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Acyclic Oxyiminium Ions. Mannich Reactions and Addition of Grignard Reagents

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Abstract—Acyclic oxyiminium ion generation from secondary hydroxylamines (**4a,b** and **6a,b**) and formaldehyde in the presence of acetic acid is reported. Trapping these electrophiles with 2-methyl furan, pyrrole or indole affords a series of novel *O*-benzyl tertiary hydroxylamines in good to excellent yield. Benzotriazole mediated synthetic methodology has also been successfully developed to generate oxyiminium ions which react with Grignard reagents, to give novel *O*-benzyl tertiary hydroxylamines.

Introduction

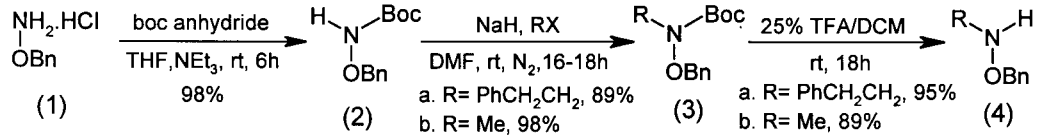
Tertiary *O*-alkyl hydroxylamines exhibit a variety of biological properties, often similar to that of their analogous tertiary amines. For example, recent studies of the biological activity of tertiary *O*-alkyl hydroxylamines report antibacterial activity,[1] anticonvulsant activity,[2] inhibition of human plasma renin,[3] promotion of chlorophyll retention in rice leaves/growth of soybean hypocotyl sections[4] and insecticidal activity.[5] As part of our ongoing interest in the sparsely studied chemistry of oxyiminium ions (or oxoiminium ions) we have been developing effective routes for the preparation of *O*-benzyl tertiary hydroxylamines with the view to the coupling this methodology with our hydroxylamine linker for the solid-phase synthesis of tertiary amines.[6] Whilst there have been examples in the literature reporting the Mannich reaction of oxyiminium ions (generated in situ from secondary hydroxylamines and an appropriate carbonyl compound) with acetophenone,[7] *N*-methyl piperazine,[8] 1,2,4,5-tetrahydro-3,2-benzoxazepine[8] and cyanide,[9] to our knowledge there are no examples in the literature using aromatic heterocycles as the nucleophilic component.

We now report Mannich reactions of secondary hydroxylamine (**4a,b** and **6a,b**), formaldehyde, and 5-membered heterocycles to give the corresponding Mannich bases in moderate to excellent yield. We also report the utilisation of benzotriazole for the generation of oxyiminium ions and their subsequent reactions with a range of Grignard reagents to give novel tertiary *O*-benzyl hydroxylamine derivatives.

Results and Discussion

Thus, *O*-benzyl hydroxylamine hydrochloride (**1**) was reacted with Boc anhydride (Scheme 1)[10] to give Boc protected *O*-benzyl hydroxylamine hydrochloride (**2**) in excellent yield. This was then alkylated with alkyl halides[11] to give carbamates (**3a** and **b**) in excellent yields. Deprotection with TFA/DCM proceeded smoothly to give secondary *O*-benzyl hydroxylamines (**4a** and **b**) in excellent yield. Alternatively, secondary *O*-benzyl hydroxylamines were prepared via the reduction of oxime ethers (Scheme 2).[12,13]

Using secondary hydroxylamine (**4a**), formaldehyde and a range of nucleophiles a series of *O*-benzyl Mannich bases



Scheme 1.

Keywords: acyclic oxyiminium ion; Mannich reaction; Grignard reagent.
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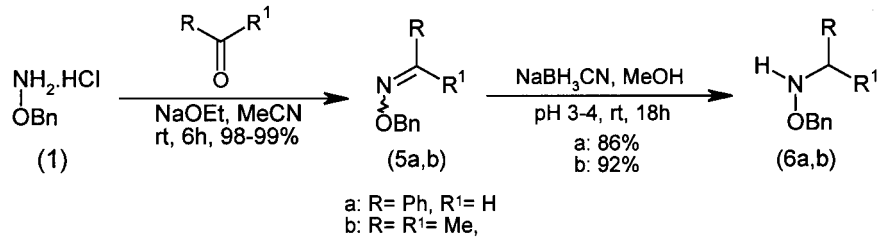
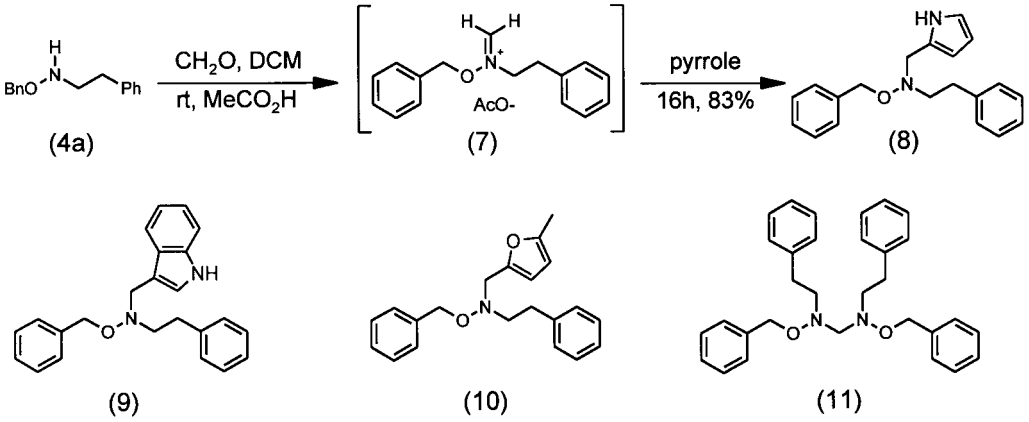


