A novel [2,3] intramolecular rearrangement of *N*-benzyl-*O*-allylhydroxylamines

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A novel [2,3]-sigmatropic rearrangement whereby *N*-benzyl-*O*-allylhydroxylamines undergo transformation to the corresponding *N*-allylhydroxylamines, which can subsequently be reduced to the corresponding allylamines, is described and evidence for the intramolecular nature of this process presented.

Intramolecular sigmatropic rearrangements have found widespread use in synthetic organic chemistry primarily due to the high selectivities observed in these transformations. In particular, effective use has been made of a variety of [2,3] processes, such as the Meisenheimer[1] and Stevens rearrangements[2] to control stereochemistry as they tend to proceed at significantly lower temperatures than [3,3] processes[3] and thus lead to better observed selectivities. For example, Anderson *et al.* have recently developed an aza-[2,3]-Wittig rearrangement which proceeds with excellent stereocontrol.[4]

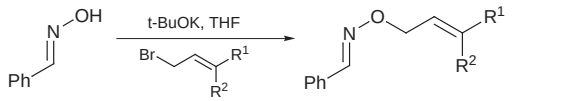
During continuation of our lithium amide studies[5] we discovered that *N*-benzyl-*O*-allylhydroxylamine gives *N*-allyl-*N*-benzylhydroxylamine when treated with n-BuLi, a process which may be attributed to a novel [2,3] sigmatropic rearrangement analogous to the [2,3] Wittig rearrangement.[6] We now report our initial investigations into the nature of this rearrangement and demonstrate its synthetic use.

The substrates for all of the rearrangements were easily prepared in two steps and high yield starting from *syn*-benzaldehyde oxime **1** (Scheme 1). *O*-Allylation was achieved by formation of the potassium salt of the oxime and subsequent quenching by treatment with the appropriate allyl bromide.[7] The *O*-allyl oximes **2a**–**d** were reduced with pyridine–borane complex in EtOH–10% HCl to give the desired substrates **3a**–**d** in excellent overall yield.[8] In most cases purification of the intermediates and substrates was achieved by distillation.

The rearrangement was carried out by treatment of the simple *N*-benzyl-*O*-allylhydroxylamine **3a** in dry THF with 1 equiv. of n-BuLi at −78 °C for 1 h, followed by warming to room temperature for 30 min before quenching with water. This afforded the [2,3] rearrangement product **4a** in essentially quantitative yield by examination of the crude ^{1}H NMR spectrum. Purification of this compound proved to be difficult due to decomposition, although it was finally achieved by chromatography on previously deactivated silica gel (1% Et_3N). The hydroxylamine thus obtained as an oil was isolated in 61% yield and the structure confirmed by ^{1}H and ^{13}C NMR spectroscopy and HRMS. With conditions for the rearrangement identified,‡ it was repeated for the other substrates (Scheme 2). All gave the [2,3] rearrangement product, although in the case of the rearrangement to a trisubstituted centre (**3c** → **4c**), the reaction was found to be only 10% complete by ^{1}H NMR spectroscopy after 48 h. However, by heating the reaction mixture to reflux for 2 h after the initial addition of n-BuLi at −78 °C, the reaction proceeded to completion and the [2,3] product was obtained in 60% isolated yield. The hydroxylamines formed in all of these reactions were all very prone to decomposition during purification. Thus, isolated yields of the allylhydroxylamines were always considerably lower than the quantitative yields for the crude reaction observed by ^{1}H NMR spectroscopy. Attempted thermal rearrangement of **3a** by heating under reflux in xylene for 7 h led to only a trace amount of the desired rearrangement product in the ^{1}H NMR spectrum (< 5%).

