quantities of 3,4-dimethyl-2-(α-[^{2}H]-α-hydroxyethyl)-thiazolium triflate, Et_3N and PhNO; (b) simulated spectrum of PhND–O˙.

that radicals were not derived from either the solvent or the base. The signals generated were attributed exclusively to PhNH–O$^{\bullet}$[11] (Fig. 1a).

4. Compound **6e**, the 2α-deuteriated analogous to **6a**, obtained by $NaBD_4$ reduction of **12** followed by N-methylation of the resulting alcohol, on reaction with **7a**, originated spectrum Fig. 1a and not that of PhND–O$^{\bullet}$ (Fig. 1b) showing that a $C_{2\alpha}$–H homolytic bond cleavage is not involved in the production of the above radical.
5. The spectrum generated from 2-chloronitrosobenzene (which also furnished the corresponding *N*-acetoxyaniline) was found to be identical with that of 2-chlorophenylhydronitroxide recorded in the literature.[12]
6. The simplified spectrum resulting from pentadeuteriated nitrosobenzene[13] and its simulated spectrum were consistent with the structure of pentadeuteriated hydronitroxide.
7. ESR signals due to phenylhydronitroxide radical have been often observed during the electrochemical reduction of nitrosobenzene even in supposedly 'dry solvents' and this was attributed to the protonation of the initially formed anilinoxyl radical by the adventitious presence of water molecules.[14] To eliminate this possibility the reaction was conducted in dry CH_2Cl_2 with NaH[15] (which assured anhydrous conditions of the medium) as the base. Since the same radical was observed by ESR it was concluded that phenylhydronitroxide is not formed from anilinoxyl and subsequent protonation (Scheme 8).



Scheme 8.

These observations were consistent with a hydrogen atom abstraction from the OH group of enamine **13b** by PhNO. The complementary heterocyclic radical (not discernable by virtue of the strong signals of PhNH–O[16]), engendered simultaneously, could have one of the following canonical structures, namely the enoxyl **22**, the α-keto radical **23** or the ketyl **24** (Scheme 9).

Ring opening of a ketyl of type **25** (cf. Scheme 9) is known.[17] Therefore, the reaction of the cyclopropyl salts[18] **6c** and **6d** (Table 1, entries 11 and 12) with PhNO were examined under standard conditions. In the event[19] none of butyric acid derivatives **26d** and **26f** could be detected when run against authentic samples on TLC (Scheme 10). Only products **27c** and **27e** were formed and these characterised as their *p*-nitrobenzoyl derivatives **27d** and **27f**, respectively.

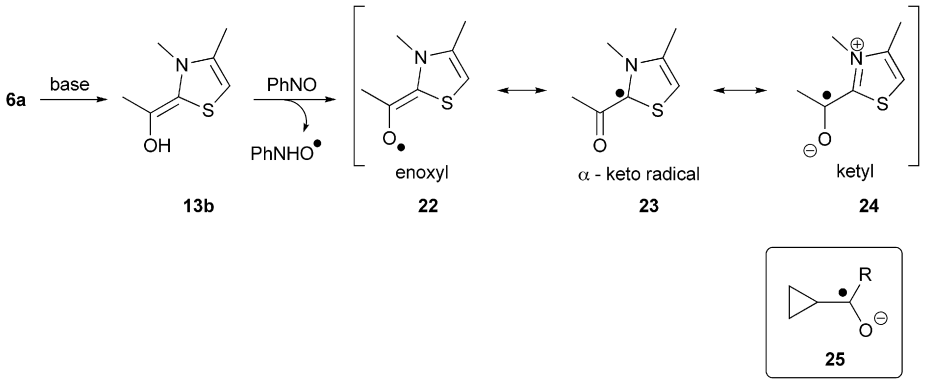
Substrates incorporating a potential cyclopropyl radical probe gave products with the cyclopropyl ring intact, but theoretical calculations reveal this to be due to the endothermicity of the ring opening. This probe therefore cannot per se be used as a test to exclude the intervention of such radical species.

Calculations using Gaussian 03 (revision d.02) were done on the diphenylcyclopropyl substituted radical **6′**↔**6″**↔**6‴**. At the optimised geometry, the calculated spin densities suggest that although representations **6′** and **6‴** are both more realistic than **6″**, the unpaired electron is nevertheless also delocalised around the thiazolium ring. This would account for the reluctance of the radical to ring open the cyclopropyl ring (see Fig. 2), a process calculated as being endothermic in free energy by 15.9 kcal mol^{-1} and hence very unfavoured.

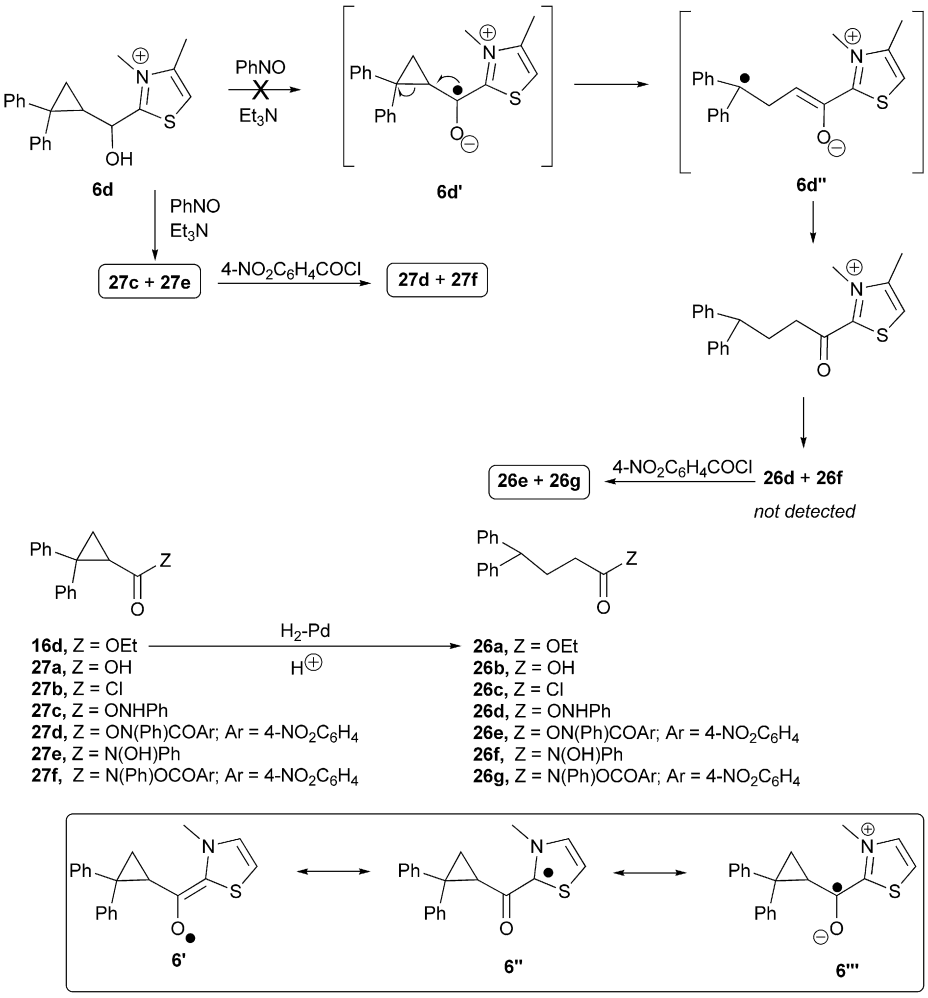
On these grounds ketyl **24** cannot be definitely excluded as an intermediate in the reaction leading to PhNH–O$^{\bullet}$.

