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Reactions of 2-Acylthiazolium Salts with *N*-Arylhydroxylamines[¥]

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Abstract: 2-Acylthiazolium salts, easily obtained by alkylation of the corresponding 2-acylthiazoles with methyl triflate, react with *N*-arylhydroxylamines to furnish the *O*-acyl derivatives of relevance in the induction of cancer by aromatic amines. © 1999 Elsevier Science Ltd. All rights reserved.

Following the important suggestion of Miller[1] that the carcinogenicity of certain aromatic amines is due to their biotransformation into the corresponding electrophilic *O*-activated hydroxylamine derivatives (**1** → **2**) that react with the nucleic acid bases of DNA (**Scheme 1**), considerable amount of *in vivo* and *in vitro* studies[2] involving such substances have been reported. The results obtained with *O*-diphenylphosphinyl [**2**, X = $P(O)Ph_2$] and *O*-pivaloyl-*N*-arylhydroxylamines [**2**, X = $C(O)C(CH_3)_3$] do indeed show that these substances undergo reactions on the nitrogen atom with aromatic carbon and nitrogen nucleophiles by an S_N2 process[3] under appropriate conditions. The greater nucleophilicity associated with the nitrogen atom of *N*-arylhydroxylamines, however, does not allow, in the absence of strong electronic deactivation, or steric crowding around the nitrogen atom, of a direct introduction of an acetyl group on the oxygen atom. Such *N*-acetoxyarylamines have been implicated in cancer induction[4] and shown to be enzymatic metabolites of carcinogenic amines.[5]

$$\underset{\mathbf{1}}{\mathrm{ArNHOH}} \longrightarrow \underset{\mathbf{2}}{\mathrm{ArNH{-}OX}} \xrightarrow{\mathrm{DNA}} \mathrm{Adducts}$$

Scheme 1

Recently Marques and Beland showed that such compounds readily react with DNA to furnish C-8 substituted dG adducts.[6] We have reported that these labile *N*-acetoxyanilines are readily obtained and with high regioselectivity from arylhydroxylamines and acetyl cyanide.[7] Subsequently and more importantly, it was

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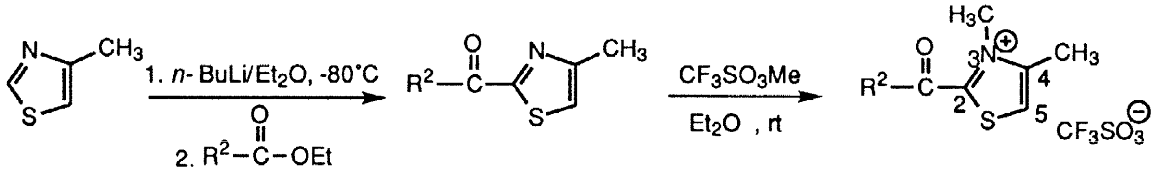
disclosed that a 2-acetylthiazolium salt, modelled on the biologically relevant 2-acetylthiamine,[8] is also an effective *O*-acetylating agent[9] for arylhydroxylamines. We report herein full details pertaining to the latter study.

The requisite 2-acylthiazolium salts **3** (**Scheme 2**) could be obtained by *N*-methylation with methyl triflate of the 2-acylthiazole **4** , which in turn were secured with ease by reaction of the thiazole **5** with BuLi and the corresponding ethyl ester.[10] These salts are, in general, crystalline compounds and have reasonable shelf-lives at room temperatures, when protected from moisture. Their reactions with a variety of arylhydroxylamines and the products isolated therefrom are presented in **Scheme 3** and **Table** respectively.

