Unsymmetrically substituted furoxans. Part 18.[1] Smiles rearrangement in furoxan systems and in related furazans

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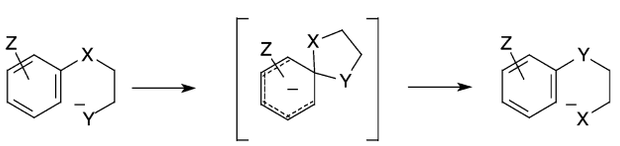
The preparation and the base-promoted Smiles rearrangement of phenylfurazans (series **a**), 3-phenylfuroxan (series **b**) and 4-phenylfuroxan (series **c**) bearing 2-hydroxyethylthio (**1**), 2-hydroxyethylsulfonyl (**2**), carbamoylmethylthio (**3**) and carbamoylmethylsulfonyl (**4**) functions at the hetero-ring are described. Under similar conditions compounds of the series **a** and **b** gave the expected Smiles rearrangment products with the only exception being the amide derivatives **3** which were hydrolysed to their corresponding acid. The behaviour of the 4-phenylfuroxan series to Smiles rearrangment was quite different. Under conditions close to those adopted for the corresponding 3-phenyl isomers, **1c** and **2c** decomposed into unidentified polar products. **3c** afforded as principal product 3-mercapto 4-phenylfurazan while **4c** afforded (*Z*)-2-hydroxyimino-2-phenylacetonitrile. Possible mechanisms of formation of these products are discussed.

Introduction

The finding that derivatives of furoxan (1,2,5-oxadiazole 2-oxide) can behave under physiological conditions, in the presence of thiol cofactors, as NO-donors brought about a renewed interest in this heterocycle system.[2a]† The overall reaction mechanism appears to be very complex and release of nitric oxide radical ($NO^{\bullet}$) or intermediate formation of nitroxyl anion (NO^{-}), or both, could be involved.[2c] It is known that furoxans bearing suitable groups at the 3- or 4-position of the ring undergo nucleophilic substitutions. In the literature there are several scattered reports in which this reactivity has been used for synthesising a variety of new derivatives of this system.[3,4] A few papers are specifically devoted to this aspect. Nucleophilic displacement of benzenesulfonyl and nitro groups received particular attention from our group[5] and from a Russian team.[6] The Smiles rearrangement is a nucleophilic intramolecular substitution which follows the reaction pathway shown in Scheme 1.



Scheme 1

X represents a leaving group, such as S, SO, SO_2, O, *etc.*, Y usually is the conjugate base of OH, NH_2, CONH, SO_2NH, and Z an activating group-withdrawing group.[7] The scope of the reaction has been extended to a variety of molecular systems, but little is known about this rearrangement in many heterocycles. As a development of our research on furoxan chemistry, we now report the base-promoted Smiles rearrangement of phenylfuroxans bearing 2-hydroxyethylthio (**1b**, **1c**), 2-hydroxyethylsulfonyl (**2b**, **2c**), carbamoylmethylthio (**3b**, **3c**), and carbamoylmethylsulfonyl (**4b**, **4c**) functions at the hetero-ring (Scheme 2). The rearrangement was also investigated in related furazans (1,2,5-oxadiazoles) (**1a**–**4a**) for comparison.

† According to a convention[2b] we use the term nitric oxide (NO) as a generic family name. When necessary in the discussion, we specify the particular redox form to which we refer.

Results and discussion

Preparation of the models

Hydroxyethylthio derivatives were obtained in good yields according to the sequence of reactions reported in Scheme 2. Nucleophilic substitution of the nitro group in 3-nitro-4-phenylfurazan **5** by 2-hydroxyethanethiol **6** in distilled THF in the presence of 50% NaOH gave the expected hydroxyethylthio derivative **1a**. Related furoxan compounds **1b**, **1c** were obtained in similar manner by nucleophilic displacement of the benzenesulfonyl group in 3-phenyl-4-phenylsulfonylfuroxan **7** and in its 4-phenyl isomer **9** respectively. In the preparation of **1c**, sodium methoxide was used and the reaction was run at −10 °C. All the thio derivatives were easily transformed into the corresponding sulfonyl derivatives **2a**–**c** by trifluoroperacetic acid oxidation. Analogous procedures were used for the preparation of the amide derivatives **3a**–**c**, **4a**–**c**.

Smiles rearrangements

Furazan derivatives (Scheme 3). Rearrangement of 2-hydroxyethylthio derivative **1a** was effected in ethanol solution using 1.2 equivalents of NaOH. After several hours of stirring at room temperature no rearrangement product was observed. By contrast, when the reaction mixture was refluxed for 5 h, 3-hydroxy-4-phenylfurazan **12** and thiirane **13** were isolated in good yields. Smiles rearrangement of **1a** to the intermediate **11**, and subsequent transformation of this compound into **12** by loss of **13**, can easily explain this result. It is known that 2-(2,4-dinitrophenylthio)ethanols behave similarly.[8] Rearrangement of the 2-hydroxyethylsulfonyl group in **2a** was effected in acetone solution using 2 equivalents of NaOH. After 10 min of stirring