In an attempt to trap the heterocyclic radical, derived from the thiazolium moiety, the reaction was performed in the presence of an equivalent of TEMPO relative to nitrosobenzene. A solid residue obtained on removal of the solvent in vacuum was leached several times with dry ether to remove unreacted TEMPO and other ether-soluble substances such as azoxybenzene. The resulting polar residue was purified by PTLC to furnish a low yield of nitrone **21a** and acetate **20a**, both identical with their respective authentic samples. In the absence of PhNO only **20a** was isolated (33%). A reasonable mechanism (Scheme 11) for the reaction would consist of an oxidation of **6a** to **12** followed by acetylation of the former to **20a**. The formation of **21a** from **20a** and PhNO is already referred to in Scheme 6.

With TEMPO in excess (5 equiv), relative to nitrosobenzene, practically no azoxybenzene, PhN(OH)Ac or PhNHOAc were formed. Virtually all PhNO remained unreacted.[20] Clearly, in reactions involving the thiazolium salt **6a** in basic medium, TEMPO is acting as the oxidant.[21] If this were to be so, then TEMPOL or its anion should be formed. The failure to isolate it under normal conditions could be due to its facile air reoxidation. Therefore, the experiment was repeated in degassed CH_2Cl_2 under dry argon (Scheme 12). When a significant quantity of TEMPOL was detected on the TLC,[22] acetic anhydride was added to the reaction mixture and *N*-acetoxytetramethylpiperidine (**28**), mp 63 °C (lit.[23] 63.5–65 °C) was formed and isolated by PTLC in 43% yield. Its IR and ^{1}H NMR spectra were identical with an authentic sample obtained from TEMPOL,[24] Ac_2O and Et_3N.



Scheme 9.



Scheme 10.

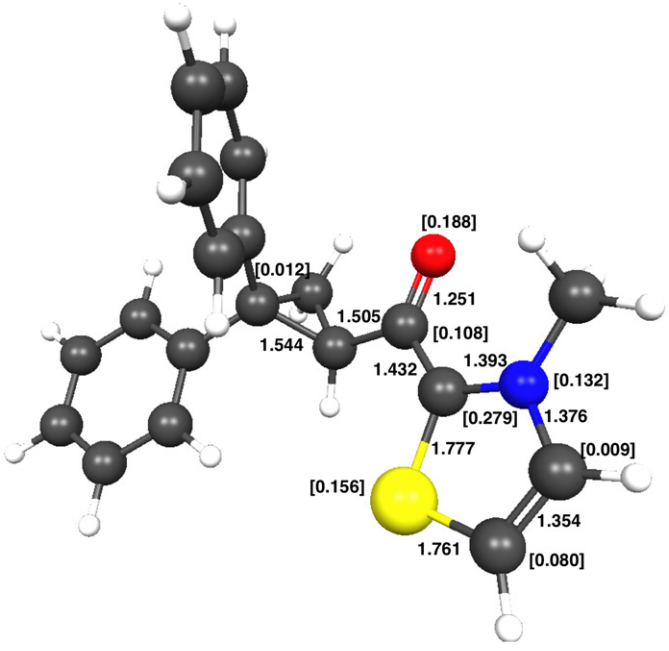
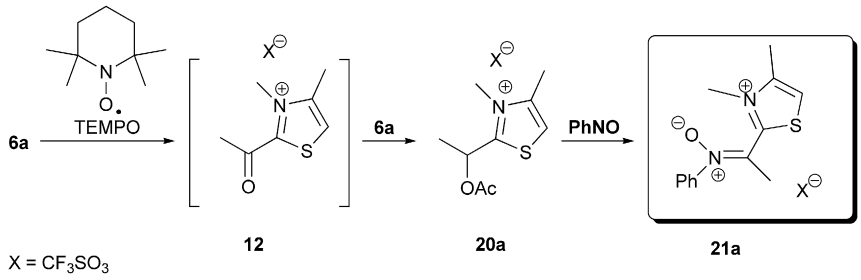


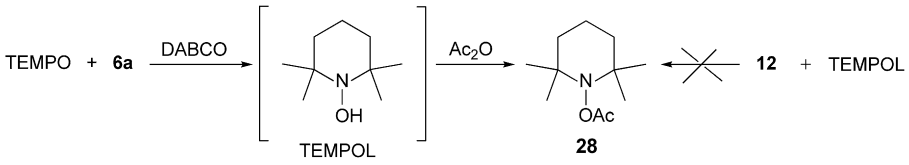
Figure 2. Spin density (ROB3LYP/cc-pVDZ) calculation on radical **6′↔6″↔6‴**. Numbers in brackets refer to spin densities.

These results could be best interpreted as involving a hydrogen atom abstraction[25] by TEMPO from enamine to furnish TEMPOL and the enoxyl **22**. Further reaction of TEMPO, which is present in excess, with the α-keto radical[26] **23** would give the tetrahedral intermediate **29** from which **12** could be formed along with TEMPO anion (Scheme 13). We ascribe the failure of TEMPO to undergo acetylation by **12** to unacceptable steric congestion in the tetrahedral intermediate produced in an ionic reaction. In fact no acetylation was observed between these two substances (TEMPOL+**12**) in the presence of base. Therefore acetylation of alcohol **6a** occurs by default to give **20a**.

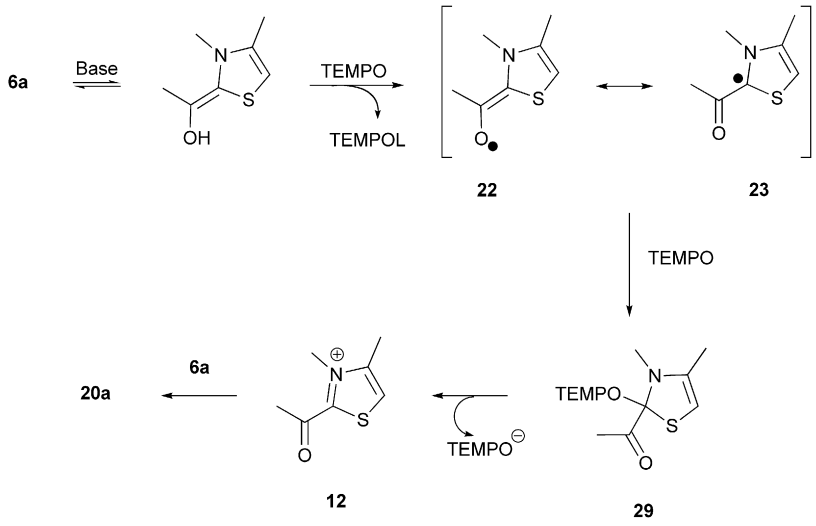
During the mechanistic studies, it was assumed that azoxybenzene formation could be due, inter alia, to a condensation between PhNHOAc and PhNO. Indeed a mixture of these two substances in the presence of Et_3N rapidly produced a high yield of azoxybenzene. However, azoxybenzene would also be expected for a reaction between PhNO and PhNHOH if the latter were to be formed by a *hydride transfer* from enamine **13b** to PhNO (Scheme 14). In fact, on mixing PhNHOH, PhNO and Et_3N in CH_2Cl_2, a good yield of azoxybenzene was obtained. On monitoring this reaction by ESR spectroscopy signals due to PhNH–O$^{\bullet}$ were also observed.[27] Its concentration, as determined with reference to an external sample of TEMPO of known concentration, was 3.3×10^{-4} M. The maximum concentration of phenylhydronitroxide, achieved after 20 min, for a 0.1 M solution each of PhNO and thiazolium salt **6a** containing Et_3N (1 equiv) in CH_2Cl_2 was determined to be



Scheme 11.