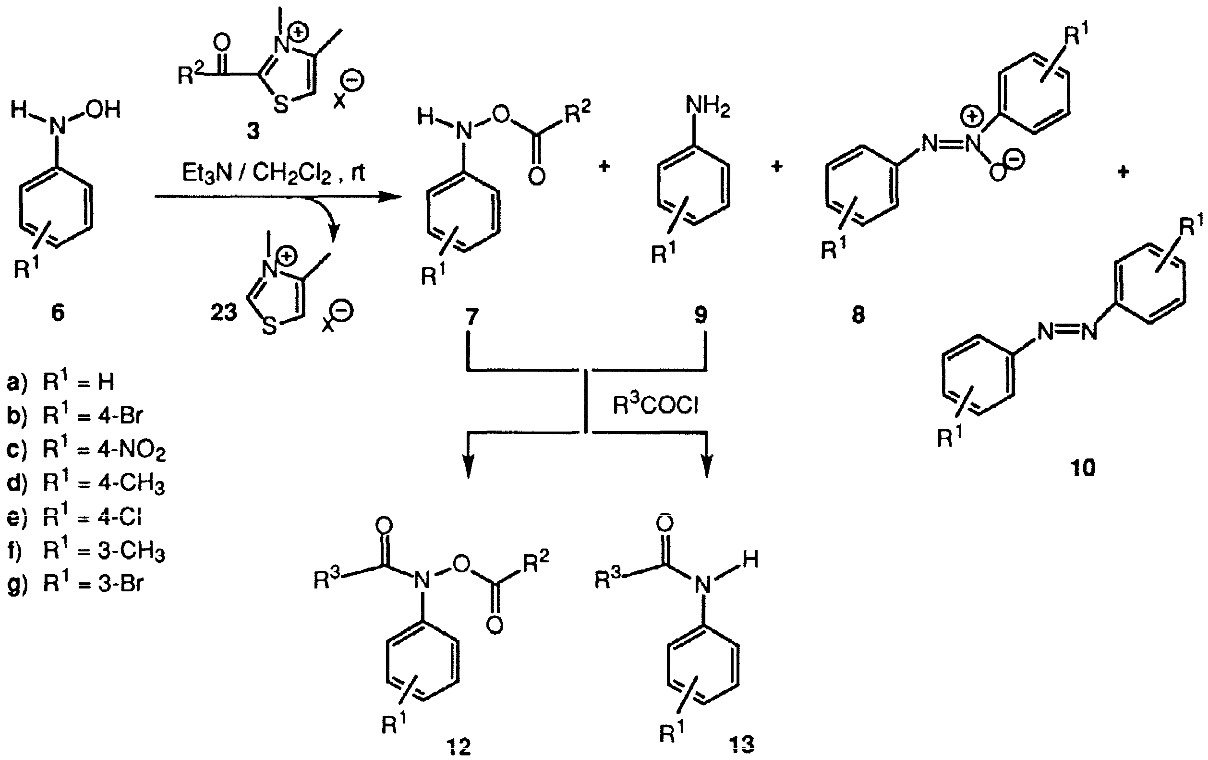


5 **4** **3**

A) $R^2 = CH_3$
B) $R^2 = C_6H_5$
C) $R^2 = CH_2C_6H_5$
D) R^2 = cyclopropyl

Scheme 2

An inspection of the latter shows that arylhydroxylamines **6**, in general, generate the corresponding *O*-acyl compounds **7**, which were isolated (in modest to good yields), and characterised as their respective *N*-*p*-nitrobenzoyl derivatives **12** ($R_3 = p\text{-}NO_2C_6H_4$). Varying amounts of the azoxy compounds **8**, the azo derivatives **10**, and the *N*-arylamines **9**, are invariably formed[11] in these reactions. Noteworthy, however, is the failure [12] of *p*-methylphenylhydroxylamine (**6d**) to furnish, *at room temperature*, in any significant amount, either the *O*-acyl derivative **7Ad** or products derived therefrom.[13] Instead, a new yellow compound **11**, with mp. 147-9 °C, was isolated in 23% yield. The structure **11** was ascribed on the basis of its molecular formula, $C_9H_{11}NO_2S$ (by mass spectrometry and elemental analysis), and its IR spectrum, which contained a strong absorption at 1736 cm^{-1} , consistent with the presence of a β-amino, α,β-unsaturated lactone. Its ^1H NMR spectrum displayed 3 singlets of 3 protons each, at δ 1.78, 2.07 and 3.17 ppm, assigned to methyl groups at C-3, C-7a and the N-4 of the furothiazine skeleton, respectively. The olefinic protons appeared as a singlets, 1H each, at δ 4.74 (C-2), and at 5.34 ppm (C-5). Further evidence for the presence of a carbonyl group and the quaternary carbon C-7a is provided by its ^{13}C NMR spectrum which possessed resonances at 171.1 and 79.5 ppm respectively.[7,13,14] A possible mechanism for the formation of **11**, depicted in **Scheme 4**, presupposes the involvement of the tetrahedral intermediate[12] **15a**, derived from **6d** and **3A**. Fragmentation of **15a**, with the rupture of the *C–O* bond,[15] probably facilitated by the electron donating ability of the *p*-methyl group which stabilises the developing positive charge on the nitrogen, leads to **16** and thence, by protonation, to the 'active aldehyde' analog **17**. The latter, on reaction with another molecule of **3A** gives the *O*-acetyl compound[16] **18**, which on deprotonation and subsequent carbanion addition to the 2-position of the thiazolium ring of **2A** leads to **19**. Ring opening of this species leads to **20** which, on expulsion of **16** and electrocyclisation of the resulting hetero-triene **21**, generates the bicyclic iminium salt **22**, which tautomerises to

