

Synthesis of *O*-alkylhydroxylamines by electrophilic amination of alkoxides

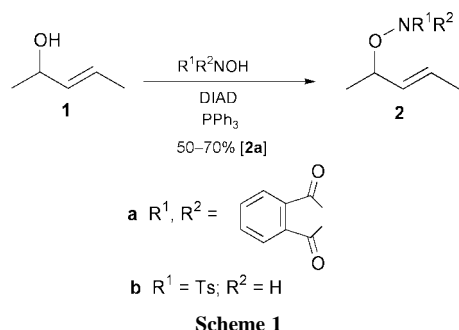
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The 3-trichloromethyloxaziridine **7** reacts smoothly with lithium alkoxides, derived from a representative range of alcohols, transferring an NHBoc function to the oxygen to provide good to excellent yields of *N*-Boc-*O*-alkylhydroxylamines **8–16** by this new *O*-amination protocol.

In pursuance of our studies of various electrophile-driven 5-*endo* cyclisation processes,¹ we required access to the hydroxylamines represented by structures **2** and **6** and sought to obtain these by a Mitsunobu displacement² using the corresponding and readily available alcohols **1** and **5**, as this seemed the best of a relatively limited number of options.³ Unfortunately, both approaches suffered from serious drawbacks. For the allylic alcohol **1**, the Mitsunobu method using *N*-hydroxyphthalimide,⁴ under standard conditions delivered good yields of the required substrate **2a**; in contrast, when *N*-(4-toluenesulfonyl)hydroxylamine (TsNHOH)⁵ was used as the nucleophile, yields were very poor (Scheme 1). However, when



applied to unsymmetrical substrates, both the S_N2 and S_N2' pathways were followed (Fig. 1) to give both possible products

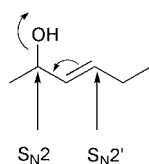
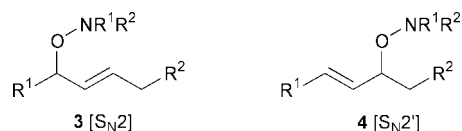
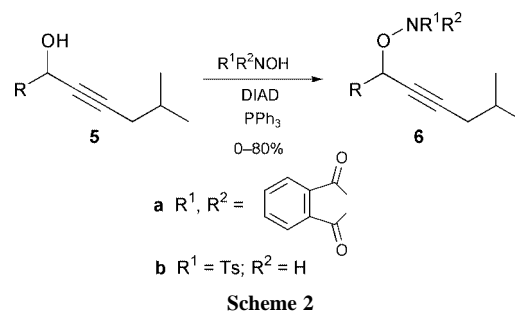


Fig. 1

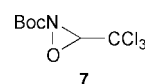
(i.e. hydroxylamines **3** and **4**). For propargylic alcohols **5**,



Mitsunobu displacement with either nucleophile (R^1R^2NOH) gave very variable, precursor dependent yields of the required products **6** (Scheme 2). Despite these problems, and the additional necessity of converting the phthalimides (e.g. **2a**, **6a**), into the corresponding *N*-tosylates (e.g. **2b**, **6b**) we were able to access the latter substrates in sufficient quantities to demonstrate that the projected 5-*endo*-trig and 5-*endo*-dig cyclisations generally work extremely well to provide a new entry into



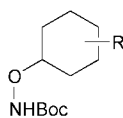
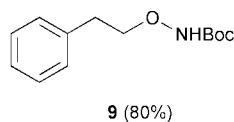
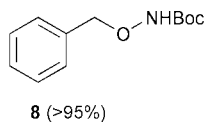
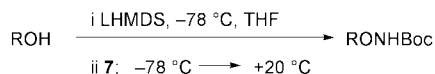
isoxazolidines and isoxazolines, respectively.⁶ We were therefore prompted to find an alternative and more efficient approach to these classes of compounds (**2–4** and **6**), both for this reason and also because approaches to hydroxylamines in general are somewhat lacking.⁷ We were attracted by recent reports from the Vidal–Collet group⁸ that various electron-deficient oxaziridines could behave as positive nitrogen sources ($+NHBoc$), rather than as the more familiar positive oxygen sources ($+OH$), popularized by the work of Davis and his colleagues.⁹ However, while such species were reported to react efficiently with various amines and enolates and both sulfur and phosphorus nucleophiles, there was no report of similar reactions with alcohols or the derived alkoxides.⁸ Such a transformation has been achieved using chloramine, but only with a large excess of alkoxide and in relatively poor yields,¹⁰ and it was not until a very recent report that 3,3'-di-*tert*-butyloxaziridine reacts with a range of potassium alkoxides in DMPU and in the presence of 18-crown-6 to provide *O*-alkylhydroxylamines in 10–86% yields that such a process had synthetic value.¹¹ We report herein, that the highly electron deficient oxaziridine **7** reacts



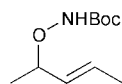
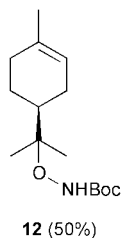
smoothly with lithium alkoxides using very practical conditions, despite our fears that it would simply act as a proton source for these basic species.

