Addition-Rearrangement Reactions of *N*-(Arylsulphonyloxy)amines and 3,4-Dihydro-2*H*-pyran

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A series of *N*-alkyl-*O*-(arylsulphonyl)hydroxylamines (NSA) was treated with 3,4-dihydro-2*H*-pyran (DHP). Acid-catalysed addition to the double bond followed by cationic rearrangement gave cyclic imidates from hydride migration (major) and ring expansion (minor), which were reduced to amino alcohols for analysis. The results indicate that NSA function as nucleophiles which capture the oxonium ion produced by protonation of DHP, and give new NSA derivatives that rearrange to the observed products.

The preparation and reactions of compounds with arylsulphonyloxy leaving groups attached to nitrogen have been reported in the literature on several occasions,[1] however, little systematic attention has been paid to their chemical properties until recently. Only *N*-arylsulphonyloxy derivatives of ammonia have received much attention as electrophilic aminating agents.[2] We recently reported that a variety of amines can be converted into their *N*-arylsulphonyloxy derivatives by reaction with bisarylsulphonyl peroxides.[3] Having a useful method for the preparation of these rather unstable materials enabled us to investigate their chemistry in some detail.

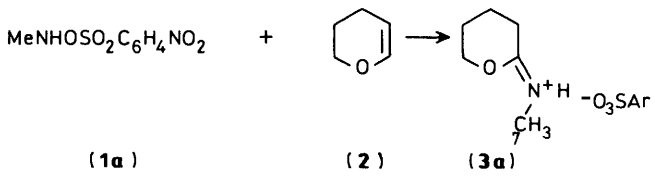
Studies of base-promoted eliminations of *N*-(arylsulphonyloxy)amines (NSA) indicated that there is a large amount of N–O bond heterolysis in the activated complex,[4] to the extent that in the absence of base, NSA decompose by ionization of the N–O bond to give skeletally rearranged imine products.[5] Cationic rearrangement is concerted with ionization, and free nitrenium ions are not produced.[6] These cationic rearrangements provide a method to prepare azacyclic compounds from carbocyclic precursors.[7]

The ease of N–O heterolysis in NSA, which leads to electron deficient nitrogen species, suggested that under appropriate conditions, they might react electrophilically with electron donors, and thus serve as electrophilic aminating agents. The development of electrophilic aminating agents has been a problem of longstanding interest, which has not yielded a general solution.[8] One requirement for an electron donor function to react with NSA in this fashion is that it be non-basic, in order to minimize base promoted elimination as a competitive pathway.

An appropriate electron donor function might be an enol ether, since enol ethers are effective, non-basic electron donors which react readily with electrophiles. We report that NSA do not electrophilically aminate the double bond of the enol ether DHP, but instead add to the double bond to give new NSA derivatives which upon decomposition yield cyclic imidates by carbon to nitrogen rearrangement.

Results and Discussion

Addition of DHP (**2**) to a solution of *N*-methyl-*O*-(*p*-nitrophenylsulphonyl)hydroxylamine (**1a**) in chloroform resulted in the immediate disappearance of both these reactants. Monitoring the reaction by ^{1}H n.m.r. spectroscopy showed that the signals for (**1a**) and (**2**) disappeared upon mixing and signals of a new compound replaced them (Scheme 1). The crude reaction product was identified as the imidate salt (**3a**) on the basis of spectral data (see Experimental section).



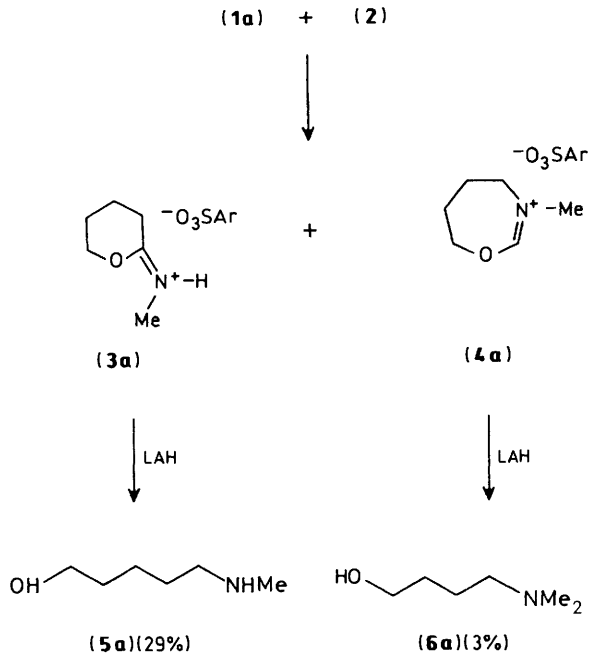
(**1a**) (**2**) (**3a**)

Scheme 1.