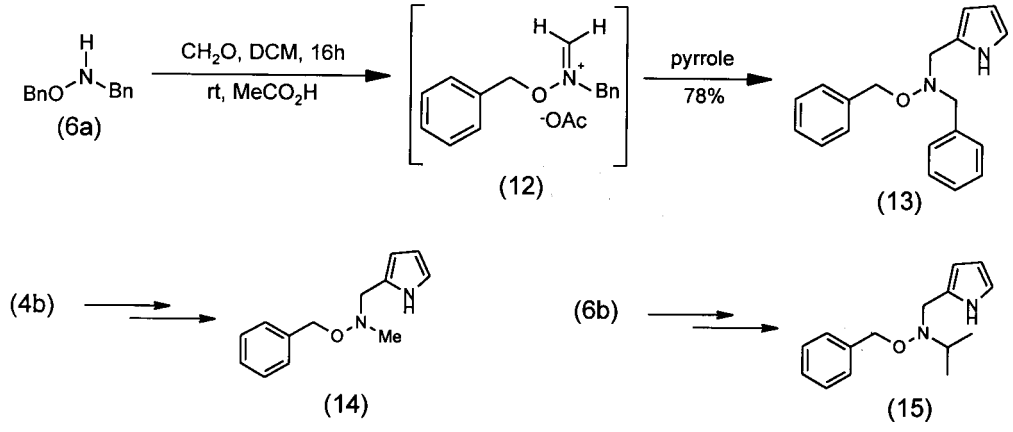
Scheme 2.

were successfully synthesised (Scheme 3). The nucleophiles chosen to map out the reaction's scope were those that would lead to Mannich bases of pharmacological interest, e.g. 2-methylfuran, pyrrole, indole, phenol, 1,3-dimethoxy benzene, thiophene and 2-methoxythiophene.[14] Initial reactions gave predominately the aminal (**11**), an unwanted side product,[15] by reaction of the oxyiminium ion intermediate (**7**) with unreacted (**4a**), together with a very poor yield of the Mannich base (<10%). However, with optimisation (excess nucleophile and acetic acid) it was possible to minimise the formation of (**11**) (<15%) and obtain the *O*-benzyl Mannich bases in good to excellent yield.

Surprisingly, the use of excess formaldehyde actually promoted formation of (**11**). A typical reaction of (**4a**) (1 equiv.), formaldehyde (1 equiv.) (37% soln, in methanol), pyrrole (5 equiv.) and acetic acid (10 equiv.) in DCM at r.t. proceeded smoothly to give the expected Mannich base (**8**) in excellent yield via oxyiminium ion (**7**). The reaction could be repeated with indole under analogous conditions using methanol as the solvent to give (**9**) (82%). The use of DCM as solvent for this particular nucleophile resulted in greater formation of aminal (**11**) than with pyrrole. Moreover, using 2-methylfuran as nucleophile required more forcing conditions. Conditions analogous to pyrrole, resulted in exclusive formation of aminal (**11**). However, boiling (**4a**) (1 equiv.), paraformaldehyde (1 equiv.), 2-methyl furan (5 equiv.) and acetic acid (10 equiv.) in DCE under reflux proceeded smoothly to give (**10**) (72%). Unfortunately, the use of phenol, 1,3-dimethoxybenzene, thiophene and 2-methoxythiophene, under a variety of conditions resulted in virtually exclusive formation of (**11**) showing that these nucleophiles were less reactive.

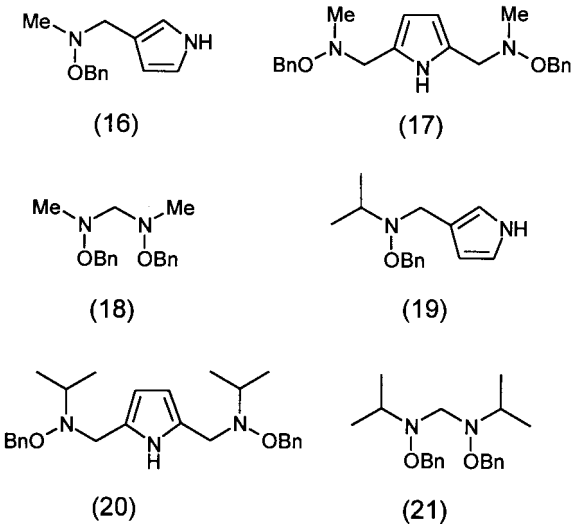


Scheme 3.



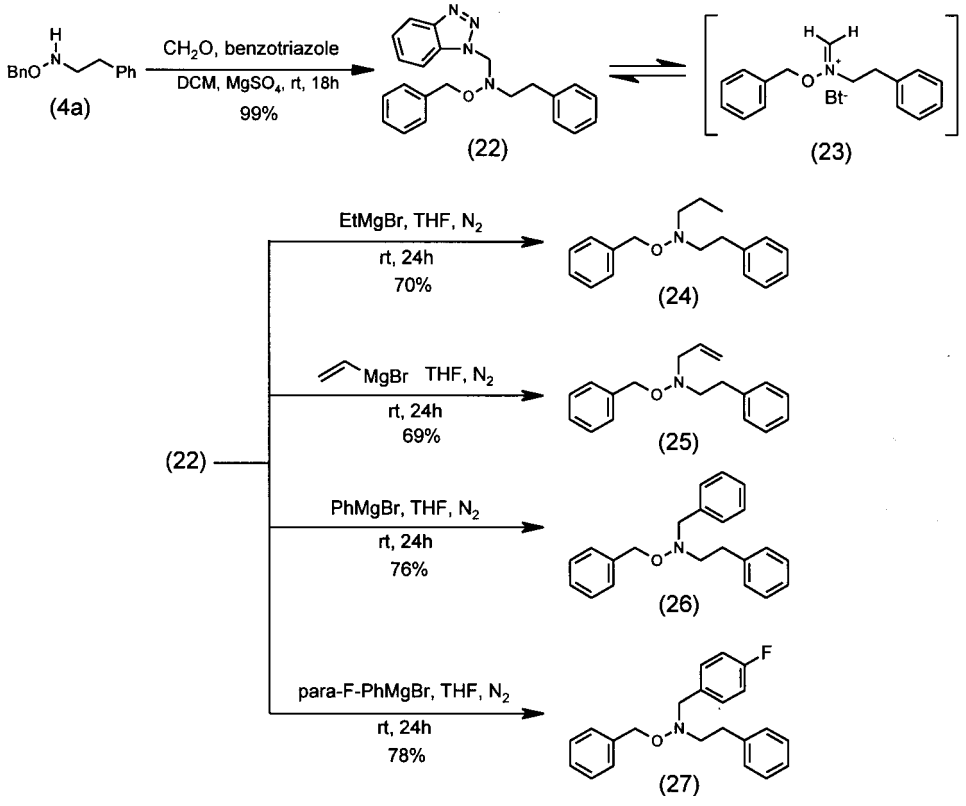
Scheme 4.