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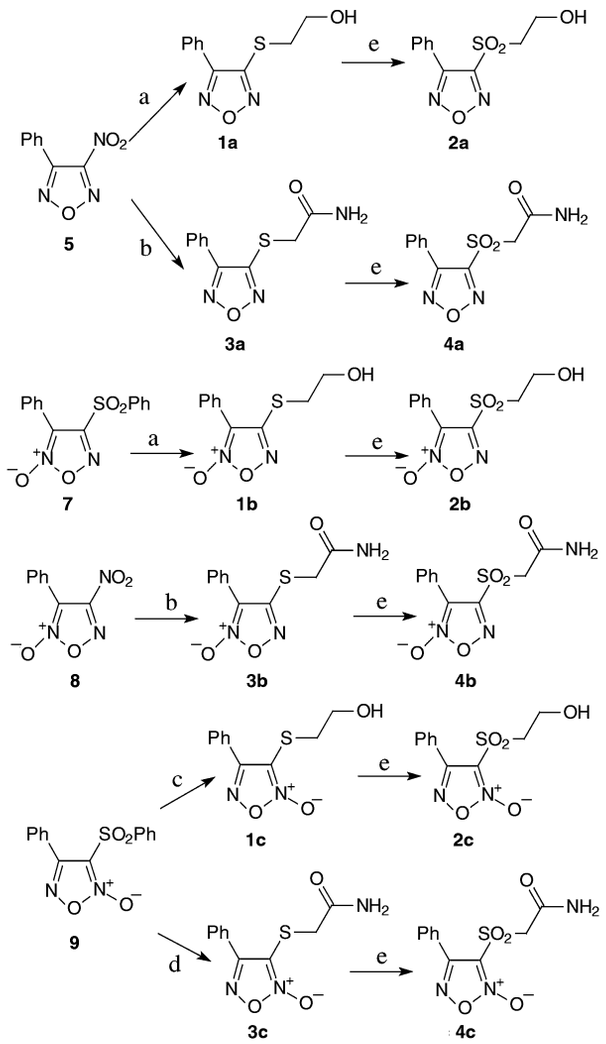
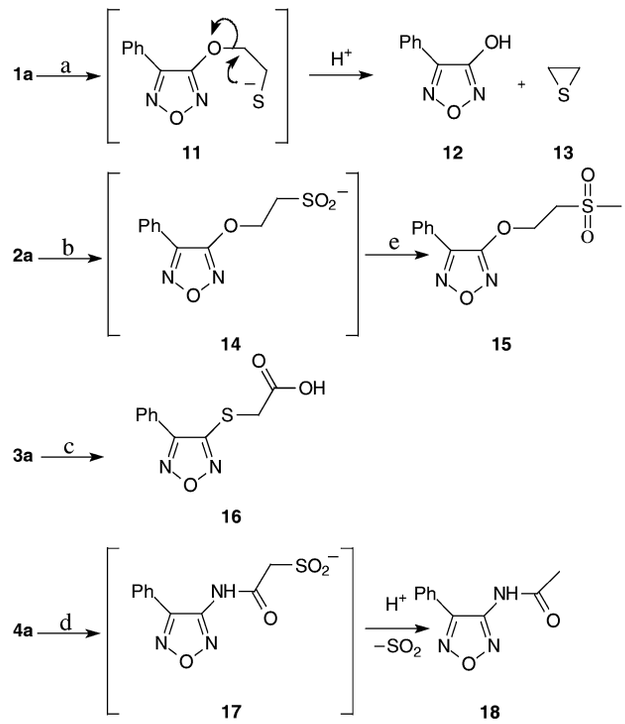


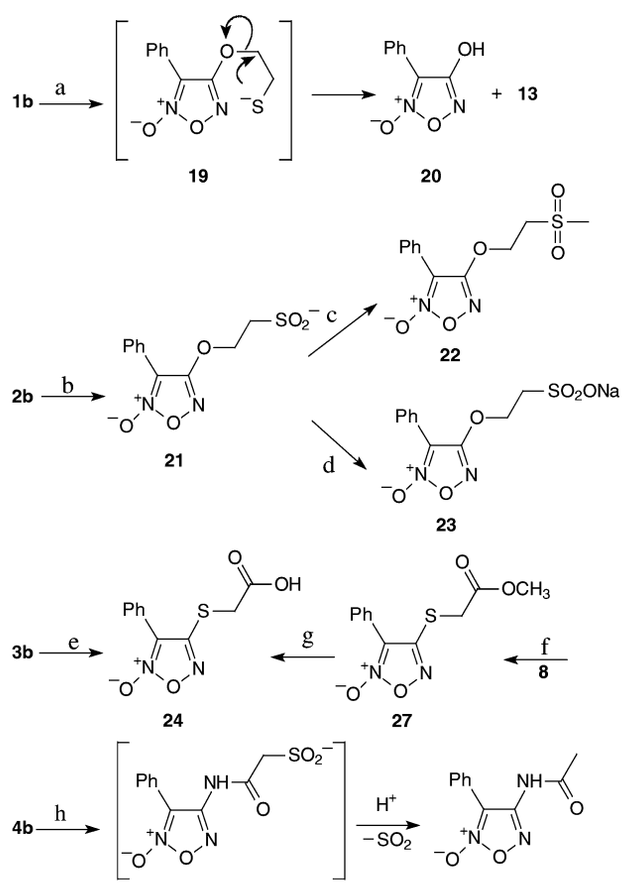
Scheme 2 *Reagents and conditions*: a) 2-hydroxyethanethiol **6**, 50% aq. NaOH, THF, N_2, rt; b) 2-mercaptoacetamide **10**, 50% aq. NaOH, CH_3OH, N_2, rt; c) **6**, CH_3ONa, dry THF, N_2, −10 °C; d) **10**, CH_3ONa, dry THF, N_2, −10 °C; e) 80% aq. H_2O_2, CF_3COOH, rt.

at room temperature the expected sulfinic acid **14** was formed in good yield. The compound was not isolated but immediately transformed into the corresponding methyl sulfone **15** by treatment with a large excess of methyl iodide. Rearrangement of carbamoylmethylthio derivative **3a** was attempted in boiling ethanol in the presence of 2 equivalents of NaOH. After 2 h no Smiles product was isolated, but only the carboxylic acid **16** was recovered (60% yield), deriving from the hydrolysis of the amide function present in **3a**. When the rearrangement was tried in dry THF using 1.2 equivalents of NaH, again no Smiles product was obtained either at room temperature or at 55 °C. Treatment of the carbamoylsulfonylfurazan **4a** in acetone at 55 °C, in the presence of 2.5 equivalents of NaOH, afforded in good yield 3-acetamido-4-phenylfurazan **18**. This shows that the expected rearrangement may be effected. Evidently the sulfinic acid **17** loses SO_2 during the latter stage of the process. Similar behaviour was shown by 2-(2-nitrophenylsulfonyl)-*N*-phenylacetamide when subjected to Smiles rearrangement.[9]

3-Phenylfuroxan derivatives (Scheme 4). The base-promoted Smiles rearrangement in this series of derivatives was performed under conditions close to those adopted for the furazan series and the results obtained were similar. 4-Hydroxy-3-phenylfuroxan **20** was isolated in good yield as the Smiles rearrangement product obtained by treatment of **1b** in EtOH at room temperature with 4 equivalents of NaOH. Loss of **13** from the intermediate **19** can explain this result. Rearrangement



Scheme 3 *Reagents and conditions*: a) 1.2 equivalents of 50% aq. NaOH, refluxing ethanol, 5 h; b) 2 equivalents of 50% aq. NaOH, acetone, rt, 10 min; c) 2 equivalents of 50% aq. NaOH, refluxing ethanol, 2 h; d) 2.5 equivalents of NaOH, acetone, 55 °C, 6 h; e) 20 equivalents of CH_3I, CH_3OH, 4 h, rt.



Scheme 4 *Reagents and conditions*: a) 4 equivalents of 50% aq. NaOH, EtOH, rt, 20 h; b) 2.5 equivalents of 50% aq. NaOH, acetone, rt, 10 min; c) CH_3I; d) 30% aq. H_2O_2; e) 2 equivalents of 50% aq. NaOH, EtOH, 55 °C, 5 h; f) methyl 2-mercaptoacetate, 50% aq. NaOH, CH_3OH, N_2, rt; g) 20% aq. HCl, 1,4-dioxane, 60 °C, 4 h; h) 2.5 equivalents of 50% aq. NaOH, acetone, 55 °C, 5 h.

of **2b** effected at room temperature in acetone in the presence of 2.5 equivalents of NaOH quantitatively afforded the unstable sulfinic acid **21**, which was characterised both by the corresponding methyl sulfone **22** and the sodium salt of the sulfonic acid **23**. This latter compound was obtained by 30% aq. H_2O_2 oxidation of **21** in water. Also the rearrangements of the carbamoyl derivatives **3b** and **4b** parallel the rearrangements of the furazan analogues **3a** and **4a**. In fact, under similar conditions, the carboxylic acid **24** (yield 25%) and the acetamido derivative **26** (yield 40%) were respectively isolated as principal reaction products.