Scheme 12.



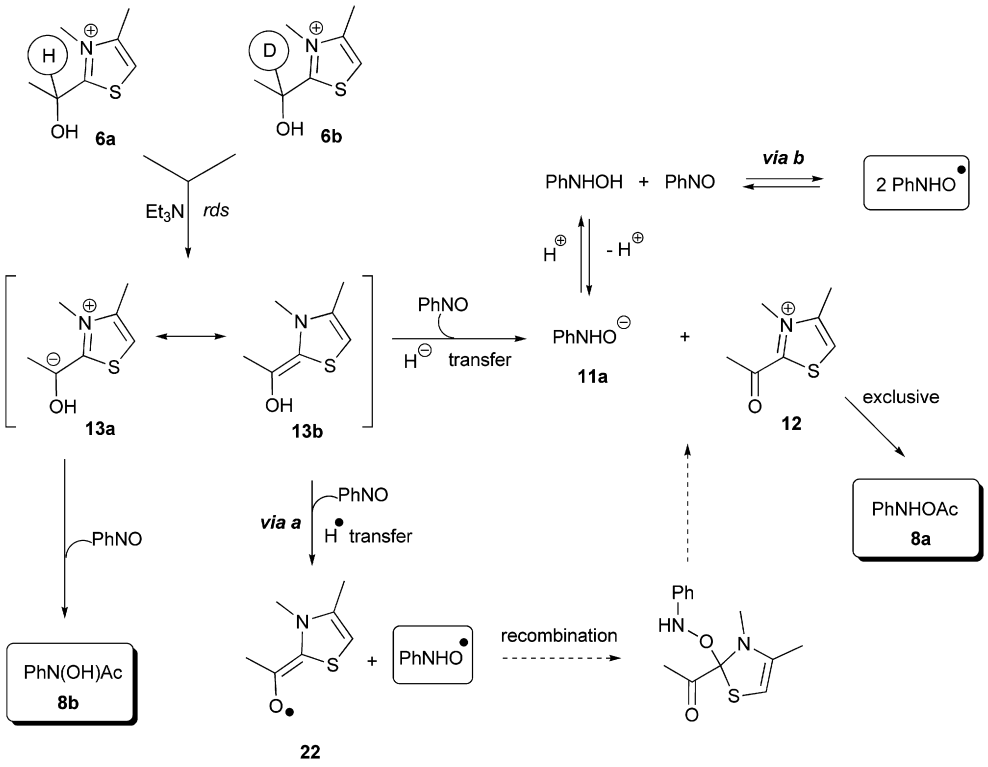
Scheme 13.

9×10^{-5} M. The nitroso group could accept an H atom from enol **13b** to produce directly the radical species (Scheme 14, via a). Alternatively in a preponderant ionic reaction, a hydride ion transfer could occur from **13b** to produce $PhNHO^{-}$. The latter, in its subsequent reaction with PhNO leading to azoxybenzene, could also originate phenylhydronitroxide (Scheme 14, via b) or react directly with the 2-acetylthiazolium (**12**) to give PhNHOAc (**8a**).[28] Whatever the genesis of the radicals, their eventual conversion into PhNHOH and thence to PhNHOAc (Scheme 14), could follow the same chemistry as outlined for the formation of TEMPOL (Scheme 13).

Finally, the mechanism referred to above should display a primary kinetic isotopic effect if the deprotonation, i.e., enamine **13b** formation, were to be the rate determining step (Scheme 14). Therefore the reactions of PhNO with **6a** and the deuterium labelled 3,4-dimethyl-2-(α-[^{2}H]-α-hydroxyethyl)-thiazolium triflate (**6e**), under pseudo-first order conditions (excess base and alcohol), were conducted. The rate constants as determined by the disappearance of nitrosobenzene (UV) were found to be k_{o}^{H} $(8.8\pm0.4)\times10^{-3}$ s^{-1} and k_{o}^{D} $(1.8\pm0.1)\times10^{-3}$ s^{-1}, respectively, for the non-deuterated **6a** and the deuterated **6e** substrates. The value of k_{o}^{H}/k_{o}^{D} of 4.9, obtained for the primary kinetic isotope effect, is in close agreement with that found for the deprotonation of similar substances.[29]

3. Conclusions

While the involvement of an ionic mechanism for the formation of a 'thiamine active aldehyde' analogue in the rate determining step and its subsequent attack to the electrophilic nitroso group appears the most likely pathway for the base catalysed reaction under study; two different hydrogen abstracting reactions are proposed to account for the generation of a small concentration of PhNH–O$^{\bullet}$ radicals. While substrates incorporating a potential cyclopropyl radical clock gave products with the cyclopropyl ring intact, a result supported by the calculated high endotermicity of the reaction, an attempted trapping of the corresponding C–heterocyclic radicals by TEMPO was not successful. Thus evidence for the operation of a preponderant ionic pathway, involving the



Scheme 14.

conjugate base of the thiazolium salt and ArNO, while favoured for the formation of the isomeric *O*- and *N*-acylated aromatic hydroxylamines, cannot rule out the intervention of radical intermediates.

4. Experimental

4.1. General

Melting points were recorded on a Reichert-Thermovar hot stage apparatus and are uncorrected. Ordinary mass spectra were recorded on a Fisons Trio or AEI MS-9 spectrometers. High resolution mass spectra were recorded on an AutoSpeQ spectrometer. ^{1}H and ^{13}C NMR spectra recorded in $CDCl_3$ on a Bruker ARX 400 spectrometer (400 MHz for ^{1}H and 100.63 MHz for ^{13}C). Chemical shifts reported are relative to tetramethylsilane as the internal reference (δ_H 0.00) for ^{1}H NMR spectra and to $CDCl_3$ (δ_C 77.00) for ^{13}C NMR spectra. Chemical shifts are expressed in parts per million, downfield from TMS (δ=0) or residual dichloromethane (δ_H=5.32, δ_C=53.1) as internal standards. IR spectra were run on Perkin–Elmer 683 and Spectrum 1000 instrument with absorption frequencies expressed in reciprocal centimetres. Electronic spin resonance spectra (ESR) were recorded at rt on a Bruker EMX spectrometer. Typical conditions were as follows: microwave power, 2 mW; modulation amplitude, 0.1 G at 100 KHz; time constant, 20.48 ms; sweep time 83.886 ms. The ESR parameters for the various radical species were determined by signal simulations using the software 'SimFonia' from Bruker. Spin concentration was calculated with reference to pure TEMPO (sublimed) of known concentration as external standard under the following condition: microwave power, 2 mW; modulation amplitude, 0.4 G at 100 KHz; time constant, 20.48 ms; sweep time 83.886 ms; sweep width 200 G and receiver gain at 2×10^3. Microanalyses were performed on a Carlo Erba 1106R microanalyser. All reagents and solvents were purified and dried by standard methods[30] before use. Usual work-up implies that organic extracts were washed with water and dried over anhydrous sodium sulfate or magnesium sulfate, filtered and solvent removed from the filtrate under reduced pressure. Analytical thin-layer chromatography and preparative TLC (PTLC) were performed on E. Merck Kieselgel 60, F_{254} silica gel (0.2 mm thick) and 0.5, 1 or 2 mm thick plates (20×20 cm), respectively. Column chromatography was performed on E. Merck Kieselgel 60 (240–400 μm) silica gel.