The rearrangement of the crotylhydroxylamine **3b** rules out the possibility of a 1,2 anionic shift which would have given rise to the *N*-benzyl-*N*-crotylhydroxylamine instead of the observed product. However the possibility still existed that the reaction was intermolecular and not intramolecular. In order to demonstrate that the process was indeed intramolecular the rearrangement was carried out with two different substrates **3b** and **5** with 2 equiv. of n-BuLi (Scheme 3). If an intermolecular process was being observed then the mixed products **4a** and **7** from this rearrangement would be observed. All four of the possible products that could arise from this reaction were prepared in an analogous manner to the hydroxylamines prepared earlier. When the crude ^{1}H NMR spectrum of the mixed reaction was analysed, only peaks due to the respective intramolecular rearrangement products **4b** and **6** were present, and not the crossover products **4a** and **7** confirming that this reaction was indeed an intramolecular process.

Based on these results the reaction is comparable to a [2,3]-Wittig rearrangement, and thus reasonably proceeds *via* a transition state which is similar to that suggested for this process (Scheme 4).[6] Deprotonation of the N–H proton affords the



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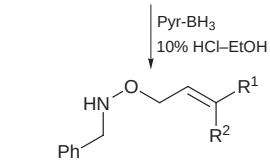
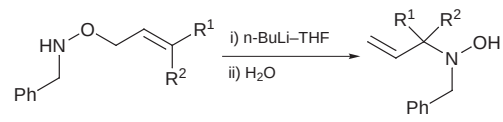
Compound	Yield
2a $R^1 = R^2 = H$	91%
2b $R^1 = H$, Me; $R^2 = Me$, H	86%
2c $R^1 = R^2 = Me$	89%
2d $R^1 = Ph$; $R^2 = H$	95%



Compound	Yield
3a $R^1 = R^2 = H$	94%
3b $R^1 = H$, Me; $R^2 = Me$,H	85%
3c $R^1 = R^2 = Me$	80%
3d $R^1 = Ph$; $R^2 = H$	84%

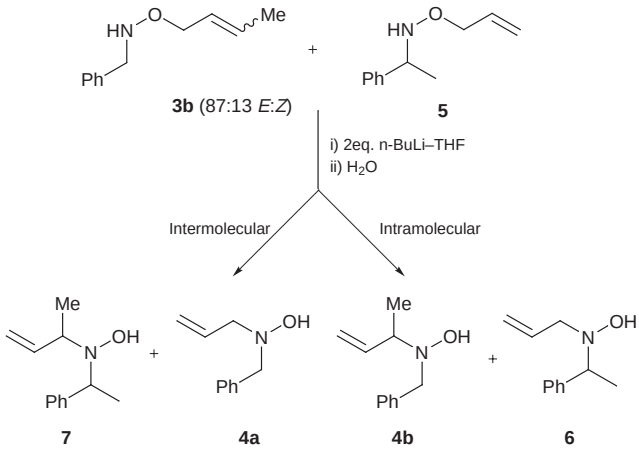
Scheme 1



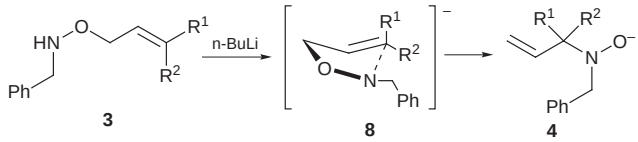
Compound	Compound	Yield[a]
3a $R^1 = R^2 = H$	**4a** $R^1 = R^2 = H$	61%
3b $R^1 = H$, Me; $R^2 = Me$, H	**4b** $R^1 = H$, Me; $R^2 = Me$, H	59%
3c $R^1 = R^2 = Me$	**4c** $R^1 = R^2 = M$ e	60%
3d $R^1 = Ph$; $R^2 = H$	**4d** $R^1 = Ph$; $R^2 = H$	40%