4-Phenylfuroxan derivatives (Scheme 5). The behaviour of the 4-phenyl series to Smiles rearrangement is quite different from that of the 3-phenyl one. Under conditions close to those adopted for the corresponding 3-phenyl isomers, 2-hydroxyethylthio derivative **1c** and 2-hydroxyethylsulfonyl derivative **2c** decomposed into unidentified polar products. One of the possible pathways for this extended decomposition is reported in Scheme 5A. The initially formed anionic spiro intermediate **28** could irreversibly open to the unstable tertiary nitroso derivative **29**, following the breaking of the endocyclic furoxan O1–N2 bond. It is reasonable to think that during the decomposition of this structure NO is also formed. In effect we detected by Griess reaction the presence of nitrite [**1c**, 35%, **2c**, 9% (mol/mol)], which is one important final oxidative product of NO, among the polar reaction compounds.

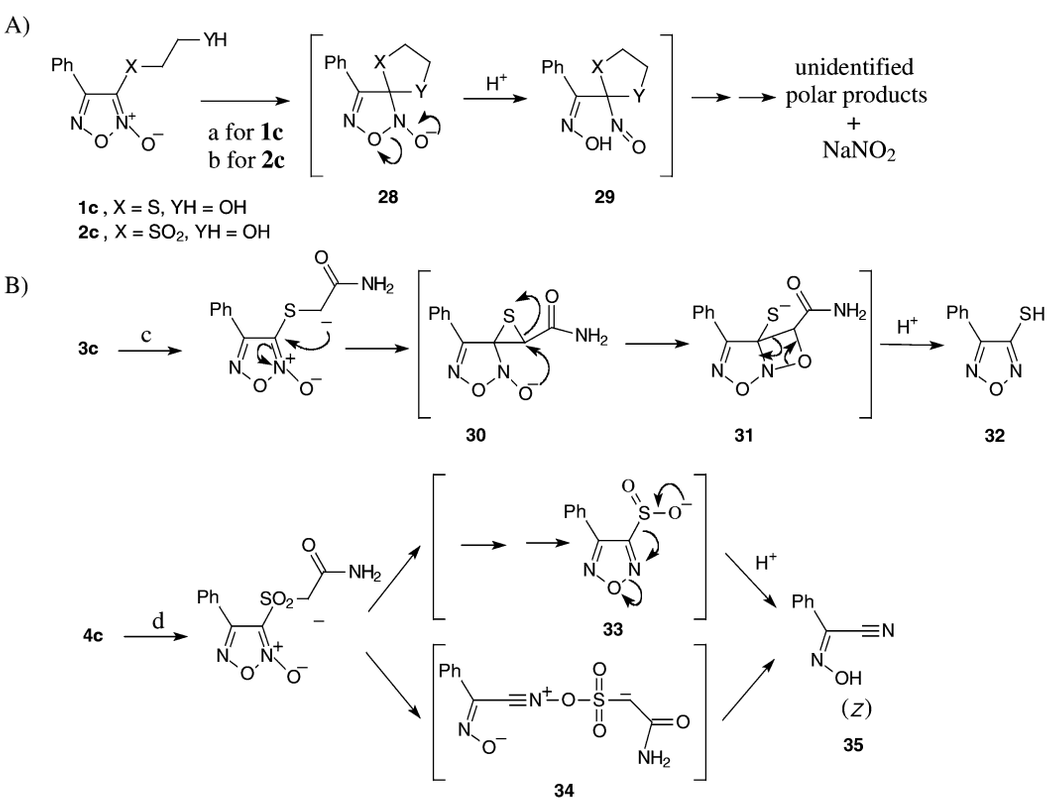
In a previous work we showed that a few furoxans are able to release nitric oxide, under physiological conditions, and also in the absence of thiol cofactors.[10] All of these structures bear at the 3-position a chain potentially able to undergo Smiles rearrangement. This suggests that another mechanism capable of rationalising spontaneous NO-release by these compounds could be that depicted in Scheme 5A. Interestingly, **2c** is also able to afford, under physiological conditions, nitrite (3.9% mol/mol after 1 h of incubation).

Rearrangment of **3c** affords as principal product a compound of molecular formula $C_8H_6N_2OS$ ($M^+ = 178$ Da). Its IR spectrum shows at 2485 cm^{-1} a typical sharp SH absorption. ^{13}C NMR results are in keeping with the presence of two furazan carbons at δ_C 153.1 and 145.9, respectively. On this basis structure **32** was assigned to the compound. A possible mechanism of formation is given in Scheme 5B in which the intermediates **30** and **31** are involved.

The principal compound formed in the rearrangement of **4c** is the *Z* form of 2-hydroxyimino-2-phenylacetonitrile **35**. Formation of this structure could be justified by a mechanism similar to that proposed for the formation of **32**, involving the intermediate **33**. An interesting alternative possibility is represented by the intermediate formation of **34**. In fact, it is known that the hydrochlorides of the adducts of sulfenes to nitrile oxides afford nitriles by alkaline hydrolysis.[11] If this is the case, migration of the furoxan exocyclic oxygen to sulfur of the SO_2 group should occur with concomitant opening of the O1–N2 endocyclic bond.

Experimental

Mps were measured on a Büchi 530 capillary apparatus and are uncorrected. Mps with decomposition were determined after introduction of the sample into the bath at a temperature 10 °C lower than the mp; a heating rate of 3 °C min^{-1} was used. The compounds were routinely checked by IR spectroscopy (Shimadzu FT-IR 8101M) and mass spectrometry (Finnigan-Mat TSQ-700) and the spectra were in keeping with the proposed structures. ^1H and ^{13}C NMR spectra were recorded at 200 and 50 MHz respectively, with a Bruker AC-200 spectrometer. The assignments of the spectra were confirmed by DEPT pulse sequence. Column chromatography was performed on silica gel (Merck Kieselgel 60, 230–400 mesh ASTM) with the indicated solvent system. Thin-layer chromatography (TLC) was carried out on commercially available pre-coated plates (Merck Kieselgel $60F_{254}$ silica). Petroleum ether 40–60 °C (PE) was used as a co-eluent. Anhydrous magnesium sulfate was used



Scheme 5 *Reagents and conditions*: a) 4 equivalents of 50% aq. NaOH, EtOH, rt, 2 h; b) 2.5 equivalents of 50% aq. NaOH, acetone, rt, 20 min; c) 2.5 equivalents of 50% aq. NaOH, EtOH, rt, 15 min; d) 2.5 equivalents of 50% aq. NaOH, acetone, rt, 4 h.

as the drying agent of the organic extracts. Solvent removal was achieved under reduced pressure at room temperature. Elemental analyses of the new compounds were performed by REDOX (Cologno M.) and are reported below for each compound. Compounds **5**,[12] **7**,[5c] **8**,[13] **9**,[5c] **10**[14] were synthesised according to literature methods.