4.2. Starting materials

4.2.1. General procedure for the preparation of nitrosoarenes

These substances were prepared from the corresponding nitro compounds by reduction first with zinc dust in boiling aq ethanol followed by oxidation of the resulting arylhydroxylamines with aq $FeCl_3$ as described.[31] Nitrobenzene-d_5[32] was processed as above to give nitrosobenzene-d_5 (25%), mp 65–67 °C (ethanol) (lit.[33] 65–67 °C).

4.2.2. General procedure for the preparation of 2-acyl-4-methylthiazoles

The 2-acyl-4-methylthiazoles mentioned in the present work were prepared as described[7a] earlier except for **18d**, which was obtained as follows: **16d**→**19f**→**19g**→**18d**.

*4.2.2.1. (2′,2′-Diphenylcyclopropyl)-bis-(4-methyl-2-thiazoyl)-carbinol (**19f**).* Ethyl-2′,2′-diphenylcyclopropane carboxylate[7b] (**16d**) (2.8 g, 10.53 mmol) was treated with 2-lithio-4-methylthiazole [from 4-methylthiazole, 1.93 mL, 21.06 mmol and *n*-BuLi (1.6 M in *n*-hexane, 2 equiv)] to give **19f** as a pale yellow solid (73%), mp 95–96 °C (CH_2Cl_2–*n*-hexane); ν_{max}(KBr)/cm^{-1} 3426; δ_H ($CDCl_3$) 1.23 (1H, dd, *J* 4.7 and 9.1 Hz), 2.11 (1H, t, *J* 5.4 Hz), 2.39 (3H, s), 2.45 (3H, s), 3.10 (1H, dd, *J* 6.3 and 9.1 Hz), 3.77 (1H, exchangeable with D_2O), 6.75 (1H, s), 6.91 (1H, s), 6.98 (2H, d, *J* 4.7 Hz), 7.08–7.13 (4H, m), 7.20–7.25 (2H, m), 7.45 (2H, d, *J* 7.4 Hz); δ_C 14.2, 17.1, 17.3, 35.5, 36.3,

114.2, 115.1, 126.1, 126.3, 127.9, 128.2, 128.7, 130.0, 140.2, 146.8, 151.3, 152.7, 173.7; HRMS(EI): m/z $C_{24}H_{22}N_2OS_2$ requires: 418.11735, found: 418.11731.

*4.2.2.2. Compound **19g**.* Compound **19f** (500 mg, 1.2 mmol) in dry ether (10 mL) was treated with CF_3SO_3Me (135.35 μL, 1.2 mmol) and the resulting mixture stirred overnight at rt. The solid that had separated was collected by filtration and crystallised (ethanol–Et_2O) to give thiazolium salt **19g** (626 mg) as a colourless solid (90%), mp 155–156 °C (CH_2Cl_2–*n*-hexane); ν_{max}(KBr)/cm^{-1} 3426; δ_H (DMSO-d_6) 1.47 (1H, dd, *J* 5.0 and 8.6 Hz), 2.30 (3H, s), 2.60 (3H, s), 3.08–3.11 (2H, m), 4.12 (3H, s), 7.04 (5H, s), 7.16–7.36 (5H, m), 7.88 (1H, s), 8.41 (1H, s), 10.04 (1H, s, exchangeable with D_2O); HRMS (FAB) m/z $C_{25}H_{25}N_2OS_2$ requires: 433.14083, found: 433.13968.

*4.2.2.3. 2-(2′,2′-Diphenylcyclopropanoyl)-4-methylthiazole (**18d**).* Compound **19g** (500 mg, 1.2 mmol) dissolved in a minimum quantity of ethanol was treated with DABCO (134 mg, 1.2 mmol). Usual work-up (after 10 min) followed by crystallisation of the resulting residue provided **18d** (294 mg, 77%) as a colourless solid, mp 122–124 °C (CH_2Cl_2–*n*-hexane); ν_{max}(KBr)/cm^{-1} 1672; δ_H ($CDCl_3$) 1.78 (1H, dd, *J* 4.3 and 7.8 Hz), 2.51 (1H, d, *J* 5.2 Hz), 2.60 (3H, s), 4.12 (1H, t, *J* 7.0 Hz), 7.15–7.32 (8H, m), 7.45 (2H, d, *J* 7.5 Hz); δ_c 17.3, 21.6, 32.5, 44.9, 121.0, 126.6, 128.0, 128.5, 129.8, 130.1, 139.4, 145.1, 155.3, 189.0; HRMS m/z $C_{20}H_{17}NOS$ requires: 319.10308, found: 319.10270.

4.2.3. General procedure for the preparation of 2-(α-hydroxyethyl)-4-methylthiazole and 2-(α-hydroxybenzyl)-4-methylthiazole from the corresponding keto compounds

The appropriate ketone (1 mmol) in ethanol (5 mL) was reduced with a suspension of $NaBH_4$ (12.5 mg; 0.33 mmol) in ethanol (5 mL). On completion of the reaction (TLC control, SiO_2, MeOH–CH_2Cl_2; 2%), solvent was removed under reduced pressure, the residue mixed with water and extracted with Et_2O (3×5 mL). The product worked-up in the usual manner was purified by column chromatography.

*4.2.3.1. 2-(α-Hydroxyethyl)-4-methylthiazole (**19a**).* 2-Acetyl-4-methylthiazole[7a] (**18a**) gave **19a**[2b] as a colourless oil (85%); ν_{max}(film)/cm^{-1} 3300; δ_H (CD_3CN) 1.48 (3H, d, *J* 6 Hz), 2.37 (3H, s), 3.70 (1H, br), 5.05 (1H, q, *J* 6 Hz), 6.98 (1H, s).

*4.2.3.2. 2-(α-Hydroxy-α-deuterioethyl)-4-methylthiazole (**19e**).* 2-Acetyl-4-methylthiazole (**18a**) gave **19e** by reduction with $NaBD_4$ in 68%, as an oil; ν_{max}(film)/cm^{-1} 3300; δ_H (CD_2Cl_2) 1.54 (3H, s), 2.36 (3H, s), 3.35 (1H, s), 6.82 (1H, s); m/z (FAB) 144 (MH^+).

*4.2.3.3. 2-(α-Hydroxybenzyl)-4-methylthiazole (**19b**).* 2-Benzoyl-4-methylthiazole[7a] (**18b**) gave **19b** in 44% yield, mp 94–95 °C (butanone–Et_2O) (lit.[34] 96 °C); δ_H ($CDCl_3$) 2.40 (3H, s), 4.90 (1H, br), 6.05 (1H, s), 6.85 (1H, s), 7.45 (5H, m).