While the structure of (**3a**) seemed secure from the spectral data, (**3a**) was hygroscopic and unstable. Attempts to hydrolyse (**3a**) under basic or acidic conditions gave complex product mixtures as noted for other imidates.[9] Use of concentrated sulphuric acid also gave complex mixtures, contrary to the literature report.[10] If water was added to the crude product and the mixture was continuously extracted with dichloromethane, valerolactone (56%), 5-hydroxyvaleric acid (7%), and 5-hydroxy-*N*-methylvaleramide (6%) were obtained, as well as some polymerized 5-hydroxyvaleric acid. The total yield of hydrolysis products from (**3a**) was thus >69%, indicative of efficient conversion of (**2**) into (**3a**).

In order to obtain a stable product, several reduction methods were examined. The best procedure was found to be lithium aluminium hydride (LAH) reduction. To our surprise two products, identified as the amino alcohols (**5a**) (29%) and (**6a**) (3%) were obtained. The isolation of both (**5a**) and (**6a**) indicates that the crude imidate is, in fact, a mixture of two products, (**3a**) and (**4a**) although the minor isomer (**4a**) is present in very low amounts and was not detected in the ^{1}H n.m.r. spectrum of the crude product (Scheme 2). The rather modest yields of reduction products presumably reflected inefficiency in the reduction step (or work-up), since the imidate appears to be the only reaction product by n.m.r. The major reduction product (**5a**), however, does confirm the structural assignment of the major imidate product, (**3a**).

A series of NSA (**1b**—**d**) were prepared and treated with DHP. Reduction of the product mixture gave the amino alcohols (**5b**) and (**6b**—**d**) (Table). Identities of these products were established by comparison with authentic samples. Again the reduction step was problematic, since the crude yields from the reduction gave high material balances, but the amino alcohol products comprise only *ca.* 50% of the crude reduction period. The remainder appears to be ring-opened material that does not contain nitrogen. The acid-catalysed addition of NSA to DHP is sensitive to steric effects in the NSA, and works best for primary alkyl substituents on the amine. If t-butylamine is converted into the NSA derivative, it fails to undergo addition to DHP.



Scheme 2.

Table. Reduction products of imidate salts formed in the reaction of *N*-arylsulphonyloxyamines (NSA) with dihydropyran

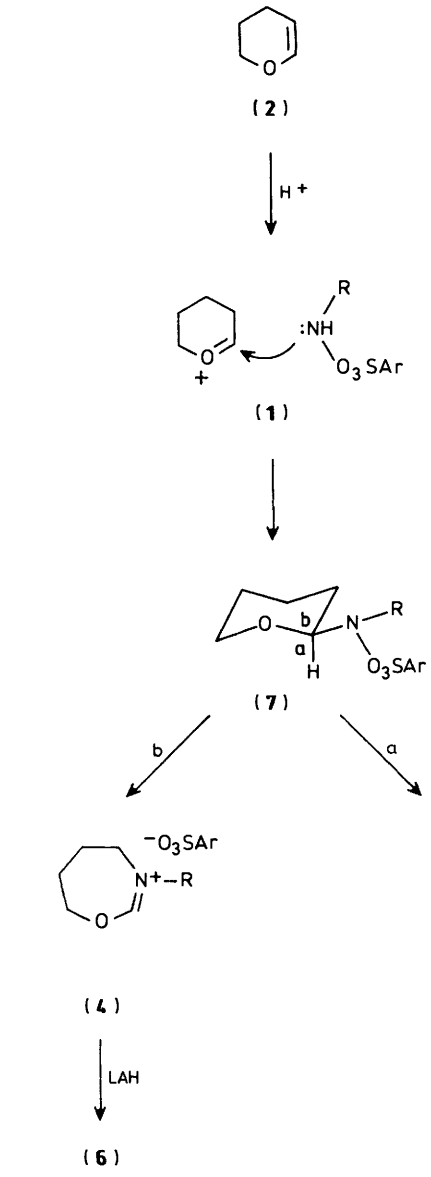
NSA	Yield (%)[a]	
$RNHOSO_2C_6H_4NO_2$-*p*	$HO(CH_2)_5NHR$	$HO(CH_2)_4NMeR$
(1)	(5)	(6)
1a, R = Me	29	3
1b, R = Et	32	13
1c, R = Pr	35	12
1d, R = Bu	36	12

[a] Reported yields are isolated yields of purified product.