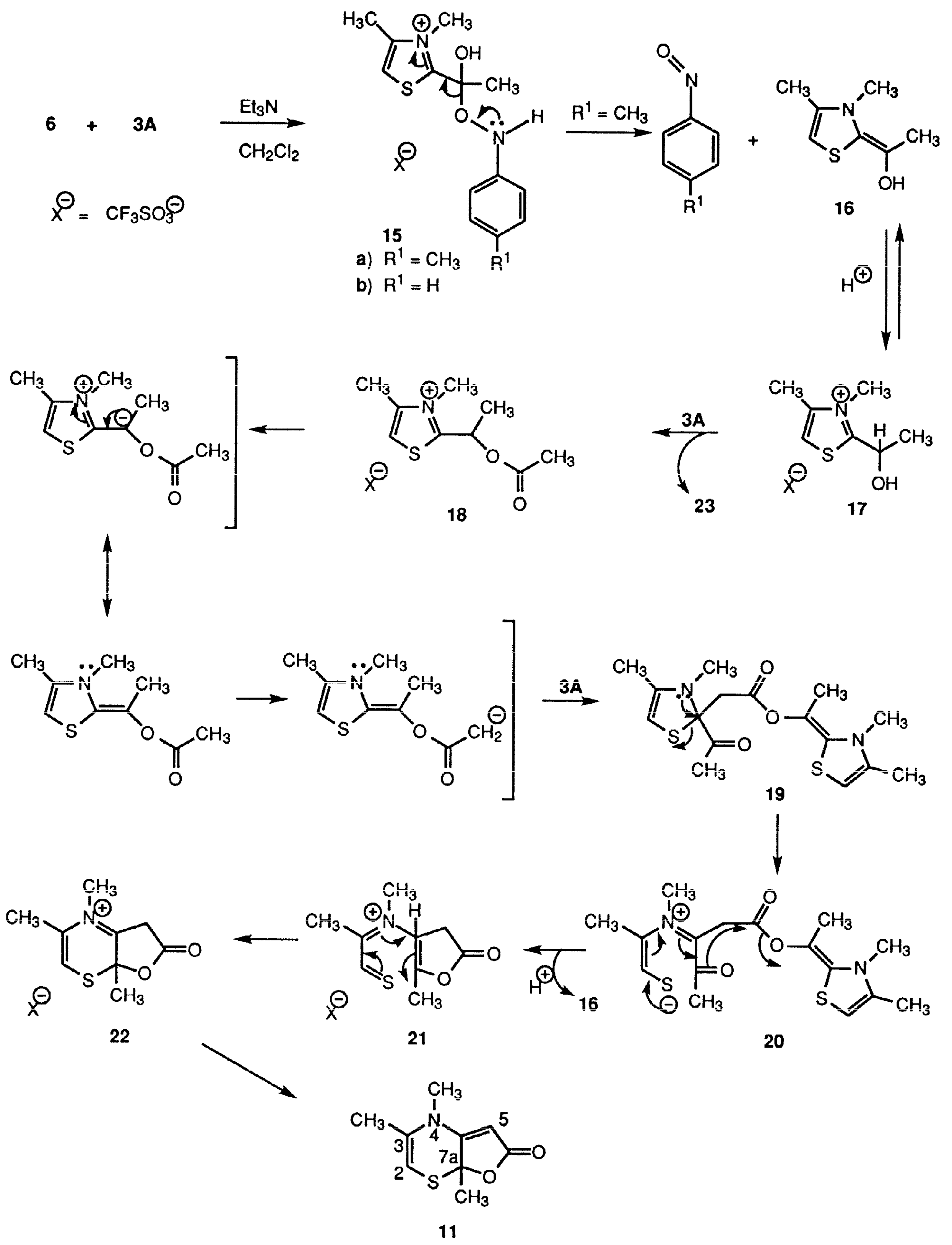


Scheme 3

Table. Reaction of Aromatic Hydroxylamines 6 with 2-Acylthiazolium salts 3 in the presence of Base.

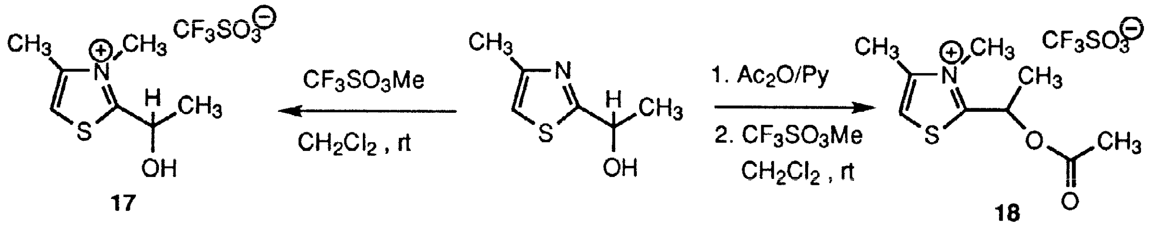
Entry	N-Aryl-hydroxylamine	2-Acyl-thiazolium Salt	Products			
	6	3	O-Acylhydroxyl-amine 7	Azoxy-benzene 8	N-Aryl-amine 9	Others
1	6a	3A	7Aa (51%)[a]	8a (7%)	—	—
2	6b	3A	7Ab (35%)[a]	8b (26%)	9b (34%)[a]	—
3	6c	3A	7Ac (53%)[a]	8c (10%)	—	—
4	6d	3A	7Ad (traces)	8d (40%)	9d (28%)[a]	10d (8%) 11 (23%)
5	6e	3A	7Ae (38%)[a]	8e (41%)	9e (21%)[a]	—
6	6f	3A	7Af (29%)[a]	8f (9%)	9f (24%)[a]	—
7	6a	3B	7Ba (68%)[b]	8a (19%)	—	—
8	6a	3C	7Ca (53%)[a]	8a (4%)	9a (29%)[a]	—
9	6g	3C	7Cg (83%)[a]	8g (18%)	—	—
10	6a	3D	7Da (59%)[a]	8a (6%)	—	—

a) Products quantified after reaction with *p*-nitrobenzoyl chloride, to give 12 / 13 (R^3 = 4-$NO_2C_6H_4$).
b) Product quantified after reaction with acetyl chloride, to give 12 (R^3 = CH_3).


6 + 3A
Et3N
CH2Cl2
X⊖ = CF3SO3⊖
15
a) R1 = CH3
b) R1 = H
R1 = CH3
16
H⊕
17
3A
23
18
3A
19
20
H⊕
16
21
22
11
5
4
7a
3
2

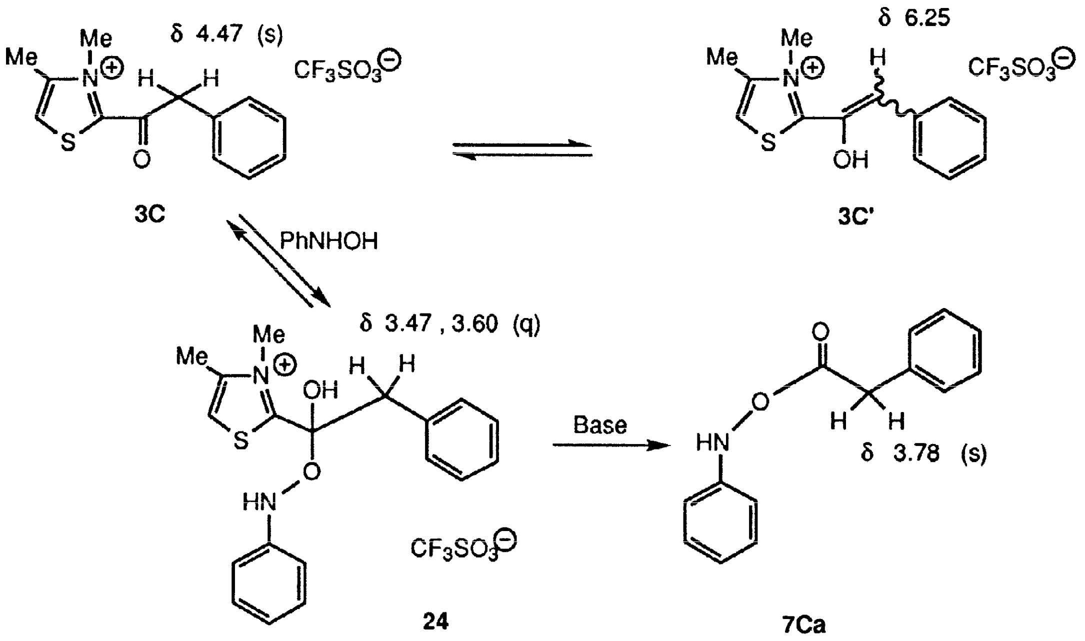
Scheme 4

compound **11**.[17] In keeping with the proposed mechanism is the observation that a solution of **18** (prepared as shown in **Scheme 5**),[18] and Et_3N in CD_2Cl_2 rapidly generated **11** (55% by ^1H NMR; 47% by isolation) only on addition of **3A** (1 eq). At the end of the reaction (ca. 10 min), as monitored by ^1H NMR, the spectrum revealed the presence of compounds **11**, **18** and 3,4-dimethylthiazolium triflate (**23**) in the ratio of 1:2:1. No signals attributable to **17** could be observed. Clearly the latter, formed concomitantly, suffers acetylation[16] at a faster rate than the rate determining step of the overall process.