*4.2.3.4. 4-Methyl-2-thiazolyl cyclopropylcarbinol (**19c**).* 2-Cyclopropanoyl-4-methylthiazole[7a] (**18c**) gave **19c** in 77% yield, as an oil, ν_{max}(film)/cm^{-1} 3250; δ_H ($CDCl_3$) 0.71–0.50 (4H, m), 1.30 (1H, m), 2.42 (3H, s), 3.77 (1H, d, *J* 2.4 Hz), 4.32 (1H, dd, *J* 2.4 and 8.1 Hz), 6.83 (1H, s). The alcohol was used as such for the subsequent quaternisation reaction.

4.2.4. General procedure for 2-substituted thiazolium triflates

The appropriate thiazole-alcohol **19** (1.26 mmol) in dry ethyl ether (10 mL) was treated with methyl trifluoromethylsulfonate (135.5 μL, 1.26 mmol) and the mixture allowed to stand at rt (24 h). The solid that separated was collected and crystallised to give the corresponding triflates.

*4.2.4.1. 2-(α-Hydroxyethyl)-3,4-dimethylthiazolium triflate (**6a**).* Compound **19a** yielded **6a** (91.5%), mp 83–85 °C (Et_2O–butanone); ν_{max}(KBr)/cm^{-1} 3350; δ_H (DMSO-d_6) 1. 60 (3H, d, *J* 7.3 Hz), 2.46 (3H, s), 3.83 (3H, s), 4.90 (1H, m), 5.34 (1H, m), 7.57 (1H, s); δ_c 13.7, 22.2, 37.0, 64.7, 117.9, 122.5, 147.2. Anal. Calcd for $C_8H_{12}F_3NO_4S_2$: C, 31.27; H, 3.94; N, 4.56; S, 20.87%. Found: C, 31.03; H, 3.82; N, 4.52; S, 20.99.

*4.2.4.2. 2-(α-Hydroxy-α-deuterioethyl)-3,4-dimethylthiazolium triflate (**6e**).* Compound **19e** yielded **6e** (85%), mp 84–86 °C (butanone–Et_2O); ν_{max} (KBr)/cm^{-1} 3300; δ_H (CD_2Cl_2) 7.44 (1H, s), 5.70 (1H, s), 3.93 (3H, s), 2.51 (3H, s), 2.51 (3H, s), 1.61 (3H, s); HRMS (FAB) m/z $C_7H_{11}DNOS$ requires: 159.0702, found: 159.0697.

*4.2.4.3. 2-(α-Hydroxybenzyl)-3,4-dimethylthiazolium triflate (**6b**).* Compound **19b** yielded **6b** (92.4%), mp 88–89 °C (Et_2O–butanone); ν_{max}(film)/cm^{-1} 3300; δ_H ($CDCl_3$) 7.52 (1H, s), 6.38 (2H, m), 3.86 (3H, s), 2.50 (3H, s); δ_c 13.7, 37.3, 70.6, 118.2, 118.4, 127.4, 129.1, 129.6, 136.8, 147.5. Anal. Calcd for $C_{13}H_{14}F_3NO_4S_2$: C, 42.27; H, 3.82; N, 3.79. Found: C, 42.58; H, 3.80; N, 3.63.

*4.2.4.4. 2-(α-Hydroxycyclopropylmethyl)-3,4-dimethylthiazolium triflate (**6c**).* Compound **19c** yielded **6c**, as a pale yellow oil (95%), ν_{max}(film)/cm^{-1} 3300; δ_H ($CDCl_3$) 0.73 (4H, m), 1.32 (1H, m), 2.57 (3H, s), 4.07 (3H, s), 4.94 (1H, t, *J* 6.3 Hz), 5.57 (1H, d, *J* 6.30 Hz), 7.52 (1H, s); δ_C ($CDCl_3$+DMSO-d_6) 2.7, 3.3, 13.9, 69.1, 118.1, 122.4, 147.2; HRMS (FAB) m/z $C_9H_{14}NOS$ requires: 184.07960, found: 184.0780.

*4.2.4.5. 2-(α-Hydroxy-2′,2′-diphenylcyclopropylmethyl)-3,4-dimethylthiazolium triflate (**6d**).* Compound **19d** yielded **6e** (92%), mp 150–151 °C (Et_2O–butanone); ν_{max}(KBr)/cm^{-1} 3350; δ_H (DMSO-d_6) 1.47 (1H, dd, *J* 5.3 and 8.6 Hz), 1.63 (1H, t, *J* 5.5 Hz), 2.20 (1H, dd, *J* 9.1 and 15.4 Hz), 2.50 (3H, s), 3.85 (3H, s), 4.19 (1H, t, *J* 8.4 Hz), 6.89 (1H, d, *J* 6.9 Hz, exchangeable with D_2O), 7.19 (1H, t, *J* 7.0 Hz), 7.26–7.38 (7H, m), 7.55 (2H, d, *J* 7.4 Hz), 7.93 (1H, s), 8.97 (1H, exchangeable with D_2O); δ_c 30.4, 31.0, 50.3, 126.3, 127.8, 128.5, 129.2, 137.6, 137.9, 143.9, 167.6; HRMS (FAB) m/z $C_{21}H_{22}NOS$ requires: 336.14221, found: 336.14360.

*4.2.4.6. 2-(α-Acetoxyethyl)-3,4-dimethylthiazolium triflate (**20a**).* 2-(α-Acetoxyethyl)-4-methylthiazole[7a] gave **20a** (92%), mp 103–104 °C (butanone–Et_2O); ν_{max}(KBr)/cm^{-1} 1740; δ_H (DMSO-d_6) 1.65 (1H, d, *J* 6.6 Hz), 2.14 (3H, s), 2.51 (3H, s), 3.98 (3H, s), 6.41 (1H, q, *J* 6.6 Hz), 7.01 (1H, s). Anal. Calcd for $C_{10}H_{14}F_3NO_5S_2$: C, 34.38; H, 4.04; N, 4.01%. Found: C, 34.40; H, 4.06; N, 3.97.

*4.2.4.7. 2-[α-(Trimethylsilyloxy)-ethyl]-3,4-dimethylthiazolium triflate (**20b**).* 2-[α-(Trimethylsilyloxy)-ethyl]-3,4-dimethylmethylthiazole (**20a**) was first prepared by stirring at rt a mixture of 2-(α-hydroxyethyl)-4-methylthiazole (3 mmol) with TMSCl (1 equiv) and hexamethyldisilasane (1 equiv) in pyridine. It was then filtered, the filtrate concentrated under reduced pressure to yield the silyl derivative as a colourless liquid (88%); δ_H (DMSO-d_6) 0.12 (9H, s), 1.44 (3H, d, *J* 6 Hz), 2.31 (3H, s), 5.07 (1H, q, *J* 6.0 Hz), 7.10 (1H, s). This compound, without further purification, was quaternised as described above for alcohol **19** to give **20b** (87%), mp 98–100 °C (butanone–Et_2O); δ_H (CD_3CN) 0.20 (9H, s), 2.40 (3H, s), 3.80 (3H, s), 5.50 (1H, q, *J* 6.0 Hz), 7.70 (1H, s); HRMS (FAB) m/z $C_{10}H_{20}NOSSi$ requires: 230.1035, found: 230.1058.