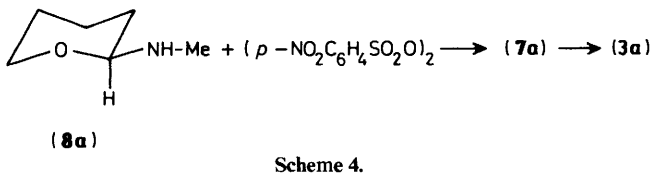
Since electrophilic attack normally occurs at C-3 of the DHP ring,[11] imidates (**3**) and (**4**) are probably not produced by electrophilic attack of (**1**) on the electron-rich double bond of (**2**). A more likely route involves protonation of (**2**) followed by *nucleophilic* addition of (**1**) to the intermediate oxonium ion to give a new NSA (**7**). (Scheme 3). Preparations of (**1**) invariably contain some acidic decomposition products, and the imidate salt (**3**) could itself function as an acid catalyst for the addition reaction. Addition of 4-methyl-2,6-di-t-butylpyridine (1.5 equiv.) to the reactants (**1a**) and (**2**), prior to mixing, completely suppresses the reaction. Addition of 0.25 equiv. results in an induction period, during which the base is neutralized by decomposition of (**1a**), followed by a rapid reaction between the remaining (**1a**) and DHP.

The resulting *N*-arylsulphonyloxy intermediate (**7**) rearranges by two competing pathways (Scheme 3). Hydride migration from carbon to nitrogen (path a) gives (**3**) while migration of C-3 (path b) gives the ring expanded imidate (**4**). This scenario is further supported by the observation that reaction of the amine (**8a**) with *p*-nitrophenylsulphonyl peroxide (*p*NPSP), which should also yield (**7a**), produces (**3a**) as the only observable product [although (**4a**) is probably present in small amounts] (Scheme 4).

It is of interest that the two migratory pathways of (**7**) are competitive. Normally hydrogen has a much higher migratory aptitude than an alkyl group in cationic rearrangements in



Scheme 3.



Scheme 4.

NSA.[5c,6,12] One explanation for the results is that the stabilizing effect of oxygen on the migration origin lessens the importance of migratory aptitude in determining which group migrates to electron deficient nitrogen, thus the two pathways become competitive. Stabilization of the migration origin has been shown previously to influence the regiochemical preference of migration.[5c]

Stereoelectronic effects might also increase the proportion of (**4**) in the product mixture. The ratio of hydride migration to ring expansion is constant (3:1) for the series of n-alkyl substituents in (**1b**—**d**) but different than the 10:1 ratio found for (**1a**). This difference could be due to steric effects which result in a different conformation preference in (**7b**—**d**) than in (**7a**).

The requirement for an antiperiplanar relationship between the arylsulphonyloxy leaving group and the migrating group is somewhat dependent on conformational effects and can lead to a stereoelectronic bias in the rearrangement step. This was earlier shown to be an important factor favouring ring expansions of cyclohexylamines,[5c,7] which are carbocyclic analogues of the present system. The same factors may be important in the oxa-analogues, (7).

In summary the results show that NSA undergo facile acid-catalysed addition to the double bond of DHP to produce new NSA derivatives, (7). Subsequent cationic rearrangement of the addition product leads to both hydride migration from carbon to nitrogen (major) and ring expansion (minor). Competing rearrangement of the *N*-alkyl substituent does not appear significant. The results also indicate the NSA do not function as electrophilic aminating agents towards DHP, and it is unlikely that their development as electrophilic aminating agents holds much promise.

Experimental

N.m.r. spectra were obtained on a Varian XL 200 or a Jeol-PS-100 spectrometer. I.r. spectra were obtained on a Perkin-Elmer 1310 spectrophotometer. M.p.s were obtained with a MelTemp apparatus and are uncorrected. Elemental analyses were performed by Desert Analytics, Tucson, AZ. All starting materials were obtained commercially. Methylamine (Matheson gas), 40% aqueous methylamine (Aldrich), and 70% aqueous ethylamine were used as received. Butylamine, propylamine, dihydrofuran and 3,4-dihydro-2*H*-pyran were distilled prior to use. Ethylamine was collected from 70% aqueous ethylamine by adding solid potassium hydroxide. Solvents were reagent grade and were used without further purification. *p*-Nitrophenylsulphonyl peroxide (*p*NPSP) was prepared by the method of Dannley.[13]

N-*Methyl*-O-p-*nitrophenylsulphonylhydroxylamine* (**1a**).[14]—The same general literature procedure[14] was used to prepare *N*-alkyl-*O*-*p*-nitrophenylsulphonylhydroxylamines (**1a—d**), except for the quantity of amine used and the temperature at which the products were isolated from solvent. Due to their thermal instability, the characterization of (**1a—b**) was generally limited to n.m.r. and iodometric titration unless otherwise noted. The percent of active oxygen (a.o.) was determined by iodometric titration using sodium thiosulphate (0.0054M) to titrate 8 mg samples of (**1a—b**) in ethyl acetate (1 ml), potassium iodide (10% aqueous, 2.5 ml) and acetic acid (2.5 ml). A general procedure is given for (**1a**).

