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Convenient methods for the hydrolysis of oxazolidinones to vicinal aminoalcohols

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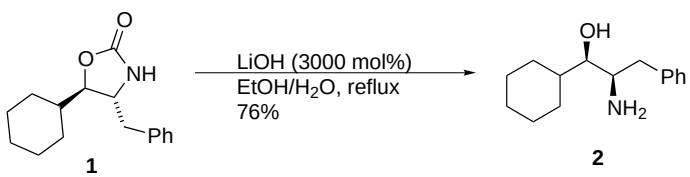
Abstract—We have developed two convenient methods for hydrolysis of 2-oxazolidinones to the corresponding vicinal aminoalcohols. *N*-Substituted oxazolidinones can be readily hydrolyzed using Dowex 1×8-100 resin. *N*-Unsubstituted oxazolidinones cannot be hydrolyzed using Dowex resins but are effectively hydrolyzed using polymer supported ethylenediamine. © 2002 Published by Elsevier Science Ltd.

2-Oxazolidinones (e.g. **1**) are both a useful intermediate in the synthesis of aminoalcohols[1–10] as well as a potential protecting group for vicinal aminoalcohols.[11] Typical reaction conditions for the conversion of the oxazolidinone ring to an amino alcohol involve the use of a hydroxide base, water and some type of organic co-solvent (heating is often needed for *N*-unsubstituted oxazolidinones). For example, the hydrolysis of oxazolidinone **1** requires the addition of 3000 mol% of LiOH in refluxing $EtOH/H_2O$ to effect conversion to the aminoalcohol **2**[12] (Scheme 1). A liability with this type of hydrolysis is that most reaction conditions employ some form of aqueous reaction medium. The product vicinal aminoalcohols often have some degree of water solubility; thus, product isolation can be problematic. One proposed solution to this reaction is to first activate the oxazolidinone ring toward hydrolysis by acylation of the nitrogen.[13,14] This solution does have its limitations in that selectivity in hydrolysis of the oxazolidinone versus the acyl group on the nitrogen can be difficult to control.[15] Other methods for hydrolysis of an oxazolidinone include hydrogen peroxide[4] and 6 M HCl and $FeCl_3$.[16] A new method that could eliminate the extreme conditions and improve product clean up should be widely applicable.

We hoped that a polymer-supported base might be a useful method for the hydrolysis of oxazolidinones to vicinal aminoalcohols. Such a reaction could be carried out in non-aqueous solvents and work-up should consist of only filtration and concentration. The most readily available polymer supported bases are the Dowex types of polystyrene resins.[17] These resins contain either a benzyltrimethylammonium functionality or a benzyldimethyl(2-hydroxyethyl)ammonium group. Conversion of the chloride counterion to a hydroxyl thus provides a polymer-supported hydroxide for hydrolysis of an oxazolidinone.

We chose to initially use the Dowex 1×8-100 resin and *N*-benzyl oxazolidinone **3a** as a test oxazolidinone. Stirring the oxazolidinone with 350 mol% of supported hydroxide for 18 h in THF/MeOH provided (after filtration and concentration) the hydrolysis product in 98% yield. We choose a series of substituted oxazolidi-



1 2

Scheme 1.

Keywords: oxazolidinones; hydrolysis; amino alcohols; solid supported reagents/reactions.

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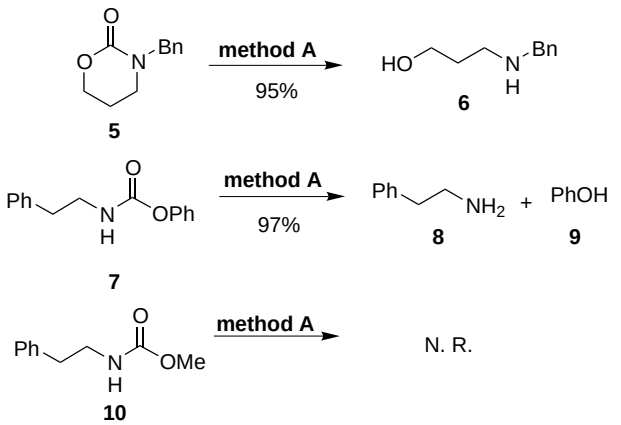
nones in order to examine the scope and utility of this simple hydrolysis method (Table 1).