Preparation of the models

3-(2-Hydroxyethylthio)-4-phenylfurazan 1a. To a stirred solution of **5** (2.00 g, 10.5 mmol) in THF (40 cm^3) kept under nitrogen at 0 °C was added, first, 2-hydroxyethanethiol **6**, (0.82 g, 10.5 mmol) and then 50% aq. NaOH portionwise (0.84 g, 10.5 mmol). The reaction mixture was stirred under nitrogen and allowed to attain room temperature. After 3 h, ice was added and the product was extracted with diethyl ether. The combined organic layers were washed with water, dried, and evaporated. Flash chromatography (eluent: PE–EtOAc 8 : 2) of the obtained residue afforded the *title product* (2.13 g, 88%) as a colourless oil (Found: C, 53.9; H, 4.8; N, 12.1. $C_{10}H_{10}N_2O_2S$ requires C, 54.0; H, 4.5; N, 12.6%); ν_{max}(film)/cm^{-1} 3410br; δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.85 (2H, m, Ph), 7.50 (3H, m, Ph), 4.03 (2H, t, CH_2O), 3.47 (2H, t, CH_2S), 2.15 (1H, br s, OH); δ_C (50 MHz; $CDCl_3$; Me_4Si) 152.5 (C3 Furaz.), 150.6 (C4 Furaz.), 130.7 (C*p* Ph), 128.9, 127.9 (C*o*, C*m* Ph), 125.0 (C*i* Ph), 61.1 (CH_2O), 35.4 (CH_2S); *m*/*z* (EI) 222 (M^+, 33%), 161 (100%).

4-(2-Hydroxyethylthio)-3-phenylfuroxan 1b. To a stirred solution of **7** (1.50 g, 5.0 mmol) in THF (30 cm^3) kept under nitrogen at 0 °C was added, first, 2-hydroxyethanethiol **6** (0.77 g, 10.0 mmol) and then 50% aq. NaOH portionwise (0.80 g, 10.0 mmol). The reaction mixture was stirred under nitrogen and allowed to attain room temperature. After 24 h, ice was added and the product was extracted with diethyl ether. The combined organic layers were washed with water, dried, and evaporated. Flash chromatography (eluent: PE–EtOAc 6 : 4) of the residue afforded the *title product* (0.90 g, 76%) as a white solid, mp 53–54 °C (from EtOAc-PE) (Found: C, 50.2; H, 4.2; N, 11.65. $C_{10}H_{10}N_2O_3S$ requires C, 50.4; H, 4.2; N, 11.8 %); ν_{max}(KBr)/cm^{-1} 3250br (OH); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.87 (2H, m, Ph), 7.54 (3H, m, Ph), 4.02 (2H, t, CH_2O), 3.46 (2H, t, CH_2S), 2.06 (1H, br s, OH); δ_C (50 MHz; $CDCl_3$; Me_4Si) 153.9 (C4 Furox.), 130.7 (Cp, Ph), 128.9, 127.2 (C*o*, C*m* Ph), 122.1 (C*i* Ph), 114.3 (C3 Furox.), 60.5 (CH_2O), 33.7 (CH_2S); *m*/*z* (EI) 238 (M^+, 20%), 134 (100%).

3-(2-Hydroxyethylthio)-4-phenylfuroxan 1c. A methanolic solution of NaOMe (0.09 g, 3.64 mmol of Na in 5 cm^3 of dry MeOH) and 2-hydroxyethanethiol **6**, (0.26 cm^3, 3.64 mmol) was added dropwise to a solution of **9** (1.00 g, 3.31 mmol) in dry THF (20 cm^3). The temperature was maintained at −10 °C for 30 min, then AcOH was added, solvent was removed *in vacuo*, and the residue was recovered with water. The product was extracted with DCM, and the combined organic layers were washed with water, dried, and evaporated. Flash chromatography (eluent: DCM–EtOAc 10 : 0→9.5 : 0.5) of the residue afforded the *title product* (0.73 g, 92%) as a white solid, mp 29–32 °C (from Et_2O–PE) (Found: C, 50.7; H, 4.3; N, 11.7. $C_{10}H_{10}N_2O_3S$ requires C, 50.4; H, 4.2; N, 11.82%); ν_{max}(KBr)/cm^{-1} 3650–3150 (OH); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.94 (2H, m, Ph), 7.53 (3H, m, Ph), 3.71 (2H, q, CH_2O), 3.12 (2H, t, CH_2S), 2.67 (1H, t, OH); δ_C (50 MHz; $CDCl_3$; Me_4Si) 157.1 (C4 Furox.), 131.2 (C*p* Ph), 128.6, 127.5 (C*o*, C*m* Ph), 125.8 (C*i* Ph), 111.0 (C3 Furox.), 61.0 (CH_2O), 34.5 (CH_2S); *m*/*z* (EI) 238 (M^+, 3%), 134 (100%).

3-(2-Hydroxyethylsulfonyl)-4-phenylfurazan 2a. To a stirred solution of **1a** (1.12 g, 5.00 mmol) in TFA (3 cm^3) was added dropwise over a period of 30 min a solution of 80% aq. H_2O_2 (0.86 g, 20.00 mmol) in TFA (2 cm^3). Stirring was continued for 4 h at room temperature and then the reaction mixture was poured into ice–water and the product was extracted with DCM. The combined organic phases were washed with 1 M aq. $NaHCO_3$, dried, and evaporated. Flash chromatography (eluent: PE–EtOAc 8 : 2) of the residue oil afforded the *title product* (0.82 g, 65%) as a beige solid, mp 60.5–62 °C (from PE–EtOAc) (Found: C, 47.15; H, 3.9; N, 10.9. $C_{10}H_{10}N_2O_4S$ requires C, 47.2; H, 4.0; N, 11.0%); ν_{max}(KBr)/cm^{-1} 3590sh, (OH), 1354vs/1316vs/1296vs (three-components band, SO_2), 1150vs (SO_2); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.95 (2H, m, Ph), 7.57 (3H, m, Ph), 4.20 (2H, t, CH_2O), 3.84 (2H, t, CH_2S), 2.30 (1H, br s, OH); δ_C (50 MHz; $CDCl_3$; Me_4Si) 154.6 (C3 Furaz.), 152.3 (C4 Furaz.), 131.9 (C*p* Ph), 129.3, 129.0 (C*o*, C*m* Ph), 122.8 (C*i* Ph), 58.2, 55.9 (2 × CH_2); *m*/*z* (EI) 254 (M^+, 42%), 116 (100%).