To a cooled (−78 °C) solution of methylamine (333 cm^3 gas, 665 Torr, 12 mmol) in dichloromethane (5 ml) was quickly added a suspension of *p*NPSP[13] (1.62 g, 4.01 mmol) in dichloromethane (90 ml). The solution rapidly turned yellow and a heavy precipitate formed. After being stirred for 0.5 h at −78 °C, the suspension was filtered by suction through a cooled (−78 °C) 1-in pad of silica gel wetted with dichloromethane in a fritted glass funnel. The solvent was evaporated from the filtrate at 0 °C under vacuum into a liquid nitrogen-cooled trap to give as a yellow tinted crystalline solid, the title compound (**1a**) (0.38 g, 83% purity by a.o. determination, 34%), m.p. 87—89 °C (lit.,[16] m.p. 83—85 °C); δ_H(200 MHz; $CDCl_3$) matched the published spectrum.[14]

N-*Ethyl*-O-p-*nitrophenylsulphonylhydroxylamine* (**1b**). Using the same procedure as for (**1a**), *p*NPSP (1.62 g, 4.01 mmol) was added to ethylamine (373 mg, 8.3 mmol) which after filtration and evaporation of dichloromethane at −20 °C gave as a white waxy solid, the *title compound* (**1b**) (0.55 g, 62% purity by a.o., 35%); δ_H(200 MHz; $CDCl_3$) 0.98 (3 H, t, *J* 7 Hz, CH_3), 3.07 (2 H, q, *J* 7 Hz, CH_2), and 8.23 and 8.45 (4 H, ABq, *J* 8 Hz, Ar), NH not observed. Normally (**1b**) was used immediately after isolation.

N-*Propyl*-O-p-*nitrophenylsulphonylhydroxylamine* (**1c**). Using the same procedure as for (**1a**), *p*NPSP (1.62 g, 4.01 mmol) was added to propylamine (0.50 g, 8.5 mmol) which after filtration and evaporation of dichloromethane at −20 °C gave as a white waxy solid the *title compound* (**1c**) (0.57 g, 75% purity by a.o., 41%); δ_H(200 MHz; $CDCl_3$) 0.83 (3 H, t, *J* 7 Hz, CH_3), 1.3—1.5 (2 H, m, CH_3CH_2), 2.98 (2 H, t, *J* 7 Hz, CH_2N), and 8.23 and 8.46 (4 H, ABq, *J* 8 Hz, Ar); NH not observed. Normally (**1c**) was used immediately after isolation.

N-*Butyl*-O-p-*nitrophenylsulphonylhydroxylamine* (**1d**). Using the same procedure as for (**1a**), *p*NPSP (1.62 g, 4.01 mmol) was added to butylamine (0.61 g, 8.3 mmol) which after filtration and evaporation of dichloromethane at −20 °C gave as a white waxy solid, the *title compound* (**1d**) (0.58 g, 72% purity by a.o., 38%), m.p. 44—46 °C; δ_H(200 MHz; $CDCl_3$) 0.84 (3 H, t, *J* 7 Hz, CH_3), 1.1—1.5 (4 H, m, $CH_3CH_2CH_2$), 3.01 (2 H, t, *J* 7 Hz, CH_2N), and 8.24 and 8.46 (4 H, ABq, *J* 8 Hz, Ar), NH not observed. Normally (**1d**) was used immediately after isolation.

Reaction of N-*Methyl*-O-p-*nitrophenylsulphonylhydroxylamine* (**1a**) *and Dihydropyran* (**2**).—The same general procedure was used to treat *N*-alkyl-*O*-*p*-nitrophenylsulphonylhydroxylamines (**1a—d**) with (**2**). A detailed procedure is given for (**1a**).

A solution of (**2**) (0.14 g, 1.7 mmol) in dichloromethane (25 ml) was added dropwise over 15 min to a cooled (0 °C) solution of (**1a**) (0.37 g, 83% a.o., 1.33 mmol) in dichloromethane (10 ml). The mixture was stirred at room temperature for 1 h. The solvent was removed by rotary evaporation to give as a hygroscopic dark oil, the imidate salt (**3a**); $\nu_{max.}$(neat) 3 700—2 500br, 1 690 (C=N), 1 520, 1 350, and 1 200 cm^{-1}; δ_H(200 MHz; $CDCl_3$) 1.9—2.2 (4 H, m, $CH_2CH_2CH_2CH_2$), 3.0—3.2 (5 H, m, CH_3NCCH_2), 4.70 (2 H, t, *J* 6 Hz, CH_2O), and 8.11 and 8.29 (4 H, ABq, *J* 9 Hz Ar; generally the integration was higher than 4 H when the product did not crystallize). Irradation of the multiplet at 1.9—2.2 p.p.m. collapsed the methylene triplet at 4.7 p.p.m. (6-H) to a singlet and sharpened the signal at 3.0—3.2 p.p.m. This substantiates that the C-3 methylene triplet is overlapped by the C-7 methyl group. In the presence of $Eu(fod)_3$ (25 mg), (**3a**) (40 mg, 0.17 mmol) showed δ_H(100 MHz; $CDCl_3$) 2.0—2.2 (m, $CH_2CH_2CH_2CH_2$), 3.2—3.35 (br d, CH_3), 3.4 (br t, CH_2CN), and 4.8 (br t, CH_2O). An off-resonance decoupled ^{13}C n.m.r. spectrum of (**3a**) gave δ_C(200 MHz; $CDCl_3$) 179 (s, OCN), 151 and 153 (s, CN and CS aromatic ring), 125 and 129 (d, CH aromatic ring), 75 (t, CH_2O), 29 (q, CH_3), and 16, 22, and 27 (t, ring CH_2s).