The scope of the secondary hydroxylamine component in the reaction was then explored with several analogues of Mannich bases using pyrrole as the common nucleophile (Scheme 4). Thus reaction of (**6a**), formaldehyde (37% soln, in methanol), pyrrole and acetic acid in DCM at r.t. proceeded smoothly to give (**13**) in good yield via oxyiminium ion (**12**). However, using aliphatic secondary hydroxylamines (**4b**) and (**6b**) under analogous conditions resulted in large amounts of the secondary hydroxylamine being left unreacted even after two days, suggesting that oxyiminium ion formation in this low polarity solvent mixture was slow. Using a more polar solvent (methanol) at −10°C, complete reaction of the starting material could be achieved affording (**14**) (69%) and (**15**) (55%), respectively. ^{1}H NMR monitoring of reactions at ambient temperature showed that other compounds were being formed such as the isomers (**16**) and (**19**) and the dimers (**17**) and (**20**), illustrating the high reactivity of the oxyiminium ion intermediates. Interestingly, the ^{1}H NMR spectra showed no sign of the dimers (**18**) or (**21**). It was found that repeating the reaction at −10°C minimised the formation of the side products.

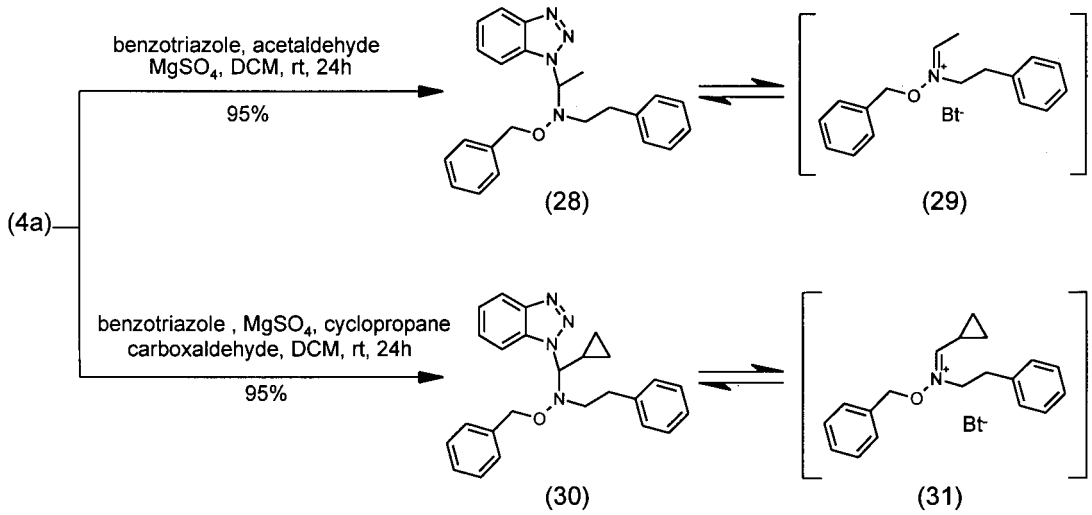


The scope of the carbonyl component in the reaction was explored by substituting formaldehyde by acetaldehyde, acetone or benzaldehyde. Unfortunately, reacting secondary hydroxylamine (**4a**) and pyrrole with any of these alternative carbonyl compounds, under a variety of conditions was unsuccessful. The ^{1}H NMR spectra of the reaction mixtures showed the presence of large quantities of starting material along with small amounts of unidentified products.

Benzotriazole has been used in place of a halogen substituent in many reactions. A recent review[16] indicates α-benzotriazolylalkyl amines and α-benzotriazolylalkyl ethers are of considerable synthetic utility in aminoalkylation (amines, hydroxylamines, hydrazines, amides, thioamides and sulphonamides) and alkoxyalkylation reactions (ethers and esters) when used in conjunction with nucleophiles such as Grignard reagents and lithium enolates. In addition, these benzotriazole derivatives are frequently more stable and less toxic than their chloro or bromo analogues. Benzotriazole has not previously been utilised for oxyiminium ion generation from *O*-alkyl hydroxylamines (only *O*-unsubstituted hydroxylamine) and offers methodology for increased *N*-alkyl diversity for the development of a hydroxylamine linker for the synthesis



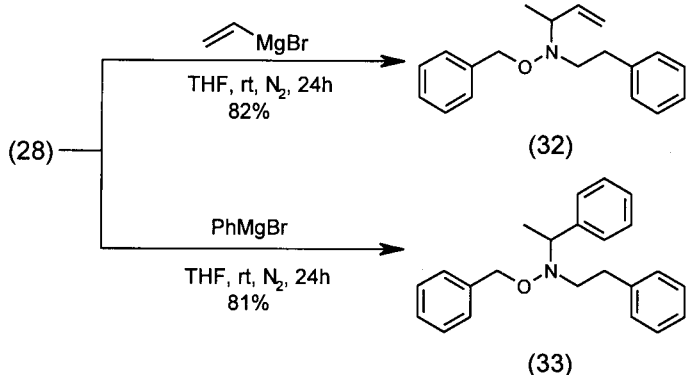
Scheme 5.



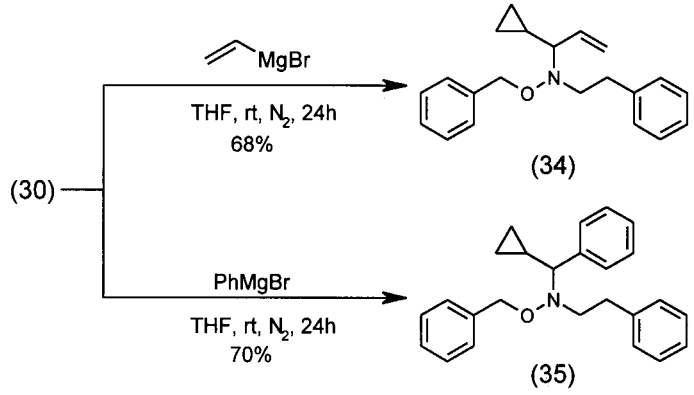
Scheme 6.

of *N*-methyl tertiary amines.[6] Additionally, benzotriazole chemistry offers the potential for mild conditions and solvents viable for chemistry on polymer supports e.g. DCM, THF.