4.3. General procedure for reactions between 2-(α-hydroxyalkyl or α-hydroxybenzyl)-3,4-dimethylthiazolium triflate (6) and arylnitroso compounds (7)

The thiazolium salt (0.5 mmol) and the arylnitroso compound (0.5 mmol) in dry CH_2Cl_2 (10 mL/mmol) at rt were treated with the appropriate base (1.1 equiv). On completion of the reaction

(0.5–2 h, TLC control; CH_2Cl_2 or CH_2Cl_2–MeOH 98:2) the products were isolated by diluting the mixture with ethyl ether and rapid washing with an ice-cold aq NaOH (0.5 N) to remove hydroxamic acid. Usual work-up of the ethyl ether solution led to a residue, which was thoroughly dried in vacuo. It was redissolved in dry THF, cooled to −30 °C before adding NaH (3 equiv). The derived Na salt thus obtained was treated with the appropriate acid chloride and the resulting mixture allowed to reach rt while being stirred. The derived *N*-acyloxy-*N*-acylaniline, and other products such as azoxybenzene, aniline (as *N*-acyl derivative) and azobenzene were isolated by PTLC. Acidification of the initial alkaline extract with aq HCl (1 N) furnished hydroxamic acids.

*4.3.1. Reaction between **7a** and **6a** (Table 1, entry 1)*

Furnished *O*-acetyl-*N*-(4′-nitrobenzoyl)-*N*-phenylhydroxylamine (45%), mp 146–148 °C (CH_2Cl_2–*n*-hexane) (lit.[35] 146–148 °C), *N*-phenylacetohydroxamic acid (14%), mp 65–67 °C (CH_2Cl_2–*n*-hexane) (lit.[36] 65–66.5 °C) and azoxybenzene (22%), mp 33–35 °C (ethanol) (lit.[37] 35 °C).

*4.3.2. Reaction between **7b** and **6a** (Table 1, entry 2)*

Furnished *O*-acetyl-*N*-(4′-nitrobenzoyl)-*N*-(4-bromophenyl)-hydroxylamine (14%), mp 164–166 °C (CH_2Cl_2–*n*-hexane) (lit.[35] 162–163 °C), *N*-4-bromophenylacetohydroxamic acid, (21%), mp 129–130 °C (CH_2Cl_2–*n*-hexane) (lit.[38] 129–130 °C) and 4,4′-dibromoazoxybenzene (59%), mp 170–171 °C (ethanol) (lit.[37] 172 °C).

*4.3.3. Reaction between **7c** and **6a** (Table 1, entry 3)*

Furnished *O*-acetyl-*N*-(4-nitrophenyl)-*N*-phenylhydroxylamine characterised as the *N*-benzoyl derivative (13%), mp 112–113 °C (CH_2Cl_2–*n*-hexane), ν_{max}(KBr)/cm^{-1} 1795, 1680; δ_H ($CDCl_3$) 2.15 (3H, s), 7.38–7.55 (7H, m), 8.18 (2H, d, *J* 8.30 Hz). Anal. Calcd for $C_{15}H_{12}N_2O_5$: C, 60.00; H, 4.03; N, 9.33. Found: C, 60.29; H, 4.08; N, 9.35%; 4,4′-dinitroazoxybenzene (48%); mp 191–192 °C (ethanol) (lit.[37] 192 °C) and 4,4′-dinitroazobenzene (23%), mp 223–224 °C (ethanol) (lit.[39] 222–223 °C).

*4.3.4. Reaction between **7d** and **6a** (Table 1, entry 4)*

Furnished *O*-acetyl-*N*-(4′-nitrobenzoyl)-*N*-(4-chlorophenyl)-hydroxylamine (5%), mp150–153 °C (lit.[7a] 152–155 °C), *N*-(4-chlorophenyl) acetohydroxamic acid (15%), mp 111–112 °C (lit.[36] 113 °C) and 4,4′-dichloroazoxybenzene (30%), mp 153–154 °C (ethanol) (lit.[37] 155–156 °C).

*4.3.5. Reaction between **7e** and **6a** (Table 1, entry 5)*

Furnished *O*-acetyl-*N*-(4′-nitrobenzoyl)-*N*-(3-methylphenyl)-hydroxylamine[7a] (11%), *N*-(3-methylphenyl) acetohydroxamic acid (19%), mp 67–69 °C (*n*-pentane) (lit.[40] 67 °C), *N*-4′-nitrobenzoyl-3-methylaniline (6%), mp 146–148 °C (lit.[41] 155 °C) and 3,3′-dimethylazoxybenzene, oil (43%) (lit.[42] 33–35 °C).

*4.3.6. Reaction between 2,4,6-tri-tert-butyl nitrosobenzene (**7f**) and **6a** (Table 1, entry 6)*

Furnished 2,4,6-tri-*tert*-butylaniline (28%) as the only isolable product, mp 145–147 °C (lit.[43] 144.5–145.5 °C), ν_{max}(CH_2Cl_2)/cm^{-1} 2955, 2928, 2860; δ_H ($CDCl_3$) 1.30 (9H, s), 1.50 (18H, s), 7.27 (2H, s); HRMS (EI) *m*/*z* $C_{18}H_{31}N$ requires: 261.2456, found: 261.2426.

*4.3.7. Reaction between **7b** and **6b** (Table 1, entry 7)*

Furnished *O*-benzoyl-*N*-(4′-nitrobenzoyl)-*N*-(4-bromophenyl)-hydroxylamine (21%), mp 142–144 °C (CH_2Cl_2–*n*-hexane), ν_{max}(KBr)/cm^{-1} 1770, 1680; δ_H ($CDCl_3$) 6.95–7.21 (3H, m), 7.34 (2H, d, *J* 8 Hz), 7.53 (2H, d, *J* 9.0 Hz), 7.75 (2H, d, *J* 8.0 Hz), 8.14–8.29 (4H, m). Anal. Calcd for $C_{20}H_{13}N_2O_5$: C, 54.44; H, 2.97; N, 6.35. Found: C, 53.91; H, 4.53; N 6.46%; *N*-4-bromophenylbenzohydroxamic acid (25%), mp 160–161 °C (CH_2Cl_2–*n*-hexane) (lit.[44] 161–163 °C) and 4,4′-dibromoazoxybenzene (46%), mp 170–171 °C (ethanol) (lit.[37] 172 °C).

*4.3.8. Reaction between **7c** and **6b** (Table 1, entry 8)*

Furnished *O*-benzoyl-*N*-(4-nitrophenyl)hydroxylamine (46%), mp 118–120 °C (CH_2Cl_2–*n*-hexane); characterised as the *N*-acetyl derivative, mp 105–106 °C (CH_2Cl_2–*n*-hexane); ν_{max}(KBr)/cm^{-1} 1760, 1695; δ_H ($CDCl_3$) 2.29 (3H, s), 7.50–7.65 (3H, m), 7.76 (2H, d, *J* 9 Hz), 8.13–8.29 (4H, m). Anal. Calcd for $C_{15}H_{12}N_2O_5$: C, 60.00; H, 4.03; N, 9.33. Found: C, 59.93; H, 4.40; N, 9.07; 4,4′-dinitroazoxybenzene (29%), mp 188–190 °C (ethanol) (lit.[37] 192 °C) and 4,4′-dinitroazobenzene (12%), mp 223–225 °C (lit.[39] 222–223 °C).