Reaction of N-*ethyl*-O-p-*nitrophenylsulphonylhydroxylamine* (**1b**) *and* (**2**). Using the same procedure as for (**1a**), (**2**) (0.19 g, 2.3 mmol) was added to (**1b**) (0.55 g, 62% purity, 1.38 mmol) to give a hydroscopic dark oil with a complex ^1H n.m.r. spectrum which could not be fully assigned.

Reaction of N-*propyl*-O-p-*nitrophenylsulphonylhydroxylamine* (**1c**) *and* (**2**). Using the same procedure as for (**1a**), (**2**) (0.18 g, 2.1 mmol) was added to (**1c**) (0.56 g, 75% purity, 1.61 mmol) to give a hygroscopic dark oil with a complex ^1H n.m.r. spectrum which could not be fully assigned.

Reaction of N-*butyl*-O-p-*nitrophenylsulphonylhydroxylamine* (**1d**) *and* (**2**). Using the same procedure as for (**1a**), (**2**) (0.17 g, 2.0 mmol) was added to (**1d**) (0.55 g, 72% purity, 1.44 mmol) to give a hygroscopic dark oil with a complex ^1H n.m.r. spectrum which could not be fully assigned.

Reduction of Reaction Products of (**1a—d**) *and* (**2**).—The same general procedure was used to reduce the products of the reaction of *N*-alkyl-*O*-*p*-nitrophenylsulphonylhydroxylamines (**1a—d**) and (**2**) with lithium aluminium hydride [LAH; 4 equivalents to starting amount of (**1a—d**)]. A representative example for (**1a**) is given.

The crude reaction products from the reaction of (**1a**) and (**2**) were stirred in anhydrous ether (25 ml), and LAH (0.24 g, 6.3 mmol) was added slowly, causing the oil to dissolve and produce a green suspension. After being stirred at room temperature overnight, the reaction mixture was quenched with water (0.24 ml), 15% sodium hydroxide (0.24 ml), and water (0.72 ml).[15] The resulting orange precipitate was collected by vacuum filtration and washed with ether (75 ml). The filtrate was dried (K_2CO_3) and the solvent removed by rotary evaporation. The resulting yellow-brown oil was distilled on a Kugelrohr apparatus (0.15 Torr, 60 °C, 1 h). The mass spectrum of the clear distillate gave a *m/z* 117 (M^+). The distillate (0.15 g) was dissolved in anhydrous ether (25 ml), and gaseous HCl was bubbled through the solution. An oil formed which was triturated with anhydrous ether (2 × 10 ml), and then stirred in dichloromethane (25 ml) with one crushed pellet of potassium hydroxide (0.15 g), which caused the oil to dissolve. The solution was filtered and evaporated, and the resulting clear oil (0.09 g) was redistilled by Kugelrohr to give as clear liquid, a mixture of (**5a**) and (**6a**) (50 mg, 0.43 mmol, 29 and 3% respectively). The products were identified and their yields were determined by the comparison of their ^{1}H n.m.r. spectra with authentic samples. The integrated areas of the protons on carbons adjacent to nitrogen (2—3 δ) formed the basis for determining the ratio of secondary, (**5a**), to tertiary, (**6a**), amino alcohols.

Reduction of the reaction products of (**1b**) *and* (**2**). By the same procedure as for (**1a**), LAH (0.33 g, 8.7 mmol) was used to reduce the reaction of (**1b**) and (**2**) to give as a clear oil, a mixture of (**5b**) and (**6b**) (80 mg, 0.61 mmol, 32 and 13% respectively) by ^{1}H n.m.r.

Reduction of the reaction products of (**1c**) *and* (**2**). By the same procedure as for (**1a**), LAH (0.33 g, 8.7 mmol) was used to reduce the reaction of (**1c**) and (**2**) to give as a clear oil, a mixture of (**5c**) and (**6c**) (110 mg, 35 and 12% respectively) by ^{1}H n.m.r.