Scheme 5

We had previously reported[9] the isolation and characterisation of a solid tetrahedral intermediate **15b** from **6a** and **3A** in the absence of base. It was therefore of interest, with a collection of thiazolium salts in our hand, to examine if similar results could also be obtained with them. Whilst such a phenomenon was not observed, the formation of a similar intermediate *in solution* in significant quantity, at room temperature, was indeed detected by ^1H NMR spectroscopy, on mixing **6a** and **3C** in CD_2Cl_2 (**Scheme 6**).



Scheme 6

The two benzylic hydrogens of **3C** which appeared as a 2H singlet, changed into a quartet with a geminal coupling constant of 14 Hz, on addition of phenylhydroxylamine, clearly indicating their magnetic non-equivalence,[7] induced by the adjacent quaternary chiral centre of substance **24**. Integration of the relevant areas of the spectrum showed that the solution contained **24**, the enol **3C'** and the salt **3C**, in the ratio of 1:1:3, respectively. Addition of DABCO to the above mixture caused rapid collapse of the quartet of **24** with simultaneous appearance of the 2H singlet at δ 3.78, due to formation of the product **7Ca**.

In conclusion, it is shown that aromatic hydroxylamines react smoothly with 2-acetylthiazolium triflates and other structurally related compounds to furnish *N*-acetoxy and *N*-acyloxyanilines. The observed general preference for the oxygen attack over that of nitrogen is to be attributed to the minimisation of steric crowding in the tetrahedral intermediates formed.

EXPERIMENTAL

General. All melting points were determined with a Köfler Reichert Thermovar melting point apparatus and were uncorrected. Infrared (IR) spectra were recorded on a Perkin Elmer 157G and a Buck Scientific 500. ^{1}H and ^{13}C NMR spectra were measured in one of the following instruments, a General Electric GE-NMR (300 MHz), a Varian Unit (300 MHz), a Brüker CXP (300 MHz) and a ARX (400MHz) spectrometer. Chemical shifts are expressed in ppm, downfield from tetramethylsilane (δ = 0) and/or residual chloroform (δ_H= 7.26, δ_C= 77.0) as an internal standard. Splitting patterns are indicated as: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad signal. Mass spectra were taken with a Kratos MS-25 RF (70 eV) and a Shimadzu QP-1000 (70 eV) mass spectrometer. Ultraviolet spectra were registered on a Shimadzu UV-240, a Perkin Elmer Lambda 6 and a Milton Roy Spectronic 1201. Microanalyses were performed on a Carlo Erba 1106R microanalyser. For thin layer chromatographic (TLC) analyses, Merck precoated plates (silica gel 60 F254, 0.2 mm) were used. These were 0.5 mm thick for preparative work. Column chromatography was performed with Merck silica gel 60 (70-230 mesh). All solvents used were dried by standard methods. The following abbreviations were used for solvents: acetonitrile (CH_3CN), tetrahydrofuran (THF), diethyl ether (Et_2O), methanol (MeOH), ethanol (EtOH), dichloromethane (CH_2Cl_2) and dimethylsulphoxide (DMSO). Petroleum ether refers to the fraction boiling between 40-60°C.

***2-Acylthiazoles.* General Procedure**: To a stirred, cooled (-78°C) solution of *n*-butyl lithium (1.6 *M* in *n*-hexane) in dry Et_2O under nitrogen atmosphere, an ethereal solution of thiazole (2.75 mmol, 0.2 *M*) was slowly added. After 1h, the requisite ethyl ester (5.5 mmol, 0.2 *M*) also in ether was added. The mixture was stirred at -78°C for *ca.* 10 m, and allowed to attain room temperature. It was then washed with an aqueous saturated solution of sodium bicarbonate (100 ml), the organic phase was dried over anhydrous sodium sulphate, the solvent was removed and the product isolated, by column chromatography and/or recrystallisation.

2-Acetyl-4-methylthiazole (4A). Obtained as a solid (64%), after column chromatography (eluent: CH_2Cl_2: MeOH, 100:1); mp: 33-35°C (from *n*-hexane), (mp: [19] 34°C); IR (KBr) 1685 cm^{-1}; ^{1}H NMR (DMSO-d_6) 7.81 (1H, s, 5-*H*), 2.63 (3H, s, CH_3CO), 2.49 (3H, s, 4-CH_3); ^{13}C NMR ($CDCl_3$) 191.2 (*C*=O), 165.6, 155.0, 121.3 (*C*-S), 25.8 (CH_3CO), 16.9 (4-CH_3).

2-Benzoyl-4-methylthiazole (4B). Obtained as a solid (45%), after column chromatography (eluent: CH_2Cl_2); mp: 41-42 °C (from Et_2O: *n*-hexane), (mp: [20] 42-43°C); IR (KBr) 1645 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) 8.40 (2H, d, *J*=8.2 Hz, *o*-Ar-*H)*, 7.75 (1H, s, 5-*H)*, 7.66 (1H, t, *J*=7.3 Hz, *p*-Ar-*H)*, 7.56 (2H, t, *J*=7.5 Hz, *m*-Ar-*H*), 2.54 (3H, s, 4-CH_3).

2-Phenylacetyl-4-methylthiazole (4C). Obtained as a solid (66%), after column chromatography (eluent: CH_2Cl_2); mp: 70-71°C (from *n*-pentane); IR (KBr) 1692 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) 7.38-7.26 (6H, m, Ar-*H*, 5-*H)*, 4.45 (2H, s, CH_2CO), 2.56 (3H, s, 4-CH_3). ^{13}C NMR ($CDCl_3$) 190.6 (*C*=O), 165.6, 155.2, 133.7, 128.4, 129.8, 126.9, 121.8 (*C*-S), 44.7 (CH_2), 17.1 (4-CH_3). Anal. Calcd for $C_{12}H_{11}NOS$: C, 66.3; H, 5.1; N, 6.5. Found: C, 66.5; H, 5.1; N, 6.4%.