4-(2-Hydroxyethylsulfonyl)-3-phenylfuroxan 2b. Prepared as **2a** starting from **1b** with stirring at room temperature for 3 h; the eluent for flash chromatography was PE–EtOAc 6 : 4. The *title product* (74%) was obtained as a beige solid, mp 62–63 °C (from EtOAc–PE) (Found: C, 44.3; H, 3.7; N, 10.3. $C_{10}H_{10}N_2O_5S$ requires C, 44.4; H, 3.7; N, 10.4%); ν_{max}(KBr)/cm^{-1} 3540s sh (OH), 1318vs/1298vs (two-components band, SO_2), 1146vs (SO_2); δ_H (200 MHz; DMSO-d_6; Me_4Si) 7.75 (2H, m, Ph), 7.64 (3H, m, Ph), 5.23 (1H, t, OH), 3.85 (2H, q, CH_2O), 3.68 (2H, t, SO_2CH_2); δ_C (50 MHz; DMSO-d_6; Me_4Si) 158.0 (C4 Furox.), 131.7 (C*p* Ph), 129.8, 128.9 (C*o*, C*m* Ph), 120.8 (C*i* Ph), 113.4 (C3 Furox.), 57.7, 54.6 (2 × CH_2); *m*/*z* (EI) 270 (M^+, 7%), 102 (100%).

3-(2-Hydroxyethylsulfonyl)-4-phenylfuroxan 2c. Prepared as **2a** starting from **1c**; the eluent for flash chromatography was DCM–EtOAc 10 : 0→9.5 : 0.5. The *title product* (60%) was obtained as a colourless solid, mp 80–81 °C (from Et_2O–PE) (Found: C, 44.7; H, 3.7; N, 10.4. $C_{10}H_{10}N_2O_5S$ requires C, 44.4; H, 3.7; N, 10.4%); ν_{max}(KBr)/cm^{-1} 3550s sh (OH), 1343vs, 1148vs (SO_2); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.73 (2H, m, Ph), 7.51 (3H, m, Ph), 4.05 (2H, t, CH_2O), 3.59 (2H, t, SO_2CH_2), 2.10 (1H, br s, OH); δ_C (50 MHz; $CDCl_3$; Me_4Si) 154.6 (C4 Furox.), 131.5 (C*p* Ph), 129.4, 128.5 (C*o*, C*m* Ph), 124.5 (C*i* Ph), 117.5 (C3 Furox.), 56.0, 55.5 (2 × CH_2); *m*/*z* (EI) 270 (M^+, 11%), 102 (100%).

3-(Carbamoylmethylthio)-4-phenylfurazan 3a. To a stirred solution of **5** (1.00 g, 5.24 mmol) in MeOH (15 cm^3), kept under nitrogen at room temperature, was added, first, 2-mercaptoacetamide **10**, (0.52 g, 5.76 mmol) and then 50% aq. NaOH portionwise (0.46 g, 5.76 mmol). The reaction mixture was stirred under nitrogen for 30 min, then water was added and methanol was evaporated off. The product was extracted with EtOAc. The combined organic layers were washed with brine, dried, and evaporated. Crystallisation of the residue with MeOH afford the *title product* (1.11 g, 90%) as a white solid, mp 164–165 °C (from MeOH) (Found: C, 51.1; H, 3.8; N, 17.8. $C_{10}H_9N_3O_2S$ requires C, 51.05; H, 3.9; N, 17.9%); ν_{max}(KBr)/cm^{-1} 3391s, 3189s (NH_2), 1640vs, 1620vs ($CONH_2$); δ_H (200 MHz; DMSO-d_6; Me_4Si) 7.83 (3H, m, Ph and NH), 7.66 (3H, m, Ph), 7.39 (1H: br s, NH), 4.11 (2H, s, CH_2); δ_C (50 MHz; DMSO-d_6; Me_4Si) 167.9 (CO), 152.5 (C4 Furaz.), 151.5 (C3 Furaz.), 131.6 (C*p* Ph), 129.5, 128.0 (C*o*, C*m* Ph), 124.5 (C*i* Ph), 36.8 (CH_2); *m*/*z* (EI) 235 (M^+, 100%).

4-(Carbamoylmethylthio)-3-phenylfuroxan 3b. Prepared as **3a** starting from **8** with stirring at room temperature for 15 min. The *title product* was obtained (90%) as a white solid, mp 171–172 °C (from MeOH) (Found: C, 48.0; H, 3.6; N, 16.7 $C_{10}H_9N_3O_3S$ requires C, 47.8; H, 3.6; N, 16.7%); ν_{max}(KBr)/cm^{-1} 3384s, 3177s (NH_2), 1661vs ($CONH_2$); δ_H (200 MHz; DMSO-d_6; Me_4Si) 7.83 (2H, m, Ph), 7.64 (3H, m, Ph), 7.79,

7.39 (2H, 2 br s, NH_2), 4.06 (2H, s, CH_2); δ_C (50 MHz; DMSO-d_6; Me_4Si) 167.7 (CO), 154.7 (C4 Furox.), 131.1 (C*p* Ph), 129.3, 127.6 (C*o*, C*m* Ph), 122.0 (C*i* Ph), 114.2 (C3 Furox.), 35.0 (CH_2); *m*/*z* (EI) 251 (M^+, 5%), 191 (100%).

3-(Carbamoylmethylthio)-4-phenylfuroxan 3c. Prepared as **1c** starting from **9** and **10**. The product was extracted with EtOAc; the eluent for flash chromatography was DCM–EtOAc 7 : 3. The *title product* (93%) was obtained as a white solid, mp 134–136 °C (from EtOAc) (Found: C, 48.0; H, 3.6; N, 16.8. $C_{10}H_9N_3O_3S$ requires C, 47.8; H, 3.6; N, 16.7%); ν_{max}(KBr)/cm^{-1} 3441s, 3187m (NH_2), 1688vs ($CONH_2$); δ_H (200 MHz; DMSO-d_6; Me_4Si) 7.94 (2H, m, Ph), 7.58 (3H, m, Ph), 7.86, 7.24 (2H, 2 br s, NH_2), 3.74 (2H, s, CH_2); δ_C (50 MHz; DMSO-d_6; Me_4Si) 168.9 (CO), 158.0 (C4 Furox.), 131.5 (C*p* Ph), 129.2, 128.1 (C*o*, C*m* Ph), 126.2 (C*i* Ph), 111.8 (C3 Furox.), 32.6 (CH_2); *m*/*z* (EI) 251 (M^+, 4%), 191 (100%).