Thus, vigorous stirring of secondary *O*-benzyl hydroxylamine (**4a**) (1 equiv.), benzotriazole (1 equiv.) and formaldehyde (37% in methanol) (1 equiv.) in DCM gave the α-benzotriazolylalkyl *O*-benzyl hydroxylamine (**22**) in near quantitative yield, although the ^{1}H NMR spectra of the reaction mixture showed a small quantity (<5%) of aminal (**11**) (Scheme 5). The water by-product can be removed from the reaction by adding magnesium sulphate just before work up and isolation of (**22**). In solution, (**22**) enters into equilibrium with the oxyiminium ion (**23**) which can be trapped with a range Grignard reagents in dry THF to give the corresponding tertiary hydroxylamines (**24**–**27**) in 69–78% overall yield from (**4a**). The use of excess Grignard reagent and long reaction times (24 h) were required to push the reactions to completion.



Scheme 7.



Scheme 8.

The scope of the carbonyl component of the reaction was then explored by substituting formaldehyde with acetaldehyde, cyclopropane carboxaldehyde, benzaldehyde, furfuraldehyde, cyclohexane carboxaldehyde, acetone and cyclohexanone.

The α-benzotriazolylalkyl *O*-benzyl hydroxylamines (**28**) and (**30**) were successfully prepared in excellent yield in DCM under analogous conditions (Scheme 6), but analogous reactions using benzaldehyde, furfuraldehyde, cyclohexane carboxaldehyde and cyclohexanone were less successful, giving mixtures of the desired compound (60–80%) and starting material (20–40%) even when using molecular sieves to remove water. The reaction with acetone gave exclusively starting material.

Reaction of benzotrialzole derivative (**28**) (Scheme 7) or (**30**) (Scheme 8) with the vinyl and phenyl magnesium bromides (3 equiv.) in dry THF gave the novel *O*-benzyl tertiary hydroxylamines (**32**–**35**) in good yield, via trapping of the corresponding oxyiminium ions (**29**) and (**31**) (Scheme 6).

Experimental

Melting points were obtained on a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were recorded on a PU 9706 infrared spectrometer using potassium bromide discs. Microanalyses were obtained using a Carlo Erba Elemental Analyser MOD 1106. Mass spectral data were obtained using a VG-AutoSpec spectrometer operating at 70 eV using perfluorokerosine for accurate molecular weights. Nuclear magnetic resonance spectra were recorded at 250 or 300 MHz using Bruker AC 250 or General Electric QE300. Column chromatography employed Silica Gel 60 (Merck 9385). Flash chromatographic columns were run using air pressure to maintain a column flow rate of the solvent of ca. 5 cm^3 min^{-1}. The term ether (Et_2O) refers to diethyl ether, and petroleum ether refers to the fraction with boiling point 40–60°C.

Synthesis of the *O*-benzyl secondary hydroxylamines (4a,b) and (6a,b)

Boc protected *O*-benzyl hydroxylamine (2).[10] Prepared (98%) as described in the literature as colourless crystals, mp 42–45°C, (lit. 45–46°C). δ: 7.41–7.32 (m, 5H, ArH), 7.24 (br s, 1H, NH), 4.83 (s, 2H, OCH_2) and 1.48 (s, 9H, 3×Me).

General procedure for synthesis of carbamates (3a) and (3b). Sodium hydride (1.1 equiv.) was added to a stirred solution of (**2**) (1 equiv.) in anhydrous DMF and the resulting solution stirred at r.t. for 30 min. The appropriate alkyl halide (1.1 equiv.) was added and the reaction mixture stirred at r.t. for a further 16 h, then poured into water and the product extracted with hexane. The combined extracts were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure.

Carbamate (3a). The pale yellow oily residue was purified by flash chromatography, eluting with 10:1 v/v petroleum ether–diethyl ether to give the product (4.98 g, 89%), as a pale yellow oil. Found: C, 73.3; H, 7.5; N, 4.35. $C_{20}H_{25}NO_3$ requires C, 73.35; H, 7.7; N, 4.3%. *m/z* (%) (FAB): 328 (M+1, 14), 272 (70), 228 (17), 210 (18), 182 (7) and 91 (100). ν_{max} 2980, 1700, 1360, 1150, 740 and 690 cm^{-1}. δ: 7.42–7.17 (m, 10H, ArH), 4.82 (s, 2H, OCH_2), 3.62 (t, 2H, *J*=7.3 Hz, NCH_2CH_2Ph), 2.88 (t, 2H, *J*=7.3 Hz, NCH_2CH_2Ph) and 1.45 (s, 9H, 3×Me).

Carbamate (3b).[11] No further purification was required. The product (98%), a pale yellow oil, was used directly for the next step. δ: 7.44–7.32 (m, 5H, Ar H), 4.85 (s, 2H, OCH_2), 3.07 (s, 3H, NMe) and 1.50 (s, 9H, 3×Me).

General procedure for Boc deprotection. The appropriate carbamate was added to a stirred solution of 3: 1 v/v DCM-TFA (2.5 ml $mmol^{-1}$ of carbamate). The reaction mixture was stirred at r.t. for 20 h, made alkaline with 1 M sodium hydrogen carbonate solution and extracted with DCM. The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to give the product.

***O*-Benzyl-*N*-phenethyl-hydroxylamine (4a).** No further purification was necessary. The product (94%) was obtained as a pale yellow oil. Found: C, 79.0; H, 7.45; N, 6.3, $C_{15}H_{17}NO$ requires C, 79.25; H, 7.55; N, 6.15%. *m/z* (%): 228 (M+1, 5), 182 (23), 136 (65), 104 (11), 91 (100) and 77 (26). ν_{max} 3260, 3020, 2900, 1490, 1450, 1360, 1010, 740 and 690 cm^{-1}. δ: 7.36–7.17 (m, 10H, ArH), 5.55 (br s, 1H, NH), 4.72 (s, 2H, OCH_2), 3.17 (t, 2H, *J*= 7.0 Hz, NCH_2CH_2Ph) and 2.84 (t, 2H, *J*=7.0 Hz, NCH_2CH_2Ph).