2-Cyclopropanecarbonyl-4-methylthiazole (4D). Obtained as an oil (63%), after column chromatography (eluent: CH_2Cl_2); IR (film) 1670 (C=O), 1440 (cyclopropane) cm^{-1}; ^1H NMR ($CDCl_3$) 7.24 (1H, s, 5-*H)*, 3.20 (1H, m, C*H*C=O), 2.56 (3H, s, 4-CH_3), 1.32 (2H, m, 2 x C*H*, cyclopropyl), 1.14 (2H, m, 2 x C*H* cyclopropyl); m/e 167 (M^+), 139, 126, 113, 72, 69. HRMS m/z: Calcd for C_8H_9NOS: 167.0405. Found: 167.0383.

2-Acyl-3,4-dimethylthiazolium triflates. **General Methylation Procedure:** A stirred solution of the requisite 2-acyl-4-methylthiazole (1 eq) in dry Et_2O (0.2 *M*), under nitrogen atmosphere, was treated with methyl triflate (2 eq) at rt. On completion of the reaction (t.l.c. control, 16 - 24 h), the solid that had separated was isolated by decantation of the supernatant liquid and purified by crystallisation.

2-Acetyl-3,4-dimethylthiazolium triflate (3A). Obtained as a solid (97%); mp: 96-98°C (from Et_2O: butanone); UV (CH_3CN) 236 (ε 2700), 293 (ε 5900) nm; IR (KBr) 1710 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) 8.26 (1H, s, 5-*H*), 4.11 (3H, s, 3-CH_3), 2.74 (3H, s, CH_3CO), 2.58 (3H, s, 4-CH_3); ^{13}C NMR (DMSO-d_6) 185.6 (*C*=O), 39.4 (3-CH_3), 30.4 (CH_3CO) 13.9 (4-CH_3); m/e (FAB, glycerol matrix) 156 $(M)^+$, 142. HRMS m/z calcd for $C_7H_{10}NOS$ 156.0483. Found 156.0477.

2-Benzoyl-3,4-dimethylthiazolium triflate (3B). Obtained as a solid (80%); mp: 135-137°C (from Et_2O: butanone); UV (CH_3CN) 289 (ε 8100) nm; IR (KBr) 1670 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) 8.35 (1H, s, 5-*H)*, 8.00 (2H, d, *J* = 8.4 Hz, *o*-Ar*H)*, 7.87 (1H, t, *J* = 7.8 Hz, *p*-Ar*H)*, 7.69 (2H, t, *J* = 7.8 Hz, *m*-Ar*H)*, 4.08 (3H, s, 3-CH_3), 2.65 (3H, s, 4-CH_3); ^{13}C NMR (DMSO-d_6) 181.1 (*C*=O), 39.1 (3-CH_3), 13.1 (4-CH_3); Anal. Calcd for $C_{13}H_{12}F_3NO_4S_2$: C, 42.5; H, 3.3; N, 3.8; S, 17.5. Found: C, 42.5; H, 3.2; N, 3.7; S, 17.1%.

2-Phenylacetyl-3,4-dimethylthiazolium triflate (3C). Obtained as a solid (63%); mp: 145-146°C (from Et_2O: butanone); IR (KBr) 1720 (C=O) cm^{-1}; ^1H NMR (CD_2Cl_2) 7.91 (1H, s, 5-*H)*, 7.44-7.31 (5H, m, Ar-*H)*,4.47 (2H, s, CH_2), 4.26 (3H, s, 3-CH_3), 2.65 (3H, s, 4-CH_3); ^{13}C NMR (CD_2Cl_2) 185.6 (*C*=O), 39.6 (3-CH_3), 14.4 (4-CH_3); m/e (FAB, 3-nitrobenzyl alcohol matrix) 232 $(MH)^+$. Anal. Calcd for $C_{14}H_{14}F_3NO_4S_2$: C, 44.1; H, 3.7; N, 3.7. Found: C, 44.1; H, 3.7; N, 3.7%.

2-Cyclopropanecarbonyl-3,4-dimethylthiazolium triflate (3D). Obtained as an oil (80%); IR (KBr) 1700 (C=O) cm^{-1}; ^{1}H NMR (CDCl$_3$) 8.16 (1H, s, 5-*H*), 4.27 (3H, s, 3-C*H*$_3$), 2.68 (3H, s, 4-C*H*$_3$), 2.27 (1H, m, *H*-CCO), 1.49 (2H, m, 2x C*H* cyclopropane), 1.41 (2H, m, 2x C*H* cyclopropane); ^{13}C NMR (CDCl$_3$) 187.3 (*C*=O), 39.3 (3-*C*H$_3$), 15.1 (4-*C*H$_3$); HRMS m/z calcd for $C_9H_{12}NOS$ 182.0639. Found 182.0630.

Reaction between aromatic hydroxylamines (6) and 2-acylthiazolium triflates (3). **General Procedure:** To a solution of 2-acylthiazolium triflate (1 eq) in dry CH_2Cl_2 (0.1 *M*), the base (DABCO or triethylamine, 1 eq), and the arylhydroxylamine (1 eq) were added. The reaction mixture was stirred at room temperature until total disappearance of the hydroxylamine was observed (t.l.c. control, 1 - 2 h). The solvent from the reaction was evaporated and the residue redissolved in dry THF, cooled to -80°C under nitrogen, mixed with sodium hydride (3 eq) and *p*-nitrobenzoyl chloride (2 eq) was then carefully added to the reaction mixture. After total consumption of the *O*-acylated aromatic hydroxylamine (t.l.c. control, 1 - 3 h), the reaction mixture was filtered and the solvent evaporated to dryness. The products were isolated by p.t.l.c. (silica, CH_2Cl_2).

Reaction between 6a and 3A. (Table, entry 1): Azoxybenzene (8a). (7%); mp: 33-35°C (from EtOH), (mp: [21] 35°C). ***N*-Acetoxy-*N*-phenyl-4-nitrobenzamide (12Aa).** (51%); mp: 146-148°C (from CH_2Cl_2: petroleum ether), (mp:[14] 146.5-148°C).