Reduction of the reaction products of (**1d**) *and* (**2**). By the same procedure as for (**1a**), LAH (0.30 g, 7.9 mmol) was used to reduce the reaction of (**1d**) and (**2**) to give as a clear oil, a mixture of (**5d**) and (**6d**) (110 mg, 36 and 12% respectively) by ^{1}H n.m.r. The mass spectrum of the crude reduction products showed *m/z* 159 (M^+) as required. A preparation using (**1d**) (0.90 g, 73% a.o., 5 ml dichloromethane, −78 °C) and (**2**) (0.28 g, 20 ml dichloromethane, dropwise over 15 min plus 1.5 h at room temperature) was reduced with sodium borohydride[16] (0.31 g, 25 ml. abs. ethanol, 12 h, room temperature) and, after Kugelrohr distillation, gave a mixture (0.19 g) which contained (**5d**) and (**6d**) in low yield. This mixture was separated by flash chromatography[17] (MeOH as eluant). One fraction was taken that contained mostly (**6d**) (30 mg, 8%) and another contained mostly (**5d**) (50 mg, 13%).

Preparation of Authentic Amino Alcohols (**5a—d**).—The same general procedure was used to prepare 5-alkylaminopentan-1-ols (**5a—d**) from (**2**). A representative preparation of (**5a**) is described.

5-*Methylaminopentan*-1-*ol* (**5a**).[18] Freshly distilled (**2**) (4.21 g, 50 mmol) was added in one portion to a cooled (0 °C) solution of conc. hydrochloric acid (1.0 ml) and water (12.5 ml). The mixture was stirred and allowed to warm to room temperature, and it became homogeneous after 5 min. After 10 min, the solution was cooled in ice and 40% aqueous methylamine (4.89 g, 65 mmol) was added dropwise with stirring. After 30 min at room temperature, the mixture was extracted with dichloromethane (3 × 10 ml). The combined organic layers were dried (K_2CO_3), and the solvent removed by rotary evaporator. The resulting oil was taken up in absolute ethanol (10 ml), cooled (0 °C), and sodium borohydride (1.89 g, 50 mmol) was added slowly. When bubbling had subsided, the mixture was heated to 50 °C for 1 h, and then stirred at room temperature for 12 h. The reaction was cooled in ice, and sufficient conc. hydrochloric acid (4 ml) was added to give pH 8. The ethanol supernatant was decanted, and the heavy white precipitate remaining was triturated with dichloromethane (5 × 10 ml) and suction filtered. The combined organic layers were evaporated, and the remaining clear oil (5.52 g) was distilled on a Kugelrohr apparatus to give the *amino alcohol* (**5a**) (1.25 g, 21%); $\nu_{max.}$(neat) 3 280, 2 920, 1 460, and 1 050 cm^{-1}; δ_H(200 MHz; $CDCl_3$) 1.3—1.7 (6 H, m), 2.42 (3 H, s, CH_3), 2.58 (2 H, t, *J* 7 Hz, CH_2N), and 3.58 (2 H, t, *J* 6 Hz, CH_2O); the NH and OH protons were not observed. Compound (**5a**) was converted into its hydrochloride salt, m.p. 46—48 °C (acetone–ethanol) (Found: C, 46.6; H, 10.7; N, 8.9. $C_6H_{16}ClNO$ requires C, 46.9; H, 10.5; N, 9.1%).

5-*Ethylaminopentan*-1-*ol* (**5b**). By the above method, 70% aqueous ethylamine (4.06 g, 65 mmol) and (**2**) (4.21 g, 50 mmol) were used to prepare the *amino alcohol* (**5b**) (3.84 g, 59%); $\nu_{max.}$(neat) 3 280, 2 920, 1 460, and 1 050 cm^{-1}; δ_H(200 MHz; $CDCl_3$) 1.11 (3 H, t, *J* 7 Hz, CH_3), 1.3—1.7 (6 H, m), 2.5—2.8 (4 H, 2t, CH_2NCH_2), and 3.58 (2 H, t, *J* 6 Hz, CH_2O); the NH and OH protons were not observed. Compound (**5b**) was converted into its hydrochloride salt, m.p. 63—64 °C (acetone–ethanol) (Found: C, 50.2; H, 11.0; N, 8.35. C_7H_8ClNO requires C, 50.1; H, 10.8; N, 8.35%).

5-*Propylaminopentan*-1-*ol* (**5c**). By the above method, propylamine (3.72 g, 65 mmol) and (**2**) (4.21 g, 50 mmol) were used to prepare the *amino alcohol* (**5c**) (4.74 g, 65%), m.p. 37—40 °C; $\nu_{max.}$(neat) 3 280, 2 920, 1 460, and 1 050 cm^{-1}; δ_H(200 MHz; $CDCl_3$) 0.91 (3 H, t, *J* 7 Hz, CH_3), 1.3—1.7 (8, H), 2.5—2.8 (4 H, 2t, CH_2NCH_2), and 3.59 (2 H, t, *J* 6 Hz, CH_2O); the NH and OH protons were not observed. Compound (**5c**) was converted into its hydrochloride salt, m.p. 100.5—102 °C (acetone–ethanol) (Found: C, 53.1; H, 11.4; N, 7.6. $C_8H_{20}ClNO$ requires C, 52.9; H, 11.1; N, 7.7%).