Oxaziridine **7** was prepared as previously described⁸ starting from *tert*-butyl carbazate, diazotization of which provided *tert*-butyl azide. This potentially dangerous material was not isolated but only handled in solution and was immediately treated with triphenylphosphine in wet ether to give the imine $Ph_3P=NBoc$; subsequent aza-Wittig reaction with chloral and oxone® oxidation gave the oxaziridine **7**, as previously reported.⁸ The compound was purified by column chromatography⁸ and, in our hands, was sufficiently stable for use for *ca.* two months if stored below 0 °C, after which repurification was necessary. We were delighted to find that generation of the lithium alkoxide of benzyl alcohol using lithium hexamethyldisilazide (LHMDS) in tetrahydrofuran at –78 °C followed by the addition of oxaziridine **7** and slow warming to ambient temperature delivered an essentially quantitative yield of the *O*-benzyl-*N*-Boc-hydroxylamine **8** after a simple aqueous work-up.⁸ Using the same method, we tested its viability with a range of other alcohols of varying structure and the results are collected in Table 1. A primary saturated alcohol, phenethanol,

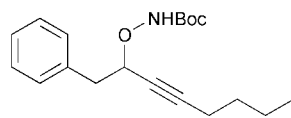
Table 1



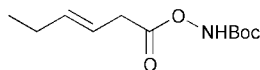
Cholesterol: **11** (70%)



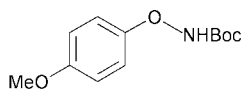
13 (96%)



14 (50%)



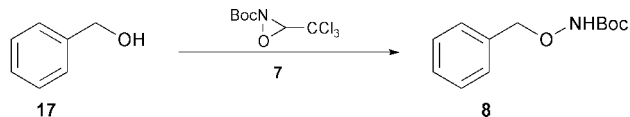
15 (80%)



16 (87%)

reacted slightly less efficiently giving the hydroxylamine derivative **9** in 80% yield. Two secondary alcohols, cyclohexanol and cholesterol, similarly gave the hydroxylamines **10** and **11** in 85 and 70% yields, respectively. Even the tertiary alcohol group in α -terpineol reacted reasonably efficiently to give the derivative **12** in 50% yield. This contrasts with the use of 3,3'-di-*tert*-butyloxaziridine,¹¹ which delivered only a 10% yield from a similar tertiary alcohol. However, it should be noted that this latter method leads directly to *O*-alkylhydroxylamines as the free bases, which could be useful in some contexts. Returning to our original substrates, we were glad to find that yields were again viable, the allylic alcohol derivative **13** being isolated in almost quantitative yield while the relatively sensitive propargylic derivative **14** was isolated in 50% yield, with the material balance being largely unreacted alcohol. Hence, it appears that the present method is especially efficient when applied to benzylic or allylic alcohols. Other oxygen-based nucleophiles also react successfully. Thus, under the same conditions, (*E*)-hex-3-enoic acid was converted into the *O*-acylhydroxylamine **15** and 4-methoxyphenol into the *O*-arylhydroxylamine **16**, both in excellent yields. In general, all of the foregoing derivatives appeared rather sensitive to chromatography over silica gel; Grade II alumina was more suitable but its use still often resulted in losses of some 10–20%¹² deprotection to give the corresponding *O*-alkylhydroxylamines (*i.e.* **2**, **6**; R¹ = R² = H) has ample literature precedent,¹³ which we have confirmed during the present work, during which we have also been able to exchange the *N*-protecting group from Boc to TS (*e.g.* **13** \rightarrow **2b**) in an efficient manner.

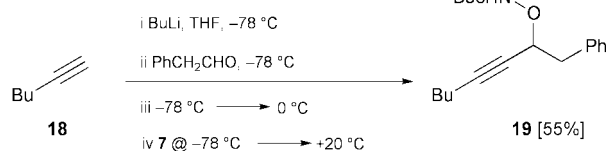
The ease with which alkoxides in general can be formed led us to briefly investigate some alternative protocols, using benzyl alcohol **17** as a test substrate. As outlined in Scheme 3, generation of the sodium alkoxide using sodium hydride in



Scheme 3 Reagents and conditions: NaH, Et₂O, 20 °C, >95% yield or BuLi, THF, –78 °C for 1 h then warming to 20 °C, >90% yield.

diethyl ether at ambient temperature followed by addition of the oxaziridine **7** again gave an excellent yield of the hydroxylamine **8** as did the use of butyllithium as base. Finally, we have succeeded in preparing suitable substrates for the 5-*endo*-dig cyclisations by a very direct, 'one-pot' method (Scheme 4). Thus, condensation of hex-1-yne **18**, after deprotonation using butyllithium, with phenylacetaldehyde, addition of the oxaziridine **7** to the resulting alkoxide and warming to ambient temperature gave a 55% yield of the desired hydroxylamine **19**. These results suggest that there could well be a number of (substrate-dependent) modifications which could usefully be applied to this type of chemistry. Further studies along these lines are underway, along with work on the 5-*endo* cyclisations, which is now viable in the light of the foregoing results.

"One-pot"



Scheme 4

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Notes and references

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