3-(Carbamoylmethylsulfonyl)-4-phenylfurazan 4a. Prepared as **2a** starting from **3a** with stirring at room temperature for 24 h; the product was extracted with EtOAc. The *title product* (86%) was obtained from the organic phases as a white solid, mp 181–182 °C (from MeOH) (Found: C, 44.8; H, 3.7; N, 15.5. $C_{10}H_9N_3O_4S$ requires C, 44.9; H, 3.4; N, 15.7%); ν_{max}(KBr)/cm^{-1} 3450s, 3350s (NH_2), 1670vs ($CONH_2$), 1335vs, 1155vs (SO_2); δ_H (200 MHz; DMSO-d_6; Me_4Si) 7.88 (H, br s, NH), 7.85 (2H, m, Ph), 7.64 (4H, m, Ph and NH), 4.67 (2H, s, CH_2); δ_C (50 MHz; DMSO-d_6; Me_4Si) 161.8 (CO), 155.2 (C4 Furaz.), 153.1 (C3 Furaz.), 131.6 (C*p* Ph), 129.7, 128.9 (C*o*, C*m* Ph), 122.9 (C*i* Ph), 61.2 (CH_2); *m*/*z* (EI) 267 (M^+, 20%), 58 (100%).

4-(Carbamoylmethylsulfonyl)-3-phenylfuroxan 4b. Prepared as **2a** starting from **3b** with stirring at room temperature for 6 h; the product was extracted with EtOAc. The *title product* (83%) was obtained from the organic phases as a white solid, mp 179–180 °C (from MeOH) (Found: C, 42.6; H, 3.25; N, 14.7. $C_{10}H_9N_3O_5S$ requires C, 42.4; H, 3.2; N, 14.8%); ν_{max}(KBr)/cm^{-1} 3461s, 3355s (NH_2), 1671vs ($CONH_2$), 1341vs, 1156vs (SO_2); δ_H (200 MHz; DMSO-d_6; Me_4Si) 7.91 (1H, br s, NH), 7.72 (3H, m, Ph and NH), 7.61 (3H, m, Ph), 4.55 (2H, s, CH_2); δ_C (50 MHz; DMSO-d_6; Me_4Si) 161.6 (CO), 157.5 (C4 Furox.), 131.4 (C*p* Ph), 129.8, 128.8 (C*o*, C*m* Ph), 120.7 (C*i* Ph), 113.5 (C3 Furox.), 60.5 (CH_2); *m*/*z* (EI) 283 (M^+, 2%), 117 (100%).

3-(Carbamoylmethylsulfonyl)-4-phenylfuroxan 4c. Prepared as **2a** starting from **3c** with stirring at room temperature for 24 h; the product was extracted with EtOAc. The *title product* (90%) was obtained as a white solid from the organic phases, mp 188–189 °C (from MeOH) (Found: C, 42.5; H, 3.25; N, 14.7. $C_{10}H_9N_3O_5S$ requires C, 42.4; H, 3.2; N, 14.8%); ν_{max}(KBr)/cm^{-1} 3441s, 3320s (NH_2), 1682vs ($CONH_2$), 1387s/1370s (two-components band, SO_2), 1148s (SO_2); δ_H (200 MHz; DMSO-d_6; Me_4Si) 8.00 (1H, s, NH), 7.79–7.53 (6H, m, Ph and NH), 4.53 (2H, s, CH_2); δ_C (50 MHz; DMSO-d_6; Me_4Si) 162.2 (CO), 155.8 (C4 Furox.), 131.6 (C*p* Ph), 129.8, 128.5 (C*o*, C*m* Ph), 124.9 (C*i* Ph), 117.2 (C3 Furox.), 57.9 (CH_2); *m*/*z* (EI) 283 (M^+, 0.4%), 117 (100%).

4-(Methoxycarbonylmethylthio)-3-phenylfuroxan 27. Prepared as **3a** starting from **8** and methyl 2-mercaptoacetate with stirring at room temperature for 15 min. From the concentrated reaction mixture a *white solid* was precipitated and was filtered off and dried (70%), mp 60–60.5 °C (from MeOH) (Found: C, 49.6; H, 3.75; N, 10.5. $C_{11}H_{10}N_2O_4S$ requires C, 49.6; H, 3.8; N, 10.5%); ν_{max}(KBr)/cm^{-1} 1738vs (CO); δ_H (200 MHz; DMSO-d_6; Me_4Si) 7.81 (2H, m, Ph), 7.64 (3H, m, Ph), 4.26 (2H, s, CH_2), 3.71 (3H, s, CH_3); δ_C (50 MHz; DMSO-d_6; Me_4Si) 168.1 (CO), 154.1 (C4 Furox.), 131.2 (C*p* Ph), 129.4, 127.6 (C*o*, C*m* Ph), 121.8 (C*i* Ph), 114.2 (C3 Furox.), 52.7 (CH_3), 32.7 (CH_2); *m*/*z* (EI) 266 (M^+, 18%), 206 (100%).

2-(3-Phenylfuroxan-4-ylthio)acetic acid 24. A solution of **27** (0.50 g, 1.88 mmol) in 1,4-dioxane (10 cm^3) and 20% aq. HCl (10 cm^3) was stirred at 60 °C for 4 h. Solvent removal afforded a residue which was dissolved in MeOH. Addition of water precipitated a white solid, which was filtered off and dried to give the *title compound* (0.38 g, 81%), mp 130–133 °C (from MeOH–water) (Found: C, 47.8; H, 3.2; N, 11.1. $C_{10}H_8N_2O_4S$ requires C, 47.6; H, 3.2; N, 11.1%); ν_{max}(KBr)/cm^{-1} 3300–2300, 1713vs (COOH); δ_H (200 MHz; DMSO-d_6; Me_4Si) 9.91 (1H, br s, OH in $CDCl_3$), 7.83 (2H, m, Ph), 7.66 (3H, m, Ph), 4.18 (2H, s, CH_2); δ_C (50 MHz; DMSO-d_6; Me_4Si) 168.8 (CO), 154.3 (C4 Furox.), 131.2 (C*p* Ph), 129.4, 127.6 (C*o*, C*m* Ph), 121.9 (C*i* Ph), 114.2 (C3 Furox.), 33.4 (CH_2); *m*/*z* (EI) 252 (M^+, 3%), 44 (100%).