***O*-Benzyl-*N*-methyl-hydroxylamine (4b).**[11] The pale yellow oily residue was purified by flash chromatography, eluting with 1:1 v/v petroleum ether–diethyl ether to give the product (89%) as a pale yellow oil. δ: 7.39–7.20 (m, 5H, ArH), 5.55 (br s, 1H, NH), 4.67 (s, 2H, OCH_2) and 2.71 (s, 3H, Me).

Oxime ethers (5a) and (5b).[12] Prepared as described in the literature.

(5a). The *E*-isomer (98%) was obtained as a colourless oil. δ: 7.40–7.20 (m, 11H, 10×ArH and imine H) and 5.20 (s, 2H, OCH_2).

(5b). The product (99%) was obtained as a colourless oil. δ: 7.38–7.25 (m, 5H, ArH), 5.05 (s, 2H, OCH_2) and 1.87 (s, 6H, 2×Me).

General procedure for reduction of *O*-benzyl oxime ethers (5a,b).[13] Sodium cyanoborohydride (5 equiv.) was added to a stirred solution of the appropriate oxime ether (1 equiv.) in methanol. Two drops of methyl orange indicator were added followed by dropwise addition of concentrated hydrochloric acid, until the solution remained pink for at least half an hour. The reaction mixture was stirred at r.t. for 16 h and the solvent removed. The residue was taken up in DCM and washed until alkaline with 1 M potassium hydroxide solution and extracted with DCM. The

combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed to give the product.

***N*,*O*-Dibenzyl-hydroxylamine (6a).**[13] Purification by column chromatography, eluting with diethyl ether afforded the product (86%) as a pale yellow oil. δ: 7.35–7.18 (m, 10H, ArH), 5.67 (br s, 1H, NH), 4.61 (s, 2H, OCH_2) and 3.98 (s, 2H, NCH_2).

***O*-Benzyl-*N*-isopropyl-hydroxylamine (6b).** Purification by column chromatography, eluting with diethyl ether afforded the product (92%) as a pale yellow oil. Found: C, 72.9; H, 9.15; N, 8.5. $C_{10}H_{15}NO$ requires C, 72.7; H, 9.15; N, 8.5 %. *m/z* (%): 165 (M+1, 2), 108 (2), 105 (4), 98 (2), 92 (9), 91 (100) and 54 (11). ν_{max} 3250, 2960, 1450, 1360, 1050, 740 and 700 cm^{-1}. δ: 7.40–7.23 (m, 5H, ArH), 5.36 (br s, 1H, NH), 4.71 (s, 2H, OCH_2), 3.19 (sept, 1H, N*CH*Me_2), and 1.08 (d, 6H, *J*=6.3 Hz, 2×Me).

Synthesis of *O*-benzyl tertiary hydroxylamines (8–10, 13, 14 and 15)

***O*-Benzyl-*N*-phenethyl-*N*-(pyrrol-2-ylmethyl)-hydroxylamine (8).** Formaldehyde (37% solution methanol, 36 mg, 0.44 mmol) was added to a stirred solution of secondary hydroxylamine (**4a**) (100 mg, 0.44 mmol), pyrrole (150 mg, 2.2 mmol) and acetic acid (270 mg, 4.4 mmol) in DCM (10 ml). The flask was wrapped in foil and the stirred at r.t. for 16 h and washed with aqueous sodium hydrogen carbonate solution. The organic layer was separated and the aqueous layer extracted with DCM (3×15 ml). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography, eluting with 4:1 v/v petroleum ether–diethyl ether to give the product (112 mg, 83%) as a pale yellow oil, which solidified slowly to colourless needles, mp 62–64°C. Found: C, 78.25; H, 7.35; N, 9.4. $C_{20}H_{22}N_2O$ requires C, 78.4; H, 7.25; N, 9.15%. *m/z* (%): 306 (M+1, 1), 227 (1), 215 (4), 182 (1), 170 (25), 157 (8), 91 (47) and 80 (100). ν_{max} 3460, 2930, 1450, 1370, 1020, 910, and 730 cm^{-1}. δ: 8.27 (br s, 1H, NH), 7.38–7.15 (m, 10H, ArH), 6.69 (m, 1H, H_a), 6.14–6.07 (m, 2H, H_b), 4.58 (s, 2H, OCH_2), 3.90 (s, 2H, NCH_2) and 2.92 (s, 4H, NCH_2CH_2Ph).

***O*-Benzyl-*N*-(indole-3-ylmethyl)-*N*-phenethyl-hydroxylamine (9).** Formaldehyde (37% solution in methanol, 36 mg, 0.44 mmol) was added to a stirred solution of secondary hydroxylamine (**4a**) (100 mg, 0.44 mmol), indole (260 mg, 2.2 mmol) and acetic acid (270 mg, 4.4 mmol) in methanol (10 ml). The flask was wrapped in foil and the stirred at r.t. for 21 h and the solvent removed under reduced pressure. The residue was taken up in DCM (10 ml) and washed with aqueous sodium hydrogen carbonate solution until alkaline. The organic layer was separated and the aqueous layer extracted with DCM (3×15 ml). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography, eluting with 3:1 v/v petroleum ether–diethyl ether to give the product (130 mg, 82%) as a pale yellow oil, which solidified slowly to colourless needles, mp 76–78°C. Found: C, 80.7; H, 6.9; N, 7.95. $C_{24}H_{24}N_2O$ requires C, 80.85; H, 6.8; N, 7.85%. *m/z* (%): 357 (M+1, 28), 240 (11), 220 (20), 207 (9), 130 (100), 103 (12), and 91 (49). ν_{max} 3420, 2920, 1450, 1360, 1090, 1010, 740, and 690 cm^{-1}. δ: 7.96 (br s, 1H, NH), 7.70–7.04 (m, 15H, ArH and 5×indole H), 4.60 (s, 2H, OCH_2), 4.11 (s, 2H, NCH_2) and 3.02–2.93 (m, 4H, NCH_2CH_2Ph).