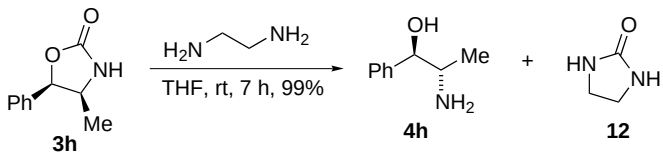
As our first oxazolidinone was sterically very unhindered we next chose a more sterically demanding oxazolidinone **3b**. Again the isolated yield was excellent. The hydrolysis is relatively insensitive to either electron donating, **3c**, or withdrawing, **3d**, groups in the nitrogen substituent. More highly functionalized oxazolidinones **3e** and **3f** again were hydrolyzed in >90% yield. Oxazolidinone **3g**, which contained an ester side-chain was hydrolyzed and as expected so was the ester side-chain.

To further confirm the scope of the resin based method we prepared oxazinanone **5**.[27] Treatment of **5** with Dowex 1×8-100 resin (method A) provided a 95% yield of amino alcohol **6** (Scheme 2). To further investigate the scope of the hydrolysis we prepared two acyclic carbamates **7** and **10**.[29] The hydrolysis of the rather easily hydrolyzed phenyl carbamate gave a 97% yield of the expected products (**8** and **9**). Hydrolysis of the methyl carbamate (**10**) produced none of the expected products presumably because of the poor leaving group (OMe) and the lack of ring strain.

We next tried to extend this method to *N*-unsubstituted oxazolidinones. The hydrolysis of *N*-unsubstituted oxazolidinones using this method provides at best 25% of the hydrolysis product (entry 8). A number of different Dowex resins[30] as well as increasing the temperature and increasing the amount of resin provided no improvement in yield. A problem with the hydroxide mediated hydrolysis of *N*-unsubstituted oxazolidinones is the competing deprotonation of the acidic hydrogen on the nitrogen. A possible solution would be to use a base that is nucleophilic but not as basic as hydroxide. Ethylenediamine would seem to be an excellent choice (pK_{a1} 10.075 as compared to 15.7 for H_2O[31]). The ability of the second amino group of ethylenediamine to form the cyclic urea and thereby drive the reaction to completion was our rationale for this base. We stirred oxazolidinone **3h** with 300 mol% of ethylenediamine at room temperature in THF for 18 h and obtained a 99% yield of the desired vicinal aminoalcohol (**4h**) along with the cyclic urea **12** (Scheme 3). While this is an effective method for the hydrolysis of the oxazolidinone ring, it does produce a byproduct that must be removed. We next examined the use of polymer sup-

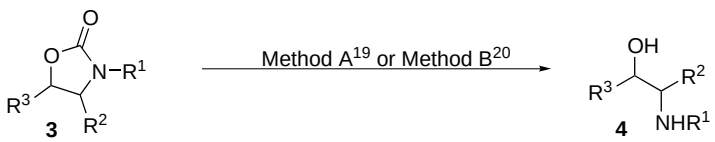


Scheme 2.



Scheme 3.