*4.3.9. Reaction between **7d** and **6b** (Table 1, entry 9)*

Furnished *O*-benzoyl-*N*-(4-chlorophenyl)-*N*-(4′-nitrobenzoyl)-hydroxamic acid (24%), mp 120–121 °C (CH_2Cl_2–*n*-hexane); ν_{max}(KBr)/cm^{-1} 1766, 1681, 1599, 1524, 1488, 1347, 1010 cm^{-1}; δ_H ($CDCl_3$) 7.35 (d, *J* 8.7 Hz, 2H), 7.41 (d, *J* 8.4 Hz, 2H), 7.50 (t, *J* 7.6 Hz, 2H), 7.65 (t, *J* 7.5 Hz, 1H), 7.78 (d, *J* 8.7 Hz, 2H), 8.02 (d, *J* 7.5 Hz, 2H), 8.18 (d, *J* 8.8 Hz, 2H). Anal. Calcd for $C_{20}H_{13}ClN_2O_5$: C, 60.54; H, 3.30; N, 7.06. Found: C, 60.65; H, 3.43; N, 7.55; *N*-4-chlorophenylbenzohydroxamic acid (17%), mp 155–156 °C (CH_2Cl_2–*n*-hexane) (lit.[36] 156–157 °C) and 4,4′-dichloroazoxybenzene (31%), mp 153–154 °C (ethanol) (lit.[37] 155–156 °C).

*4.3.10. Reaction between **7e** and **6b** (Table 1, entry 10)*

Furnished *N*-(3-methylphenyl)-benzohydroxamic acid (23%), mp 67–69 °C (*n*-pentane) (lit.[40] 67 °C); *O*-benzoyl-*N*-(3-methylphenyl)-4′-nitrobenzohydroxamic acid (28%), mp 134–135 °C (CH_2Cl_2–*n*-hexane); HRMS(EI) *m*/*z* $C_{21}H_{16}N_2O_5$ requires: 376.1059, found *m*/*z*: 376.1069; and 3,3′-dimethylazoxybenzene (43%), mp 35 °C (lit.[42] 55 °C).

*4.3.11. Reaction between **7a** and **6c** (Table 1, entry 11)*

Furnished *N*-cyclopropanecarbonyloxy-*N*-phenyl-4-nitrobenzamide (50%), mp 133–135 °C (CH_2Cl_2–*n*-hexane) (lit.[7a] 133–135 °C); azoxybenzene (19%) and traces of a substance (ca. 1%), presumably the hydroxamic acid, giving a positive test with $FeCl_3$ spray on TLC.

*4.3.12. Reaction between **7a** and **6d** (Table 1, entry 12)*

Furnished *N*-(2,2-diphenylcyclopropanecarbonyloxy)-*N*-phenyl-4′-nitrobenzamide (**27d**) (23%), mp 133–135 °C (CH_2Cl_2–*n*-hexane), *O*-(4′-nitrobenzoyl)-*N*-(2,2-diphenylcyclopropancarbonyloxy)-*N*-phenylhydroxylamine (**27f**) (2%), mp 55–56 °C (CH_2Cl_2–*n*-hexane) both identical in all respects (TLC, mp, ^{1}H NMR, IR spectra) with the respective authentic samples prepared as described below.

4.4. Preparation of authentic samples 26d–26g and 27c–27f

*4.4.1. N-(2′,2′-Diphenylcyclopropanecarbonyloxy)-N-phenyl-N-4-nitrobenzamide (**27d**)*

2,2-Diphenylcyclopropane carboxylic acid[7b] (100 mg, 0.42 mmol), DEPC[45] (70 μL, 0.46 mmol) and Et_3N (59 μL) in CH_2Cl_2 (6 mL) were stirred (10 min). Phenylhydroxylamine (48 mg, 42 mmol) in CH_2Cl_2 (6 mL) was added. After 2 min, the mixture containing **27c** was cooled to −78 °C, NaH (35 mg; 1.47 mmol) added and the mixture stirred at that temperature (30 min). 4-Nitrobenzoylchloride (117 mg, 0.84 mmol) in CH_2Cl_2 (2 mL) was then added dropwise. On completion of the reaction (TLC control) HOAc (0.5 mL) in CH_2Cl_2 (2 mL) was added and the product worked-up in the usual manner to give a solid. PTLC purification furnished **27d**, mp 144–145 °C (EtOAc–*n*-hexane); ν_{max}(KBr)/cm^{-1} 1779, 1681; δ_H ($CDCl_3$) 1.81 (1H, dd, *J* 5.0 and 8.0 Hz), 2.24 (1H, t, *J* 5.3 Hz), 2.68 (1H, t, *J* 6.3 Hz), 7.09–7.37 (15H, m), 7.63 (2H, d, *J* 8.4 Hz), 8.10 (2H, d, *J* 8.4 Hz); δ_C 21.6, 26.0, 42.0, 123.3, 126.9, 127.2, 127.5, 127.6, 128.4, 128.6, 129.2, 129.7,

138.6, 139.5, 143.7, 164.60, 168.0; HRMS (EI) m/z: $C_{29}H_{22}N_2O_5$ requires: 478.152872, found: 478.15364.

*4.4.2. N-Hydroxy-N-phenyl-2,2-diphenylcyclopropane-carboxamide (**27e**)*

2,2-Diphenylcyclopropane carboxylic acid (220 mg, 0.92 mmol) in benzene (2.2 mL) containing DMF (2.2 mL) was mixed with $SOCl_2$ (100 μL, 1.37 mmol). The resulting acid chloride **27b** formed in situ was treated with $NaHCO_3$ (78 mg, 0.92 mmol) and PhNHOH (101 mg, 0.92 mmol) in ethyl ether containing a few drops of water. The solid, which was obtained, after the usual work-up, on crystallisation gave hydroxamic acid **27e** (46%), mp 133–135 °C (*n*-hexane–EtOAc); ν_{max}(KBr)/cm^{-1} 3177, 1626; δ_H ($CDCl_3$) 1.56 (1H, dd, *J* 4.8 and 8.0 Hz), 2.39 (1H, t, *J* 5.0 Hz), 2.59–2.61 (1H, m), 7.0–7.53 (15H, m), 8.69 (1H, s, exchangeable with D_2O); δ_C 19.9, 26.9, 40.2, 123.3, 126.5, 127.0, 127.6, 128.3, 128.4, 129.4, 139.6, 144.6, 157.0; HRMS (EI) m/z: $C_{22}H_{19}NO_2$ requires: 329.14157, found: 329.14130.

*4.4.3. N-(4′-Nitrobenzoyloxy)-N-phenyl-2,2-diphenylcyclo-propanecarboxamide (**27f**)*

Compound **27e** (100 mg, 0.30 mmol), DMAP (44.3 mg, 0.36 mmol) on treatment with 4-nitrobenzoylchloride (67.4 mg, 0.36 mmol) in THF (2 mL) gave **27f** as a colourless solid (125 mg, 86%), mp 55–56 °C (*n*-hexane-EtOAc); ν_{max}(KBr)/cm^{-1} 1771, 1692; δ_H ($CDCl_3$) 1.61 (1H, s), 2.38 (1H, t, *J* 5.2 Hz), 2.52 (1H, m), 7.00–7.52 (15H, m), 8.23 (4H, dd, *J* 8.8 and 2.4 Hz); δ_C 20.1, 28.1, 41.2, 123.6, 126.6, 127.1, 127.6, 128.3, 128.4, 129.8, 131.2, 132.6, 139.3, 144.6, 151.0, 162.5; HRMS (EI) m/z: $C_{29}H_{22}N_2O_5$ requires: 478.15287, found: 478.15203.