***O*-Benzyl-*N*-(5-methylfuran-2-ylmethyl)-*N*-phenethyl-hydroxylamine (10).** 2-Methylfuran (180 mg, 2.2 mmol) was added to a stirred solution of secondary hydroxylamine (**4a**) (100 mg, 0.44 mmol), paraformaldehyde (14 mg, 0.44 mmol) and acetic acid (270 mg, 4.4 mmol) in DCE (10 ml). The reaction mixture was stirred under reflux for 20 h. The solvent was removed under reduced pressure and the residue was taken up in DCM (5 ml), washed until alkaline with 1 M sodium hydrogen carbonate solution and extracted with DCM (3×15 ml). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The pale orange oily residue was purified by flash chromatography, eluting with 10:1 v/v petroleum ether–diethyl ether to give the product (103 mg, 72%), as a pale yellow oil. Found: C, 78.2; H, 7.25; N, 4.3. $C_{21}H_{23}NO_2$ requires C, 78.45; H, 7.2; N, 4.35%. *m/z* (%) (FAB): 322 (M+1, 8), 240 (7), 230 (13), 214 (8), 105 (8) and 91 (100). ν_{max} 2920, 1450, 1360, 1220, 1020, 790, 740 and 690 cm^{-1}. δ: 7.32–7.19 (m, 10H, ArH), 6.15 (m, 1H, furan H), 5.93 (m, 1H, furan H), 4.56 (s, 2H, OCH_2), 3.85 (s, 2H, NCH_2), 2.99 (s, 4H, NCH_2CH_2Ph) and 2.31 (s, 3H, Me).

***N*,*O*-Dibenzyl-*N*-(pyrrol-2-ylmethyl)-hydroxylamine (13).** Formaldehyde (37% solution in methanol, 37 mg, 0.47 mmol) was added to a stirred solution of secondary hydroxylamine (**6a**) (100 mg, 0.47 mmol), pyrrole (160 mg, 2.4 mmol) and acetic acid (280 mg, 4.7 mmol) in DCM (10 ml). The flask was wrapped in foil and stirred at r.t. for 16 h and washed with aqueous sodium hydrogen carbonate solution until alkaline. The organic layer was separated and the aqueous layer extracted with DCM (3×15 ml). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography, eluting with 4:1 v/v petroleum ether–diethyl ether to give the product (105 mg, 78%) as a pale yellow oil, which solidified slowly to colourless needles, mp 72–75°C. Found: C, 77.95; H, 6.95; N, 9.55. $C_{19}H_{20}N_2O$ requires C, 78.05; H, 6.9; N, 9.6%. *m/z* (%): 292 (M+1, 2), 170 (25), 157 (8), 91 (60) and 80 (100). ν_{max} 3400, 2930, 1450, 1360, 1020, 970, 720 and 700 cm^{-1}. δ: 8.38 (br s, 1H, NH), 7.37–7.10 (m, 10H, ArH), 6.72 (m, 1H, H_a), 6.17–6.05 (m, 2H, H_b), 4.33 (s, 2H, OCH_2), 3.90 (s, 2H, NCH_2) and 3.82 (s, 2H, NCH_2Ph).

***O*-Benzyl-*N*-methyl-*N*-(pyrrol-2-ylmethyl)-hydroxylamine (14).** Formaldehyde (37% solution in methanol, 60 mg, 0.73 mmol) was added to a stirred solution of secondary hydroxylamine (**4b**) (100 mg, 0.73 mmol), pyrrole (250 mg, 3.7 mmol) and acetic acid (440 mg, 7.3 mmol) in methanol (10 ml) at −10°C. The flask was wrapped in foil and allowed to return to r.t. with stirring over 16 h. The solvent was removed under reduced pressure, the residue taken up in DCM (10 ml) and washed with aqueous sodium hydrogen carbonate solution until alkaline. The organic layer was separated and the aqueous layer

extracted with DCM (3×15 ml). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography, eluting with 2:1 v/v petroleum ether–diethyl ether to give the product (104 mg, 69%) as a pale yellow oil, which solidified slowly to colourless needles, mp 36–38°C. Found: C, 72.2; H, 7.6; N, 13.2. $C_{13}H_{16}N_2O$ requires C, 72.2; H, 7.45; N, 12.95%. *m/z* (%): 216 (M+1, 2), 187 (2), 170 (14), 157 (5), 91 (35), and 81 (100). ν_{max} 3380, 2930, 1450, 1360, 1030, 730, and 700 cm^{-1}. δ: 8.34 (br s, 1H, NH), 7.35–7.20 (m, 5H, ArH), 6.70 (m, 1H, H_a), 6.12 (m, 2H, H_b), 4.56 (s, 2H, OCH_2), 3.82 (s, 2H, NCH_2) and 2.57 (s, 3H, Me).

***O*-Benzyl-*N*-isopropyl-*N*-(pyrrol-2-ylmethyl)-hydroxylamine (15).** Formaldehyde (37% solution in methanol, 50 mg, 0.61 mmol) was added to a stirred solution of secondary hydroxylamine (**6b**) (100 mg, 0.61 mmol), pyrrole (210 mg, 3.1 mmol) and acetic acid (370 mg, 6.1 mmol) in methanol (10 ml) at −10°C. The flask was wrapped in foil and the mixture stirred and allowed to return to r.t. over 18 h. The solvent was removed under reduced pressure, the residue taken up in DCM (10 ml) and washed with aq. sodium hydrogen carbonate solution until neutral. The organic layer was separated and the aqueous layer extracted with DCM (3×15 ml). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography, eluting with 4:1 v/v petroleum ether–diethyl ether to give the product (82 mg, 55%) as a pale yellow oil, which solidified slowly to give colourless needles, mp 46–48°C. Found: C, 73.75; H, 8.3; N, 11.2. $C_{15}H_{20}N_2O$ requires C, 73.75; H, 8.25; N, 11.45%. *m/z* (%): 244 (M+1, 2), 170 (15), 157 (6), 91 (51), and 81 (100). ν_{max} 3420, 2940, 1440, 1350, 1030, 740 and 690 cm^{-1}. δ: 8.47 (br s, 1H, NH), 7.38–7.23 (m, 5H, ArH), 6.73 (m, 1H, H_a), 6.12 (m, 2H, H_b), 4.54 (s, 2H, OCH_2), 3.96 (s, 2H, NCH_2), 3.80 (sept, 1H, $NCHMe_2$) and 1.20 (d, 6H, *J*=6.3 Hz, 2×Me).