5-*Butylaminopentan*-1-*ol* (**5d**). By the above method, butylamine (4.58 g, 63 mmol) and (**2**) (4.21 g, 50 mmol) were used to prepare the *amino alcohol* (**5d**) (5.11 g, 64%), m.p. 30—32 °C; $\nu_{max.}$(neat) 3 280, 2 920, 1 460, and 1 050 cm^{-1}; δ_H(200 MHz; $CDCl_3$) 0.91 (3 H, t, *J* 7 Hz, CH_3), 1.2—1.7 (10 H, m), 2.5—2.8 (4 H, 2t, CH_2NCH_2), and 3.58 (2 H, t, *J* 7 Hz, CH_2O); the NH and OH protons were not observed. Compound (**5d**) was converted into its hydrochloride salt, m.p. 120—121.5 °C (acetone–ethanol) (Found: C, 55.3; H, 11.5; N, 7.0. $C_9H_{22}ClNO$ requires C, 55.2; H, 11.3; N, 7.2).

Preparation of Authentic Amino Alcohols (**6a—d**).—The same general procedure was used to prepare 4-(*N*-methyl-*N*-alkylamino)butan-1-ols, (**6a—d**) by methylation of 4-(*N*-alkylamino)butan-1-ols, which were prepared from 2,3-dihydrofuran (DHF). A representative preparation of (**6a**) is described.

4-*Dimethylbutan*-1-*ol* (**6a**).[18,19] Methylaminobutan-1-ol was prepared from DHF (3.50 g, 50 mmol) and 40% aqueous methylamine (4.89 g, 65 mmol) by the same procedure used previously for the preparation of (**5a**). The crude product (3.10 g) was treated with 37% aqueous formaldehyde (9 ml, 120 mmol) in methanol (25 ml) and refluxed for 25 min. The mixture was cooled in ice and sodium borohydride (1.71 g, 45 mmol, 1.5 equiv.) was added slowly. The suspension was stirred overnight at room temperature. The solvent was removed, and the residue was triturated with dichloromethane (5 × 10 ml). The combined organic layers were filtered, dried (K_2CO_3), and evaporated to give a clear oil (1.71 g). The oil was distilled on a Kugelrohr apparatus to give the *amino alcohol* (**6a**) (0.83 g, 14% from DHF); $\nu_{max.}$(neat) 3 400br, 2 940, 1 460, and 1 050 cm^{-1}; δ_H(200 MHz; $CDCl_3$) 1.6—1.7 (4 H, m), 2.26 [6 H, s, $(CH_3)_2N$], 2.28—2.35 (2 H, br t, CH_2N), and 3.57 (2 H, br t, CH_2O); the OH proton was not observed.

4-*Ethylmethylaminobutan*-1-*ol* (**6b**). 4-Ethylaminobutan-1-ol (5.10 g, crude) was prepared by reaction of ethylamine and DHF by the same procedure used previously for the preparation of (**5b**). Treatment of the crude product (5.1 g) with 37% aqueous formaldehyde (13 ml, 173 mmol) followed by reduction with sodium borohydride (2.47 g, 65 mmol) gave the *amino alcohol* (**6b**) (1.59 g, 24% from DHF); $\nu_{max.}$(neat) 3 350br, 2 920, 1 450, and 1 050 cm^{-1}; δ_H(200 MHz; $CDCl_3$) 1.08 (3 H, t, *J* 7 Hz, CH_3C), 1.6—1.7 (4 H, m), 2.23 (3 H, s, CH_3N), 2.3—2.4 (2 H, br t, CH_2CH_2N), 2.47 (2 H, q, CH_3CH_2N), and 3.57 (2 H, br t, CH_2O); the OH proton was not observed. Compound (**6b**) was converted into its hydrochloride salt, m.p. 97—100 °C (acetone–ethanol) (Found: C, 50.2; H, 11.1; N, 8.3. $C_7H_{18}ClNO$ requires C, 50.1; H, 10.8; N, 8.35%).