4.5. Preparation of butyric acid derivatives 26a and 26b

*4.5.1. Ethyl 4,4-diphenylbutyrate (**26a**)*

Ethyl 2,2-diphenylcyclopropane carboxylate[7b] (**16d**) (0.6 g, 2.52 mmol) in ethanol (30 mL) containing concd sulfuric acid (0.3 mL) was hydrogenated in the presence of Pd/C (0.6 g) at rt (24 h) at atmospheric pressure. Filtration over Celite followed by evaporation of the solvent furnished *ethyl 4,4-diphenylbutyrate* (**26a**) as a pale yellow oil (0.575 mg, 96%); δ_H ($CDCl_3$) 1.24 (3H, t, *J* 7.1 Hz), 2.28 (2H, t, *J* 3.9 Hz), 2.36–2.42 (2H, m), 3.93 (1H, t, *J* 4 Hz), 4.10 (2H, q, *J* 7.2 Hz), 7.08–7.31 (10H, m); δ_C 14.2, 26.4, 32.8, 50.5, 60.3, 126.3, 127.7, 128.5, 144.1, 173.4; HRMS (EI) m/z: $C_{18}H_{20}O_2$ requires: 268.14633, found: 268.14568.

*4.5.2. 4,4-Diphenylbutyric acid (**26b**)*

Saponification of **26a** (70 mg, 0.26 mmol) by the general procedure[7b] furnished the corresponding acid **26b** (64%), mp 89–90 °C (*n*-hexane–Et_2O); ν_{max}(KBr)/cm^{-1} 3056; δ_H ($CDCl_3$) 2.31–2.43 (4H, m), 3.94 (1H, t, *J* 7.6 Hz), 7.17–7.13 (10H, m), 11.14 (1H, s, exchangeable with D_2O); δ_C 30.1, 30.2, 50.2, 126.5, 127.9, 128.6, 144.0, 151.0, 179.5; HRMS (EI) m/z: $C_{16}H_{16}O_2$ requires: 240.11503, found: 240.11453.

*4.5.3. N-Hydroxy-N-phenyl-4,4-diphenylbutyramide (**26f**)*

Prepared via acid chloride **26c** and PhNHOH, mp 122–124 °C (*n*-hexane–EtOAc); ν_{max}(KBr)/cm^{-1} 3170, 1626; δ_H ($CDCl_3$) 2.28–2.34 (2H, m), 3.90 (1H), 7.16–7.35 (15H), 8.97 (1H, exchangeable with D_2O); δ_C 30.4, 31.0, 50.3, 126.3, 127.8, 128.5, 129.2, 137.6, 137.9, 143.9, 167.6; HRMS (EI) m/z: $C_{22}H_{21}NO_2$ requires: 332.16505, found: 332.1650.

*4.5.4. N-(4-Nitrobenzoyloxy)-N-phenyl-4′,4′-diphenyl-butyramide (**26g**)*

Prepared in 86% yield, as described for **27c**, mp 41–42 °C (EtOAc–*n*-hexane); ν_{max}(KBr)/cm^{-1} 1770, 1688; δ_H ($CDCl_3$) 2.26–2.28 (2H, m), 2.44 (2H, dd, *J* 7.4 and 15 Hz), 3.98 (1H, t, *J* 7.8 Hz); δ_C 31.8, 30.7, 49.9, 123.7, 126.3, 127.8, 128.5, 129.6, 131.2, 132.6, 138.8, 143.9, 151.0, 162.3; HRMS (EI) m/z: $C_{29}H_{24}N_2O_5$ requires: 480.16862, found: 480.16778.

*4.5.5. N-(4′,4′-Diphenylbutyroyloxy)-N-phenyl-N-4-nitro-benzamide (**26e**)*

Prepared from **26d** (101 mg; 0.42 mmol) as described for **27c**, in 15% yield, as a colourless solid (30 mg, 15%), mp 110–112 °C (*n*-hexane–EtOAc); ν_{max}(KBr)/cm^{-1} 1785, 1676; δ_H ($CDCl_3$) 2.39 (4H, m), 7.17–7.37 (15H); δ_C (CD_3CN) 30.6, 30.7, 50.8, 124.2, 126.1, 127.5, 127.6, 128.8, 129.8, 130.5, 130.6, 140.7, 141.1, 145.3, 150.3, 172.0; HRMS (EI) m/z: $C_{29}H_{24}N_2O_5$ requires: 480.1685, found: 480.1676.

4.6. Nitrone triflate 21a from 20a and 7a

2-(1′-Acetoxyethyl)-3,4-dimethylthiazolium triflate (**20a**) (70 mg, 0.2 mmol), PhNO (21 mg, 0.2 mmol) in CH_2Cl_2 (10 mL) was treated with Et_3N (0.2 mmol) at rt. The precipitate that separated was collected by decantation and recrystallised (butanone–Et_2O) to give **21a** (95%), mp 197–198 °C; λ_{max} (CH_3CN) 349 nm (ε_{max} 18,600); ν_{max}(KBr)/cm^{-1} 1580, 1160; δ_H (DMSO-d_6) 8.06 (1H, s), 7.68–7.63 (5H, m), 4.23 (3H, s), 2.65, 2.64 (6H, 2s). Anal. Calcd for $C_{14}H_{15}F_3N_2O_4S_2$: C, 42.42; H, 3.81; N, 7.07%. Found: C, 42.24; H, 3.72; N, 7.02%.

4.7. Nitrone triflate 21b from 20a and 7c

Similarly **20a** and 4-$NO_2C_6H_4NO$ furnished nitrone **21b** (48%) as a colourless solid, mp 124–125 °C; ν_{max}(KBr)/cm^{-1} 1570; δ_H (DMSO-d_6) 2.64 (3H, s), 4.23 (3H, s), 7.98 (2H, d, *J* 7.8 Hz), 8.13 (1H, s), 8.49 (2H, d, *J* 7.8 Hz). Anal. Calcd for $C_{14}H_{14}F_3N_3O_6S_2$: C, 38.10; H, 3.20; N, 9.52%. Found: C, 38.01; H, 3.17; N, 9.49%.

4.8. *N*-Phenylacetohydroxamic acid from silylether triflate 20b

Compound **20b** (145 mg, 0.38 mmol) and PhNO (40 mg, 0.38 mmol) in CH_2Cl_2 (10 mL) was treated with Et_3N (0.53 μL, 0.38 mmol) at rt. The organic phase was extracted with ice-cold aq NaOH (0.5 N) and acidified (1 N HCl) to give *N*-phenylaceto-hydroxamic acid (47 mg, 82%) identical with an authentic sample.

4.9. Kinetic experiment

The kinetic disappearance of nitrosobenzene in a CH_2Cl_2 (Uvasol®) solution, containing 3,4-dimethyl-2-(α-deuterio-α-hydroxyethyl)-thiazolium or 3,4-dimethyl-2-(α-hydroxyethyl)-thiazolium triflates and Et_3N, was followed by UV using the chromophore at λ 750 nm under pseudo-first order conditions, in a thermostated flask at 20±1 °C. Data were acquired at predetermined intervals using the μ-Quant software. The values of k_{obs} were obtained from the expression $k_{obs}=\ln(A_o-A_f)-\ln(A-A_f)t$, where k_{obs} represents the first order rate constant (s^{-1}), A_o, A_f and A represent the absorbance at 750 nm at the beginning, at the end and at time t, respectively. A good linearity was found for the first 70% of conversion.

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