General procedure for the synthesis of benzotriazole derivatives (22), (28) and (30) from secondary hydroxylamine (4a). Benzotriazole (1 equiv.) and secondary hydroxylamine (**4a**) (1 equiv.) were dissolved in dry DCM and the solution stirred at r.t. for 5 min. The appropriate aldehyde (1 equiv.) was then added and stirring continued at r.t. for 18 h. Magnesium sulphate was then added and the mixture stirred for a further 0.5 h, filtered and the magnesium sulphate copiously washed with DCM. The filtrate was evaporated under reduced pressure to afford the product.

Benzotriazole derivative (22). No further purification was necessary. The product (99%) was obtained as a light brown oil which solidified slowly on standing to give a tan solid, mp 49–53°C. HRMS: 358.179. $C_{22}H_{22}N_4O$ requires 358.183. *m/z* (%): 358 (M+1, 7), 223 (19), 210 (17), 180 (25), 132 (35), 104 (43) and 91 (100). ν_{max} 3040, 2920, 1450, 1270, 1150, 1030, 100, 740 and 700 cm^{-1}. δ: 8.11–7.12 (m, 14H, ArH), 5.50 (s, 2H, NCH_2N), 4.55 (s, 2H, OCH_2) and 3.00 (m, 4H, NCH_2CH_2Ph).

Benzotriazole derivative (28). No further purification was necessary. The product (93%) was obtained as a light brown oil. HRMS: 372.195. $C_{23}H_{24}N_4O$ requires 372.197. *m/z* (%): 373 (M+1, 0.5), 162 (2), 119 (30), 105 (36), 91 (59), 77 (42) and 56 (100). ν_{max} 3040, 2940, 1610, 1450, 1370, 1280, 1150, 1020, 740 and 700 cm^{-1}. δ: 8.05–7.12 (m, 14H, ArH), 5.94 (q, 1H, *J*=6.8 Hz, H_a), 4.67 (AB, 2×d, 2H, *J*=10.8 Hz, OCH_2), 2.90 (m, 4H, NCH_2CH_2Ph) and 1.93 (d, 3H, *J*=6.8 Hz, Me).

Benzotriazole derivative (30). No further purification was necessary. The product (90%) was obtained as a light brown oil. HRMS: 398.213. $C_{25}H_{26}N_4O$ requires: 398.211. *m/z* (%): 399 (M+1, 1), 280 (100), 172 (10), 144 (7), 105 (26) and 91 (52). ν_{max} 3020, 2920, 1600, 1440, 1360, 1260, 1000, 740 and 690 cm^{-1}. δ: 8.08–7.12 (m, 14H, ArH), 4.87 (d, 1H, *J*=9.7 Hz, H_a), 4.61 (AB, 2×d, 2H, *J*=10.5 Hz, OCH_2), 3.06 (m, 4H, NCH_2CH_2Ph), 2.04 (m, 1H, H_b), 0.89, 0.70, 0.58 and 0.29 (4×m, 4×1H, cyclopropyl H).

General procedure for the synthesis of tertiary hydroxylamines (24–27) and (32–35) from benzotriazole derivatives and Grignard reagents. The appropriate Grignard reagent (3 equiv.) was added to a stirred solution of the appropriate benzotriazole derivative (1 equiv.) in dry THF at r.t. under nitrogen. The reaction mixture was stirred for 24 h and quenched with 20% w/w ammonium chloride solution (2 ml per 0.1 mmol of benzotriazole derivative). The aqueous layer was extracted with ether, the organic extracts combined and washed twice with 5% w/w sodium hydroxide solution (1 ml per 0.1 mmol of benzotriazole derivative) and then water until neutral, then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure.

***O*-Benzyl-*N*-phenethyl-*N*-propyl-hydroxylamine (24).** Purification of the residue by column chromatography, eluting with 10:1 v/v petroleum ether–diethyl ether afforded the product (70%) as a pale yellow oil. Found: C, 80.0; H, 8.55; N, 4.9. $C_{18}H_{23}NO$ requires C, 80.25; H, 8.6; N, 5.2%. *m/z* (%) (FAB): 270 (M+1, 23), 240 (16), 178 (100), 162 (12), 105 (12) and 91 (54). ν_{max} 2960, 1460, 1370, 1030, 740 and 690 cm^{-1}. δ: 7.4–7.17 (m, 10H, ArH), 4.74 (s, 2H, OCH_2), 2.99 (s, 4H, NCH_2CH_2Ph), 2.73 (t, 2H, *J*=7.2 Hz, NCH_2CH_2Me), 1.65 (sext, 2H, NCH_2CH_2Me) and 0.94 (t, 3H, *J*=7.2 Hz, Me).

***O*-Benzyl-*N*-allyl-*N*-phenethyl-hydroxylamine (25).** Purification of the residue by column chromatography, eluting with 10:1 v/v petroleum ether–diethyl ether afforded the product (69%) as a pale yellow oil. Found: C, 80.8; H, 7.75; N, 5.15. $C_{18}H_{21}NO$ requires C, 80.85; H, 7.9; N, 5.25%. *m/z* (%) (FAB): 268 (M+1, 53), 176 (100), 160 (19), 105 (11) and 91 (57). ν_{max} 2930, 1730, 1450, 1360, 1000, 930, 750 and 700 cm^{-1}. δ: 7.4–7.15 (m, 10H, ArH), 6.00 (m, 1H, H_b), 5.72 (m, 2H, H_a), 4.74 (s, 2H, OCH_2), 3.42 (d, 2H, *J*=6.6 Hz, NCH_2) and 2.94 (s, 4H, NCH_2CH_2Ph).