4-*Methylpropylaminobutan*-1-*ol* (**6c**). 4-Propylaminobutan-1-ol was prepared by the reaction of propylamine and DHF by the same procedure used previously for the preparation of (**5c**). Treatment of the crude product (6.2 g) with 37% aqueous formaldehyde (14 ml, 187 mmol) followed by reduction with sodium borohydride (2.67 g, 71 mmol) gave the *amino alcohol* (**6c**) (1.86 g, 26% from DHF); $\nu_{max.}$(neat) 3 400br, 2 920, 1 460, and 1 050 cm^{-1}; δ_H(200 MHz; $CDCl_3$) 0.90 (3 H, t, *J* 7 Hz, CH_2C), 1.5—1.7 (6 H, m), 2.22 (3 H, s, CH_3N), 2.2—2.4 (4 H, 2t, CH_2NCH_2), and 3.57 (2 H, br t, CH_3O); the OH proton was not observed. Compound (**6c**) was converted into its hydrochloride salt, m.p. 91—93.5 °C (acetone–ethanol) (Found: C, 53.0; H, 11.4; N, 7.65. $C_8H_{20}ClNO$ requires C, 53.0; H, 11.1; N, 7.7%).

4-*Butylmethylaminobutan*-1-*ol* (**6d**). 4-Butylaminobutan-1-ol was prepared from butylamine and DHF by the same procedure used previously for the preparation of (**5d**). Treatment of the crude product (5.02 g) with 37% aqueous formaldehyde (10 ml, 133 mmol) followed by reduction with sodium borohydride (1.96 g, 52 mmol) gave the *amino alcohol* (**6d**) (1.66 g, 21% from DHF); $\nu_{max.}$(neat) 3 400br, 2 940, 1 460, and 1 050 cm^{-1}; δ_H(200 MHz; $CDCl_3$) 0.92 (3 H, t, *J*, 7 Hz, CH_3C), 1.2—1.7 (8 H, m), 2.22 (3 H, s, CH_3N), 2.3—2.4 (4 H, 2t, CH_2NCH_2), and 3.57 (2 H, br t, CH_2O); the OH proton was not observed. Compound (**6d**) was converted into its hydrochloride salt, m.p. 85.5—87.5 °C (acetone–ethanol) (Found: C, 55.3; H, 11.6; N, 7.25. $C_9H_{22}ClNO$ requires C, 55.2; H, 11.3; N, 7.2%).

Reaction of (**1a**) *and* (**2**) *observed by* ^{1}H *N.m.r.*—To a solution of (**1a**) (31 mg, 0.13 mmol) in $CDCl_3$ (1 ml) was added (**2**) (50 µl, 0.054 mmol, 0.5 equiv.) *via* syringe. Within 5 min no vinyl protons were observed in the ^{1}H n.m.r. spectrum while peaks corresponding to imidate (**3a**) had begun to emerge. No more spectral changes were observed 10 min after the initial addition of (**2**) and (**3a**) and (**1a**) were present in approximate equimolar amounts as evidenced by equal amounts of covalently bound *p*-nitrophenylsulphonyl compound of (**1a**) (ABq 8.24 and 8.46 p.p.m.) and *p*-nitrobenzenesulphonate salt (**3a**) (ABq 8.11 and 8.29 p.p.m.).

Reaction of (**1a**) *with* (**2**) *in the Presence of* 4-*Methyl*-2,6-*di*-t-*butylpyridine observed by* ^{1}H *N.m.r.*—The addition of the sterically hindered base 4-methyl-2,6-di-t-butylpyridine (55 mg, 0.27 mmol) to (**1a**) (40 mg, 0.17 mmol) gave δ_H(100 MHz; $CDCl_3$) 2.8 (3 H, d, *J* 3 Hz, CH_3), 6.8 (1 H, q, *J* 3 Hz, NH), and 8.1 and 8.4 (4 H, ABq, *J* 5 Hz, Ar) corresponding to (**1a**), and peaks corresponding to the base. After adding (**2**) (16.0 µl, 0.18 mmol, 1 equiv.) *via* a syringe to the n.m.r. sample, the mixture was monitored by ^{1}H n.m.r. No apparent reaction with (**2**) occurred. After 1 day, (**2**) was still present, although (**1a**) had decomposed as indicated by the appearance of *p*-nitrobenzenesulphonate salt and broadening of the 4-methyl-2,6-di-t-butylpyridine peaks.

Performing the same experiment with (**1a**) (40 mg, 0.17 mmol), 4-methyl-2,6-di-t-butylpyridine (9 mg, 0.04 mmol, 0.25 equiv.), and (**2**) (16.0 ul, 0.18 mmol) showed no apparent reaction for 1 h, at which time (**2**) and (**1a**) disappeared with the appearance of peaks corresponding to (**3a**).

Reaction of 2-*Methylaminotetrahydropyran* (**8a**) *and* p*NPSP*.—To a cooled (−78 °C) solution of 2-methylaminotetrahydropyran[20] (30.9 mg, 0.268 mmol) in $CDCl_3$ (1 ml) was added *p*NPSP (107.5 mg, 0.266 mmol). The sample was allowed to warm to room temperature and its ^{1}H n.m.r. spectrum showed (**3a**) present in solution.

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