Smiles rearrangements

Rearrangement of 1a. A solution of **1a** (0.22 g, 1.00 mmol) in EtOH (5 cm^3) containing 50% aq. NaOH (1.20 mmol) was boiled (5 h). When it had cooled, thiirane **13** separated out as a white polymer and was filtered off (0.06 g, mp 162–166 °C, lit.,[8] 165–175 °C). The solution was diluted with water, washed with DCM, acidified with 1 M HCl, and extracted with DCM. Solvent removal from the dried organic phases afforded 3-hydroxy-4-phenylfurazan **12** (0.12 g, 74%), mp 176–177 °C (decomp.) (lit.,[15] 177.5–178 °C); δ_H (200 MHz; DMSO-d_6; Me_4Si) 13.35 (1H, br s, OH) 7.99 (2H, m, Ph), 7.56 (3H, m, Ph); δ_C (50 MHz; DMSO-d_6; Me_4Si) 162.3 (C3 Furaz.), 145.6 (C4 Furaz.), 130.6 (C*p* Ph), 129.3, 127.2 (C*o*, C*m* Ph), 125.3 (C*i* Ph).

Rearrangement of 2a. To a solution of **2a** (0.34 g, 1.30 mmol) in acetone (10 cm^3) was added 50% aq. NaOH (0.27 g, 3.25 mmol) dropwise. Immediately, the unstable sodium sulfinate **14** precipitated as a white solid. After 10 min the rearrangement was complete and so **14** was characterised as the methyl sulfone **15**. First, MeOH (5 cm^3) and then methyl iodide (1.66 cm^3, 26 mmol) were added. After 4 h the solvent was evaporated off, the residue was recovered with water, and the product was extracted with diethyl ether. The combined organic phases were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (eluent: PE–EtOAc 7:3). The obtained product (0.25 g, 70%) was identified as the 3-[2-(*methylsulfonyl*)*ethoxy*]-4-*phenylfurazan* **15**, mp 93–94 °C (from MeOH) (Found: C, 49.4; H, 4.5; N, 10.5. $C_{11}H_{12}N_2O_4S$ requires C, 49.25; H, 4.5; N, 10.4%); ν_{max}(KBr)/cm^{-1} 1302vs/1285vs (two-components band, SO_2), 1130vs (SO_2); δ_H (200 MHz; DMSO-d_6; Me_4Si) 7.99 (2H, m, Ph), 7.58 (3H, m, Ph), 4.84 (2H, t, CH_2O), 3.83 (2H, t, SO_2CH_2), 3.11 (3H, s, CH_3); δ_C (50 MHz; DMSO-d_6; Me_4Si) 162.9 (C3 Furaz.), 145.4 (C4 Furaz.), 131.3 (C*p* Ph), 129.3, 127.5 (C*o*, C*m* Ph), 124.2 (C*i* Ph), 66.3 (CH_2O), 52.7 (SO_2CH_2), 41.7 (CH_3); *m*/*z* (EI) 268 (M^+, 66%), 79 (100%).

Rearrangement of 3a. A solution of **3a** (0.40 g, 1.70 mmol) in EtOH (10 cm^3) containing 50% aq. NaOH (0.27g, 3.40 mmol) was boiled (2 h). When it had cooled, water was added and EtOH was evaporated off. The remaining aqueous solution was washed with diethyl ether, acidified with 6 M HCl, and then the product was extracted with diethyl ether. The combined organic phases were washed with brine, dried, and evaporated. The white solid obtained was not the expected rearrangement product but was identified as *2-(4-phenylfurazan-3-ylthio)acetic acid* **16** (0.24 g, 60%), mp 119–120 °C (from $CHCl_3$–PE) (Found: C, 50.7; H, 3.4; N, 11.7. $C_{10}H_8N_2O_3S$ requires C, 50.8; H, 3.4; N, 11.85%); ν_{max}(KBr)/cm^{-1} 3700–2375, 1725vs (COOH); δ_H (200 MHz; DMSO-d_6; Me_4Si) 11.37 (1H, br s, OH in $CDCl_3$), 7.83 (2H, m, Ph), 7.66 (3H, m, Ph), 4.22 (2H, s, CH_2); δ_C (50 MHz; DMSO-d_6; Me_4Si) 168.6 (CO), 152.4, 151.2 (C3, C4 Furaz.), 131.4 (C*p* Ph), 129.6, 128.0 (C*o*, C*m* Ph), 124.4 (C*i* Ph), 35.5 (CH_2); *m*/*z* (EI) 236 (M^+, 52%), 116 (100%).

Rearrangement of 4a. A solution of **4a** (0.27 g, 1.00 mmol) in acetone (10 cm^3) containing 50% aq. NaOH (0.20 g, 2.50 mmol) was stirred at 55 °C for 6 h. Then the reaction mixture was acidified with 1 M HCl and the product was extracted with EtOAc. The combined organic phases were washed with brine, dried, and evaporated. Flash chromatography (eluent: DCM–EtOAc 9.5 : 0.5) of the residue afforded a white solid identified as *3-acetylamino-4-phenylfurazan* **18**, (0.15 g, 75%), mp 181–181.5 °C (from EtOH) (lit.,[16] 181–182 °C); δ_H (200 MHz; DMSO-d_6; Me_4Si) 10.75 (1H, br s, NH), 7.77 (2H, m, Ph), 7.57 (3H, m, Ph), 2.13 (3H, s, CH_3); δ_C (50 MHz; DMSO-d_6; Me_4Si) 169.7 (CO), 150.9, 149.5 (C3, C4 Furaz.), 130.8 (C*p* Ph), 129.2, 127.6 (C*o*, C*m* Ph), 125.0 (C*i* Ph), 22.9 (CH_3).

Rearrangement of 1b. A solution of **1b** (0.24 g, 1.00 mmol) in EtOH (10 cm^3) containing 50% aq. NaOH (3.75 mmol) was stirred at room temperature for 20 h. Then EtOH was evaporated off and the residue was recovered with water. The white solid was filtered off (thiirane **13**, 0.04 g) and the filtrate was acidified with 1 M HCl. Filtration of the white precipitate afforded the *4-hydroxy-3-phenylfuroxan* **20** (0.11 g, 61%), mp 128 °C (decomp.) lit.,[17] 133 °C); δ_H (200 MHz; CD_3OD; Me_4Si) 8.22 (2H, m, Ph), 7.55 (3H, m, Ph), 5.03 (exchangeable proton); δ_C (50 MHz; CD_3OD; Me_4Si) 163.4 (C4 Furox.), 131.6 (C*p* Ph), 130.0, 127.6 (C*o*, C*m* Ph), 124.7 (C*i* Ph), 109.2 (C3 Furox.).