***N*,*O*-Dibenzyl-*N*-phenethyl-hydroxylamine (26).** Purification of the residue by column chromatography, eluting with 10:1 v/v petroleum ether–diethyl ether afforded the product (76%) as a pale yellow oil. Found: C, 83.05; H, 7.2; N, 4.35. $C_{22}H_{23}NO$ requires C, 83.25; H, 7.3; N, 4.4%. *m/z* (%) (FAB): 318 (M+1, 3), 226 (71), 181 (21), 136 (8), 105 (21), 91 (100) and 77 (27). ν_{max} 3020, 2920, 2840, 1450,

1360, 1020, 750 and 700 cm^{-1}. δ: 7.37–7.16 (m, 15H, ArH), 4.48 (s, 2H, OCH_2), 3.87 (s, 2H, NCH_2Ph) and 2.97 (s, 4H, NCH_2CH_2Ph).

***O*-Benzyl-*N*-(4-fluoro-benzyl)-*N*-phenethyl-hydroxylamine (27).** Purification of the residue by column chromatography, eluting with 10:1 v/v petroleum ether–diethyl ether afforded the product (78%) as a pale yellow oil. Found: C, 78.9; H, 6.6; N, 4.1. $C_{22}H_{22}FNO$ requires C, 78.8; H, 6.6; N, 4.2%. *m/z* (%) (FAB): 336 (M+1, 22), 244 (100), 228 (18), 109 (89) and 91 (49). ν_{max} 3040, 2930, 1600, 1500, 1220, 740 and 690 cm^{-1}. δ: 7.38–6.93 (m, 14H, ArH), 4.50 (s, 2H, OCH_2), 3.83 (s, 2H, NCH_2) and 2.96 (s, 4H, NCH_2CH_2Ph).

***O*-Benzyl-*N*-(1-methyl-allyl)-*N*-phenethyl-hydroxylamine (32).** Purification of the residue by column chromatography, eluting with 10:1 v/v petroleum ether–diethyl ether afforded the product (82%) as a pale yellow oil. Found: C, 81.35; H, 8.5; N, 5.0. $C_{19}H_{23}NO$ requires C, 81.1; H, 8.25; N, 5.0%. *m/z* (%) (FAB): 282 (M+1, 19), 254 (6), 190 (100), 174 (15) 136 (10), 105 (26) and 91 (63). ν_{max} 2940, 1460, 1360, 1030, 920, 750 and 700 cm^{-1}. δ: 7.43–7.12 (m, 10H, Ar H), 5.92 (m, 1H, H_b), 5.13 (m, 2H, H_a), 4.76 (s, 2H, OCH_2), 3.42 (s, 1H, H_c), 2.96 (s, 4H, NCH_2CH_2Ph) and 1.29 (d, 3H, *J*=6.5 Hz, Me).

***O*-Benzyl-*N*-(1-methyl-benzyl)-*N*-phenethyl-hydroxylamine (33).** Purification of the residue by column chromatography, eluting with 10:1 v/v petroleum ether–diethyl ether afforded the product (81%) as a pale yellow oil. Found: C, 83.3; H, 7.4; N, 4.1. $C_{23}H_{25}NO$ requires C, 83.35; H, 7.6; N, 4.2%. *m/z* (%) (FAB): 332 (M+1, 9), 240 (37), 224 (13), 105 (100) and 91 (14). ν_{max} 2920, 1450, 1360, 1020, 750 and 700 cm^{-1}. δ: 7.38–7.11 (m, 15H, ArH), 4.69 (d, 1H, *J*=10.1 Hz, one H from OCH_2), 4.60 (br s, 1H, one H from OCH_2), 3.90 (q, 1H, *J*=6.6 Hz, H_a), 2.93 (s, 4H, NCH_2CH_2Ph) and 1.49 (d, 3H, *J*=6.6 Hz, Me).

***O*-Benzyl-*N*-(1-cyclopropyl-allyl)-*N*-phenethyl-hydroxylamine (34).** Purification of the residue by column chromatography, eluting with 10:1 v/v petroleum ether–diethyl ether afforded the product (68%) as a pale yellow oil. Found: C, 81.95; H, 7.95; N, 4.4. $C_{21}H_{25}NO$ requires C, 82.05; H, 8.2; N, 4.55%. *m/z* (%) (FAB): 308 (M+1, 17), 216 (45), 200 (10), 105 (13), 91 (22) and 81 (100). ν_{max} 3400, 3080, 3030, 2940, 2860, 1650, 1460, 1370, 1020, 920, 740 and 700 cm^{-1}. δ: 7.4–7.16 (m, 10H, ArH), 5.95 (m, 1H, H_b), 5.13 (m, 2H, H_a), 4.84 (s, 2H, OCH_2), 3.00 (s, 4H, NCH_2CH_2Ph), 2.54 (t, 1H, *J*=2.8 Hz, H_c), 1.05 (m, 1H, H_d), 0.64 and 0.15 (2×m, 2×1H, cyclopropyl H), and 0.59–0.50 (m, 2H, cyclopropyl H).

***O*-Benzyl-*N*-(1-cyclopropyl-benzyl)-*N*-phenethyl-hydroxylamine (35).** Purification of the residue by column chromatography, eluting with 10:1 v/v petroleum ether–ether afforded the product (70%) as a pale yellow oil, which slowly solidified to give colourless needles, mp 37–40°C. Found: C, 83.95; H, 7.5; N, 3.7. $C_{25}H_{27}NO$ requires C, 84.0; H, 7.6; N, 3.9%. *m/z* (%) (FAB): 358 (M+1, 4), 266 (8), 250 (7), 131 (100), 105 (9) and 91 (17). ν_{max} 3070, 3040, 2940, 2880, 1490, 1460, 1360, 1030, 750 and 700 cm^{-1}. δ: 7.38–7.11 (m, 15H, ArH), 4.67 (d, 1H, *J*=9.9 Hz, one H from OCH_2), 4.53 (br s, 1H, one H from OCH_2), 3.18 (br s, 1H, H_a), 2.96 (s, 4H, NCH_2CH_2Ph) 1.31 (m, 1H, H_b), 0.75 and 0.06 (2×m, 2×1H, cyclopropyl H), and 0.59–0.49 (m, 2H, cyclopropyl H).

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