Reaction between 6b and 3A. (Table, entry 2): 4,4'-Dibromoazoxybenzene (8b). (26%); mp: 170-172°C (from EtOH), (mp: [21] 172°C). ***N*-Acetoxy-*N*-(4'-bromophenyl)-4-nitrobenzamide (12Ab).** (35%); mp: 162-164°C (from CH_2Cl_2: petroleum ether) (mp: [14] 162-163°C). ***N*-(4-Nitrobenzoyl)-4'-bromoanilide (13b).** (34%); mp: 246-248°C (from CH_2Cl_2: petroleum ether) (mp: [22] 245°C).

Reaction between 6c and 3A. (Table, entry 3): 4,4'-Dinitroazoxybenzene (8c). (10%); mp: 188-190°C (from EtOH), (mp: [21] 192°C). ***N*-Acetoxy-*N*-(4'-nitrophenyl)-4-nitrobenzamide (12Ac).** (53%); mp: 138-140°C (from CH_2Cl_2: petroleum ether); IR (KBr) 1795 , 1680 cm^{-1}; ^{1}H NMR (CDCl$_3$) 8.30-8.25 (4H, m, Ar*H*), 7.79 (2H, d, *J* = 7.8 Hz, Ar*H*), 7.61 (2H, d, *J* = 7.8 Hz, Ar-*H*), 2.15 (3H, s, C*H*$_3$CO); HRMS m/z calcd for $C_{15}H_{11}N_3O_7$ 345.0597. Found 345.0591.

Reaction between 6d and 3A. (Table, entry 4): 4,4'-Dimethylazobenzene (10d). (8%); mp: 143-145°C (from EtOH), (mp:[13] 142-143°C). **4,4'-Dimethylazoxybenzene (8d).** (40%); mp: 67-68°C (from MeOH), (mp:[21] 68°C); ^{1}H NMR (CDCl$_3$) 8.10-8.19 (4H, m, Ar-*H*), 7.25-7.28 (4H, m, Ar-*H*), 2.44 (3H, s, C*H*$_3$-Ar), 241 (3H, s, C*H*$_3$-Ar). **3,4,7a-Trimethyl-6-oxo-4*H*,6*H*,7a*H*-furo[2,3-*b*]-1,4-thiazine (11)** (23%); mp: 147-149°C (from CH_2Cl_2: petroleum ether), identical with a sample obtained by a different route (see bellow). ***N*-(4-Nitrobenzoyl)-4'-methylanilide (13d).** 28%; mp: 198-199°C (from CH_2Cl_2 : petroleum ether), (mp:[22] 203°C); IR (KBr) 3400, 1640 cm^{-1}; ^{1}H NMR (CDCl$_3$) 8.34 (2H, d, *J* = 9.0 Hz, Ar-*H*), 8.04 (2H, d, *J* = 9.0 Hz, Ar-*H*), 7.81 (1H, bs, N-*H*), 7.52 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.21 (2H, d, *J* = 8.0 Hz, Ar-*H*), 2.36 (3H, s, C*H*$_3$-Ar).

Reaction between 6e and 3A. (Table, entry 5): 4,4'-Dichloroazoxybenzene (8e). (41%); mp: 153-155°C (from EtOH), (mp:[21] 155-156°C). ***N*-Acetoxy-*N*-(4'-chlorophenyl)-4-nitrobenzamide (12Ae).** (38%); mp: 152-155°C (from CH_2Cl_2: petroleum ether); IR (KBr) 1785, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) 8.18 (2H, d, *J* = 8.5 Hz, Ar-*H)*, 7.70 (2H, d, *J* = 8.5 Hz, Ar-*H)*, 7.35-7.30 (4H, m, Ar-*H)*, 2.18 (3H, s, C*H*$_3$). **4-Nitrobenzoyl-4'-chloroanilide (13e).** (21%); mp: 228-230°C (from CH_2Cl_2: petroleum ether), (mp:[22] 235°C); IR (KBr) 3410, 1675 cm^{-1}; ^{1}H NMR ($CDCl_3$) 8.36 (2H, d, *J* = 8.4 Hz, Ar-*H)*, 8.04 (2H, d, *J* = 8.4 Hz, Ar-*H)*, 7.83 (1H, bs, N-*H)*, 7.61 (2H, d, *J* = 8.7 Hz, Ar-*H*), 7.38 (2H, d, *J* = 8.7 Hz, Ar-*H*).

Reaction between 6f and 3A. (Table, entry 6): 3,3'-Dimethylazoxybenzene (8f). (9%) yellow oil[21] ; ^{1}H NMR ($CDCl_3$) 8.11-7.96 (4H, m, Ar-*H)*, 7.42-7.20 (4H, m, Ar-*H)*, 2.47 (3H, s, C*H*$_3$- Ar), 2.43 (3H, s, C*H*$_3$-Ar). ***N*-Acetoxy-*N*-(3'-methylphenyl)-4-nitrobenzamide (12Af).** (29%) yellow oil; IR (film) 1800, 1680; ^{1}H NMR ($CDCl_3$) 8.14 (2H, d, *J* = 8.7 Hz, Ar-*H*), 7.69 (2H, d, *J* = 8.7 Hz, Ar-*H)*, 7.23-7.07 (4H, m, Ar-*H)*, 2.32 (3H, s, C*H*$_3$-Ar), 2.21 (3H, s, C*H*$_3$-CO); m/e (EI) 314 (M^+), 272, 256, 150 ; HRMS m/z calcd for $C_{16}H_{14}N_2O_5$ 314.0902. Found 314.0881. **4-Nitrobenzoyl-3'-methylanilide (13f).** (24%); mp: 144-146°C (from CH_2Cl_2: petroleum ether), (mp.[22] 155°C); IR (Kbr) 3300 (N-H), 1655 (C=O) cm^{-1}.