Rearrangement of 2b. To a solution of **2b** (0.54 g, 2.00 mmol) in acetone (10 cm^3) was added 50% aq. NaOH (0.40 g, 5.0 mmol) dropwise. Immediately, the unstable sodium sulfinate **21** precipitated as a white solid. After 10 min the rearrangement was complete and so **21** was characterised both as the sodium sulfonate and as the methyl sulfone. In the case of the oxidation, the precipitate **21** was filtered, washed with acetone, and dissolved in water (10 cm^3). To the solution was added 30% aq. H_2O_2 (0.91 g, 8.00 mmol) and the reaction mixture was stirred at room temperature for 1 h. Solvent removal afforded sodium *2-(3-phenylfuroxan-4-yloxy)ethanesulfonate* **23** (0.57, 92%), mp >233 °C (decomp.) (from Pr^iOH) (Found: C, 38.05; H, 3.2; N, 8.65. $C_{10}H_9N_2NaO_6S{\cdot}0.5H_2O$ requires C, 37.8; H, 3.2; N, 8.8%); ν_{max}(KBr)/cm^{-1} 1221vs/1188vs/1168 (three-components band, SO_3^-), 1065 (SO_3^-); δ_H (200 MHz; D_2O; Me_4Si) 7.95 (2H, m, Ph), 7.45 (3H, m, Ph), 4.68 (2H, t, CH_2O), 3.38 (2H, t, $CH_2SO_3^-$); δ_C (50 MHz; D_2O; Me_4Si) 159.5 (C4 Furox.), 128.5 (C*p* Ph), 126.3, 123.9 (C*o*, C*m* Ph), 118.7 (C*i* Ph), 107.3 (C3 Furox.), 63.2 (CH_2O), 46.7 ($CH_2SO_3^-$).

In the case of methylation, to the reaction mixture, first MeOH (10 cm^3) and then methyl iodide (0.38 cm^3, 6 mmol) were added. After 4 h the solvent was evaporated off, the residue was recovered with water, and the product was extracted with EtOAc. The combined organic phases were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (eluent: PE–EtOAc 5 : 5). The obtained product (0.23 g, 40%) was identified as the *4-[2-(methylsulfonyl)ethoxy]-3-phenylfuroxan* **22**, mp 120–121 °C (from MeOH) (Found: C, 46.5; H, 4.3; N, 9.9. $C_{11}H_{12}N_2O_5S$ requires C, 46.5; H, 4.25; N, 9.85%); ν_{max}(KBr)/cm^{-1} 1320vs/1302vs/1283vs (three-components band, SO_2), 1132vs (SO_2); δ_H (200 MHz; DMSO-d_6; Me_4Si) 8.03 (2H, m, Ph), 7.60 (3H, m, Ph), 4.67 (2H, t, CH_2O), 3.84 (2H, t, CH_2SO_2), 3.10 (3H, s, CH_3); δ_C (50 MHz; DMSO-d_6; Me_4Si) 161.6 (C4 Furox.), 131.0 (C*p* Ph), 129.1, 126.5 (C*o*, C*m* Ph), 121.7 (C*i* Ph), 107.7 (C3 Furox.), 64.4 (CH_2O), 52.6 (CH_2SO_2), 41.7 (CH_3); *m*/*z* (EI) 284 (M^+, 64%), 224 (100%).

Rearrangement of 3b. A solution of **3b** (0.50 g, 2.00 mmol) in EtOH (10 cm^3) containing 50% aq. NaOH (0.40 g, 5.00 mmol) was heated at 50 °C for 5 h. The solution was allowed to reach room temperature, diluted with water, and acidified with 3 M HCl. EtOH was evaporated off and the remaining solution was basified with 1 M NaOH, washed with DCM, acidified with 3 M HCl, and cooled. The precipitated solid was filtered off and dried under vacuum. It was identified not as the rearrangement product but as crude *2-(3-phenylfuroxan-4-ylthio)acetic acid* **24** (0.13 g, 25%) previously characterised.

Rearrangement of 4b. A solution of **4b** (0.28 g, 1.00 mmol) in acetone (10 cm^3) containing 50% aq. NaOH (0.20 g, 2.50 mmol) was stirred at 55 °C for 5 h. Then the reaction mixture was acidified with 1 M HCl and the product was extracted with EtOAc. The combined organic phases were washed with brine, dried, and evaporated. Flash chromatography (eluent: PE–EtOAc 8 : 2→5 : 5) of the residue afforded a white solid identified as *4-acetylamino-3-phenylfuroxan* **26** 0.10 g, 40%), mp 157 °C (from EtOAc–PE) (Found: C, 55.0; H, 4.15; N, 19.2. $C_{10}H_9N_3O_3$ requires C, 54.8; H, 4.1; N, 19.2%); ν_{max}(KBr)/cm^{-1} 3256s, 3227s (NH), 1690vs (CONH); δ_H (200 MHz; DMSO-d_6; Me_4Si) 10.90 (1H, br s, NH), 7.77 (2H, m, Ph), 7.57 (3H, m, Ph), 2.10 (3H, s, CH_3); δ_C (50 MHz; DMSO-d_6; Me_4Si) 169.8 (CO), 151.0 (C4 Furox.), 130.7 (C*p* Ph), 129.0, 127.2 (C*o*, C*m* Ph), 122.5 (C*i* Ph), 112.0 (C3 Furox.), 22.8 (CH_3); *m*/*z* (EI) 219 (M^+, 15%), 117 (100%).

Rearrangement of 3c. A solution of **3c** (0.50 g, 2.00 mmol) in EtOH (10 cm^3) containing 50% aq. NaOH (0.40 g, 5.00 mmol) was stirred at room temperature for 5 min. Then the solution was neutralised with 3 M HCl and the EtOH was evaporated off. The remaining aqueous solution was acidified with 3 M HCl and cooled. The white solid precipitate was filtered off and dried under vacuum. It was identified as *3-mercapto-4-phenylfurazan* **32** (0.26 g, 74%). Crystallisation solvent was MeOH–3 M HCl; mp starts to soften and decompose at 52 °C; at 87 °C the product was completely decomposed (Found: C, 54.2; H, 3.45; N, 15.5. $C_8H_6N_2OS$ requires C, 53.9; H, 3.4; N, 15.7%); ν_{max}(KBr)/cm^{-1} 2485s (SH); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.81 (2H, m, Ph), 7.56 (3H, m, Ph), 4.23 (1H, s, SH); δ_C (50 MHz; $CDCl_3$; Me_4Si) 153.1 (C4 Furaz.), 145.9 (C3 Furaz.), 130.8 (C*p* Ph), 129.2, 127.9 (C*o*, C*m* Ph), 124.7 (C*i* Ph); *m*/*z* (EI) 178 (M^+, 100%).

Rearrangement of 4c. A solution of **4c** (0.28 g, 1.00 mmol) in acetone (10 cm^3) containing 50% aq. NaOH (0.20 g, 2.50 mmol) was stirred at room temperature for 4 h. Then the solution was acidified with 1 M HCl and the acetone was evaporated off. The product was extracted from the remaing aqueous solution with EtOAc. The combined organic phases were washed with brine, dried, and evaporated. Flash chromatography (eluent: hexane–EtOAc 8 : 2) of the residue afforded a white solid identified as *(Z)-2-hydroxyimino-2-phenylacetonitrile* **35** (0.11 g, 78%), mp 128–129 °C (from H_2O) (lit.,[18] 130 °C).

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