Table 1. Hydrolysis reactions of 2-oxazolidinones[18]



Entry	Method	Compound no.	R^1	R^2	R^3	Product (% yield)
1	A	**3a**[21]	Bn	H	H	**4a**[21] (94)
2	A	**3b**[22]	$PhCH(CH_3)$	Me	Ph	**4b**[21] (93)
3	A	**3c**[24]	4-(MeO)Ph	Me	Ph	**4c**[24] (97)
4	A	**3d**[24]	$4\text{-}(NO_2)Ph$	Me	Ph	**4d**[24] (95)
5	A	**3e**[26]	*n*Bu	Bn	$TrOCH_2$	**4e** (96)
6	A	**3f**[26]	*n*Bu	Bn	$HOCH_2$	**4f** (94)
7	A	**3g**[26]	*n*Bu	Bn	$HOCH_2$[a]	**4f** (93)
8	A	**3h**	H	Me	Ph	**4h** (25)
9	B	**3h**	H	Me	Ph	**4h** (98)
10	B	**3i**[21]	H	H	Ph	**4i**[21] (99)
11	B	**3j**[21]	H	Ph	H	**4j**[21] (96)
12	B	**3k**	H	*i*Pr	H	**4k** (97)
13	B	**3l**[21]	H	H	Me	**4l**[21] (99)

[a] **3g**, $R^3 = C_6H_{11}C(O)OCH_2$.

ported ethylenediamine. While such a reagent would produce a similar cyclic urea, it could be readily removed by filtration.

Treatment of oxazolidinone **3h** with polymer supported ethylenediamine[20] at 60°C did provide the aminoalcohol **4h**. However a small amount of **12** (6%) was also produced. By first washing the resin exhaustively with THF any free ethylenediamine was removed and the reaction gave clean aminoalcohol **4h** in 98% yield after filtration and concentration (Table 1, entry 9). We then tested the resin on a variety of oxazolidinones to test its versatility.

As before we chose a variety of substituted oxazolidinones. We examined the effect of substitution at the 4-, 5-, as well as both the 4- and 5-positions (Table 1, entries 9–13). In all cases the yields were >90%.

Through the use of a solid supported base we have developed a convenient method for hydrolysis of oxazolidinones that minimizes clean up and reduces the extreme conditions previously needed. Using Dowex 1×8-100 resin as our supported base, we were able to hydrolyze a variety of *N*-substituted oxazolidinones as well as an oxazenone and a phenyl carbamate. By using resin bound ethylenediamine we were able to hydrolyze various *N*-unsubstituted oxazolidinones. Together these methods provide a more efficient method for the hydrolysis of oxazolidinones.

Acknowledgements

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18. ^{1}H NMR of all known aminoalcohols were compared to literature data. ^{1}H NMR spectra of aminoalcohols **4e** and **4f** are provided below: **4e**: 1.0 (s, 1H), 1.2 (m, 7H), 1.6 (t, $J=5.25$ Hz, 2H), 1.8 (dd, $J=4$, 7.75 Hz, 2H), 2.2 (d, $J=8.25$ Hz, 2H), 2.6 (d, $J=10.75$ Hz, 2H), 7.6 (m, 5H), 7.8 (m, 15H); **4f**: 1.0 (s, 1H), 1.2 (m, 7H), 1.6 (t, $J=5.25$ Hz, 2H), 1.8 (dd, $J=4$, 7.75 Hz, 2H), 2.2 (d, $J=8.25$ Hz, 2H), 2.6 (d, $J=10.75$ Hz, 2H), 7.6 (m, 5H).
19. The oxazolidinone was dissolved in MeOH:THF (3:1, 0.3 M) and Dowex 1×8-100 resin (350 mol% of the hydroxide form, as purchased the resin was in the chloride form and was washed with 200 mL of 3 M NaOH, 100 mL of H_2O, 50 mL of MeOH, and dried overnight under vacuum) was added. The suspension was stirred at rt until complete by TLC (18–24 h), filtered, washed with EtOAc, and concentrated to yield the product.
20. *N*-(2-Aminoethyl)aminomethyl polystyrene (300 mol%, 1% DVB, 1.3 mmol/g from Novabiochem) was washed with THF (3×25 mL) and added to a solution of the oxazolidinone (100 mol%) in THF (0.3 M). The suspension was warmed to 60°C and stirred until complete (18–24 h). The reaction was filtered, washed with EtOAc, and concentrated to provided the desired amino alcohol.
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