Reaction between 6a and 3B. (Table, entry 7). The *N*-acyloxyaniline was characterised as the *N*-acetyl derivative following the general procedure used for the preparation of the *N*-4-nitrobenzoyl derivative: **Azoxybenzene (8a)** (19%). ***N*-Benzoyloxy-*N*-phenylacetamide [12Ba (R^3 = CH_3)].** (68%) oil;[23] IR (KBr) 1775, 1700 cm^{-1}; ^{1}H NMR (CD_3CN) 8.10 (2H, d, *J* = 7.9 Hz, Ar-*H)*, 7.72-7.44 (8H, m, Ar-*H)*, 2.11 (3H, s, C*H*$_3$); m/e (EI) 255 (M^+), 105, 77.

Reaction between 6a and 3C. (Table, entry 8): Azoxybenzene (8a) (4%). ***N*-Phenylacetoxy-*N*-Phenyl-4-nitrobenzamide (12Ca).** (53%); mp: 139-140° (from CH_2Cl_2: petroleum ether); IR (KBr) 1790, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) 8.03 (2H, d, *J* = 8.5 Hz, Ar-*H*). 7.61 (2H, d, *J* = 8.5 Hz, Ar-*H)*, 7.26 (10H, m, Ar-*H)*, 3.73 (2H, s, C*H*$_2$). Anal. Calcd for $C_{21}H_{16}N_2O_5$: C, 67.0; H, 4.3; N, 7.4. Found: C, 67.0; H, 4.2; N, 7.4%. **4-Nitrobenzanilide (13a).** (29%); mp: 213-215°C (from CH_2Cl_2 : petroleum ether), (mp:[22] 216°C).

Reaction between 6g and 3C. (Table, entry 9): 3,3'-Dibromoazoxybenzene (8g). (18%); mp: 110-111°C (from EtOH), (mp:[21] 111°C); ^{1}H NMR ($CDCl_3$) 8.48 (1H, t, *J* = 2.1 Hz, Ar-*H)*, 8.42 (1H, t, *J* = 1.7 Hz, Ar-*H)*, 8.25 (1H, d, *J* = 7.1 Hz, Ar-*H)*, 8.06 (1H, d, *J* = 7.8 Hz, Ar-*H)*, 7.72 (1H, d, *J* = 7.1 Hz, Ar-*H)*, 7.55 (1H, d, *J* = 7.8 Hz, Ar-*H*), 7.44 - 7.33 (2H, m, Ar-*H*). ***N*-Phenylacetoxy-*N*-(3'-bromophenyl)-4-nitrobenzamide (12Cg).** (83%); mp: 108-109°C (from CH_2Cl_2 : petroleum ether); IR (KBr) 1780, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) 8.04 (2H, d, *J* = 8.7 Hz, Ar-*H)*, 7.60 (2H, d, *J* = 8.7 Hz, Ar-*H)*, 7.56-7.11 (9H, m, Ar-*H)*, 3.68 (2H, s, *CH*$_2$). Anal. Calcd for $C_{21}H_{15}BrN_2O_5$: C, 55.4; H, 3.3; N, 6.15. Found: C, 55.7; H, 3.4; N, 6.4%.

Reaction between 6a and 3D. (Table, entry 10): Azoxybenzene (8a) (6%). *N*-Cyclopropanecarbonyloxy-*N*-phenyl-4-nitrobenzamide (12Da). (59%); mp: 133-135°C (from CH_2Cl_2: petroleum ether); IR (KBr) 1785, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) 8.15 (2H, d, *J* = 8.7 Hz, Ar-*H)*, 7.70 (2H, d, *J* = 8.7 Hz, Ar-*H)*, 7.35-7.33 (5H, m, Ar-*H)*, 1.75 (1H, m, *H*-C-CO) 1.10 (2H, m, C*H*$_2$-cyclopropyl), 1.04 (2H, m, C*H*$_2$-cyclopropyl). Anal. Calcd for $C_{17}H_{14}N_2O_5$: C, 62.6; H, 4.3; N, 8.6. Found: C, 62.5; H, 4.3; N, 8.5%.

3,4-Dimethyl-2-(1'-hydroxyethyl)-thiazolium triflate (17). Obtained by methylation, as above, of the known[24,25] 2-(1'-hydroxyethyl)-4-methylthiazole, as white needles (92%); mp: 83-85°C (from butanone: Et_2O); IR (KBr) 3350 cm^{-1}; ^1H NMR (DMSO-d_6) 7.57 (1H, s, 5-*H*), 5.34 (1H, m, *H*-COH), 4.90 (1H, d, *J* = 0.9 Hz, O*H*), 3.83 (3H, s, 3-C*H*$_3$), 2.46 (3H, s, 4-C*H*$_3$), 1.57 (3H, d, *J* = 6.6 Hz, C*H*$_3$-CHOH) ppm; ^{13}C NMR ($CDCl_3$ + DMSO-d_6) 147.2, 122.5, 117.9, 64.7 (*C*-OH), 37.0 (3-*C*H$_3$), 22.2 (*C*H$_3$-C-OH), 13.7 (4-*C*H$_3$); m/e (FAB) 158 M^+, 140 $(M-H_2O)^+$. Anal. Calcd for $C_8H_{12}F_3NO_4S_2$: C, 31.3; H, 3.9; N, 4.6; S, 20.9. Found: C, 31.0; H, 3.8; N, 4.5; S, 21.0%.

2-(1'-Acetoxyethyl)-3,4-dimethylthiazolium triflate (18). A solution of 2-(1'-hydroxyethyl)-4-methylthiazole (2 mmoles), acetic anhydride (2 mmoles) and pyridine (2 mmoles) was kept at rt (24 h). It was then poured into an ice-cold solution of HCl (1N) and the product extracted with Et_2O (3 x 10 ml). Evaporation of the washed and dried (Na_2SO_4) ether solution yielded **2-(1'-acetoxyethyl)-4-methylthiazole** as a yellow oil (65%); IR (film) 2960, 1740 cm^{-1}; ^1H NMR (DMSO-d_6) 7.38 (1H, s, 5-*H*), 6.15 (1H, q, *J* = 6.6 Hz, CH_3-C*H*OAc), 2.49 (3H, s, 4-C*H*$_3$), 2.22 (3H, s, C*H*$_3$CO), 1.72 (3H, d, *J* = 6.6 Hz, C*H*$_3$-CHOAc), which without purification was methylated (1 h) with methyl triflate, as above, to give the title compound **18** as colourless crystals (92%); mp: 103-104°C (from butanone: Et_2O); UV (CH_3CN) 204 (ε 22600), 257 (ε 9600) nm; IR (KBr) 1740 cm^{-1}; ^1H NMR (DMSO-d_6) 7.01 (1H, s, 5-*H*), 6.41 (1H, q, *J* = 6.6 Hz, *H*-COAc), 3.98 (3H, s, 3-C*H*$_3$), 2.51 (3H, s, 4-C*H*$_3$), 2.14 (3H, s, C*H*$_3$-CO), 1.65 (3H, d, *J* = 6.6 Hz, C*H*$_3$-COAc); m/e (FAB, H_2SO_4 matrix) 200 M^+, 156 (M^+-HOAc), 141 (M^+-HOAc-CH_3). Anal. Calcd for $C_{10}H_{14}F_3NO_5S_2$: C, 34.4; H, 4.0; N, 4.0 Found: C, 34.4; H, 4.1; N, 4.0%.