[a]Refers to isolated yields

Scheme 2



Scheme 3

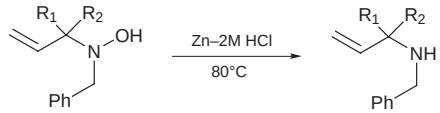


Scheme 4

lithium amide which rearranges through an envelope transition state **8**. The driving force for this reaction lies in the relative stability of the lithium oxy-anion **4** formed compared to the lithium amide precursor **8**, which is illustrated in the pK_a values of the corresponding alcohol and amine (pK_a EtOH = 15.9, pK_a $EtNH_2$ = 35). A similar [1,2] anionic process has been previously reported in which the anion derived from *N*,*O*-bis(trimethylsilyl)hydroxylamine rearranges to *N*,*N*-bis(trimethylsilyl)hydroxylamine.[9]

As already eluded to, the hydroxylamines produced were relatively unstable and were thus difficult to isolate or store for prolonged periods of time. However, the allylamines from which the hydroxylamines are derived are stable and are also useful synthons.[10] Thus, reduction of the hydroxylamines **4a**–**d** with Zn/2 M HCl at 80 °C for 1 h followed by neutralisation (NaOH) and extraction with Et_2O gave the respective amines **9a**–**d** in excellent yields (Scheme 5).

The versatility of this method for the synthesis of allylamines was demonstrated in the synthesis of *N*-allyl-*N*-benzylamine **9a**



Compound	Compound	Yield
4a $R^1 = R^2 = H$	**9a** $R^1 = R^2 = H$	90%
4b $R^1 = H, Me$; $R^2 = Me, H$	**9b** $R^1 = H, Me$; $R^2 = Me, H$	94%
4c $R^1 = R^2 = Me$	**9c** $R^1 = R^2 = Me$	92%
4d $R^1 = Ph$; $R^2 = H$	**9d** $R^1 = Ph$; $R^2 = H$	91%

Scheme 5

which was prepared in a two step process by rearrangement of the parent hydroxylamine **3a** and subsequent reduction of the crude material to afford the desired allylamine **9a** in excellent overall yield (91%).§ In a similar manner the crotyl- and cinnamyl-hydroxylamines **3b** and **3d** were rearranged then immediately reduced to give the allylic amines **9b** and **9d** in 93 and 92% overall yield respectively.

In conclusion we report a novel [2,3] rearrangement of *N*-benzyl-*O*-allylhydroxylamines to give the corresponding *N*-allyl-*N*-benzylhydroxylamines, which may be reduced to the *N*-benzylallylamines with Zn/HCl. This provides a novel approach to the synthesis of allyl substituted hydroxylamines and amines.

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Notes and References

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‡ *Typical experimental procedure:* n-BuLi (1.66 M, 0.81 mL, 1.35 mmol) was added to a solution of **3a** (200 mg, 1.23 mmol) in anhydrous THF (15 mL) at −78 °C under N_2. After stirring for 1 h the reaction was allowed to warm to room temp. and stirred for a further 30 min. The reaction was quenched with distilled water (25 mL) and extracted with Et_2O (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography on deactivated silica gel (1% Et_3N–petroleum ether) eluting with petroleum ether–Et_2O (6:1) to give the desired hydroxylamine **4a** as a clear yellow oil (122 mg, 61%).

§ *Typical proceedure for the reduction of the hydroxylamines*: **4a** (0.100 g, 0.61 mmol) was dissolved in 2 M HCl (5 mL) and zinc dust (0.200 g, 3.1 mmol) added cautiously. The reaction was heated at 80 °C for 1 h, cooled and neutralised with 2 M NaOH. The white suspension was extracted with Et_2O (3 × 15 mL) and dried ($MgSO_4$). Evaporation afforded **9a** (0.081 g, 90%).

Alternatively, the crude product **4a** obtained from rearrangement of **3a** was directly reduced by addition of 2 M HCl (3 mL) and zinc dust (0.200 g, 3.065 mmol) and heating at 80 °C. After 1 h the reaction was cooled, neutralised with 2 M NaOH, extracted with Et_2O (3 × 20 mL) and dried ($MgSO_4$). Evaporation afforded **9a** (0.082 g, 91% overall yield).

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