3,4-Dimethylthiazolium triflate (23). Prepared by the general methylation procedure (*vide supra*) of 4-methylthiazole, **23** was obtained as colourless crystals (90%), mp: 109-110°C (from butanone: Et_2O); UV (CH_3CN) 215 (ε 2100), 249 (ε 3000) nm; IR (KBr) 1260, 1030 cm^{-1}; ^1H NMR (DMSO-d_6) 10.00 (1H, s, 2-*H*), 7.92 (1H, s, 5-*H*), 4.03 (3H, s, 3-C*H*$_3$), 2.46 (3H, s, 4-C*H*$_3$); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) 158.9 (N*C*S), 146.3 (N-*C*), 121.0 (*C*-S), 39.7 (3-*C*H$_3$), 12.8 (4-*C*H$_3$). Anal. Calcd for $C_6H_8F_3NO_3S_2$: C, 27.4; H, 3.1; N, 5.3. Found: C, 27.3; H, 3.1; N, 5.4%.

3,4,7a-Trimethyl-6-oxo-4*H*,6*H*,7a*H*-furo[2,3-*b*]-1,4-thiazine (11). A solution of 2-(1'-acetoxyethyl)-3,4-dimethylthiazolium triflate (**18**) (349 mg) and 2-acetyl-3,4-dimethylthiazolium triflate (**3A**) (305 mg) in dry CH_2Cl_2 (30 ml), was treated with triethylamine (1 eq) and the mixture let stand at rt for 1 h. Removal of the solvent under reduced pressure and purification of the resulting residue by p.t.l.c. (silica, CH_2Cl_2) furnished the title compound **11** as yellow needles (47%); mp: 147-149°C (from CH_2Cl_2: petroleum ether); UV (CH_3CN) 223 (ε 7000), 255 (ε 3000), 349 (ε 2250) nm; IR (KBr) 1736 (C=O), 1618 cm^{-1}; ^1H

NMR ($CDCl_3$) 5.34 (1H, s), 4.74 (1H, s), 3.17 (3H, s), 2.07 (3H, s), 1.78 (3H, s); ^{13}C NMR ($CDCl_3$) 171.1 (*C*=O), 164.0, 133.6, 95.1, 82.2, 79.5 (O–*C*–S), 35.9, 25.1, 19.8; m/e (EI) 197 (M^+), 154. Anal. Calcd for $C_9H_{11}NO_2S$: C, 54.8; H, 5.6; N, 7.1. Found: C, 54.3; H, 5.6; N, 6.7%.

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REFERENCES AND NOTES

¥ This work is dedicated in fond memory of the late Professor Sir Derek Barton.

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11. The formation of these compounds whenever arylhydroxylamines or their *O*-esterified derivatives are involved in a reaction is a very common occurrence (see references bellow). The fluctuation in their relative proportions seems to depend on a variety of factors, such as : a) solvent; b) the nature of the leaving group attached to the nitrogen; c) the electronic nature and position of the substituent in the aromatic ring; d) the type of base (organic or otherwise) used in the reaction; e) the adventitious presence of species such as Cu^{+2} or Fe^{+2} in the reaction medium. The interplay of these factors makes it difficult to propose a general mechanism for the generation of these nitrogen containing compounds under differing conditions. For mechanistic considerations involving some of the factors mentioned above, see: Novak,

M.; Lagerman, R. K. *J. Org. Chem.* **1988,** *53*, 4762-4767; Boche, G.; Meir, C.; Kleemiss, W. *Tetrahedron Lett.* **1988,** *29*, 1777-1780; Novak, M.; Martin, K. A.; Heinrich, J. L.; Peet, K. M.; Mohler, L. K. *J. Org. Chem.* **1990,** *55* , 3023-3028; Helmick, J. S.; Novak, M. *J. Org. Chem.* **1991,** *56* , 2925-2927; Pereira, M. M. M. A. *Ph.D. Thesis*, New University of Lisbon 1992.

12. A mixture of **6d** (1 eq) and **3A** (2 eq) in CD_2Cl_2 , *cooled to* -30°C, contained in its ^{1}H NMR spectrum, among other signals, one singlet at δ 1.91, due to the sp^3 methyl group of **15a**. Also its ^{13}C NMR spectrum exhibited a resonance at δ 101.3 diagnostic of the quaternary carbon of the tetrahedral intermediate. On addition of Et_3N (1 eq), rapid collapse of **15a** was observed with concomitant appearance of singlets, 3H each, at δ 2.14 ($OCOCH_3$), 2.22 (4-CH_3) and a pair of doublets, 2H each, at δ 7.09 (J = 8 Hz) and 6.90 (J = 8 Hz) due to **7Ad**. A similar obervation was recorded for a mixture of **6d** and acetyl cyanide, under the same conditions.
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15. The nitroso compound that is formed in this reaction is not likely to remain unaltered under these conditions since, in addition to giving rise to the corresponding azoxy derivative **8d**, it would be expected to react rapidly with **18** to furnish a nitrone (*vide* ref. 18).
16. In a separate experiment it was found that, in the presence of Et_3N, **3A** rapidly acetylates **17** to **18**, with simultaneous formation of **23**.
17. We thank one of the referees for enabling us to refine certain steps in the mechanism proposed.
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