Ring Opening Reactions of *N*-Alkyl Oxazolidinones with Organolithium Reagents

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Abstract: Addition of primary, secondary and aryl organolithium reagents to *N*-methyl and *N*-benzyl oxazolidin-2-ones give *N*-acyl amino alcohols in 30–93% yields. Application to the synthesis of an imidazoyl oxazoline is demonstrated.

Key words: acylations, amides, amino alcohols, organometallic reagents, rearrangements

Growing interest in asymmetric synthesis has increased the need for methodology, which facilitates the easy installation of a stereogenic centre within a molecule. Analogues of amino acids and amino alcohols fulfil this role acting as key chiral building blocks and their applicability is self-evident given their presence in a wide range of synthetic and natural products such as those in in sphingolipids and the side chain of taxol. Chiral amino alcohols also form the basis of many stereodirecting groups in auxiliaries and catalysts,[2] an elegant example being the use of pseudoepedrine in Myers' auxiliary for asymmetric alkylation (Figure 1).[2a]

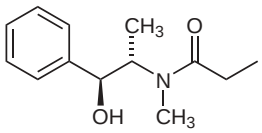

Figure 1

However, the restricted availability of certain amino alcohols, especially for those classed as regulated chemicals means that some methodologies, like those detailed above, are not available in certain regions of the world. Additionally, classical synthesis of *N*-acyl amino alcohols via condensation of an amino alcohol with an acid chloride is not always trivial, especially when the acid chloride is difficult to generate or unstable. In the process of developing methodology aimed towards a new approach to the synthesis of oxazolines, we discovered that *N*-alkyl *N*-acyl amino alcohols could be easily generated from the corresponding *N*-alkyl oxazolidin-2-ones. Herein we describe our preliminary findings of this work.

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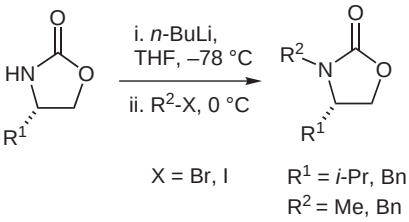
The key starting materials for this work were *N*-methyl and *N*-benzyl oxazolidin-2-ones. These have been reported as a by-product in Evans type asymmetric alkylation reactions and little mention has been made of their reactivity.[3] As representative examples, we chose two *N*-methyl and one *N*-benzyl oxazolidin-2-ones which were easily prepared by deprotonation of the oxazolidin-2-one and alkylation with methyl iodide or benzyl bromide, respectively. The reactions were found to be slow, requiring 3 equivalents of alkyl halide, but excellent yields were achieved for the (*S*)-valine and (*S*)-phenylalanine derived oxazolidinones (Scheme 1, Table 1). These materials were obtained essentially pure as determined by ^{1}H NMR spectroscopy, and were used in crude form throughout.[4]



Scheme 1

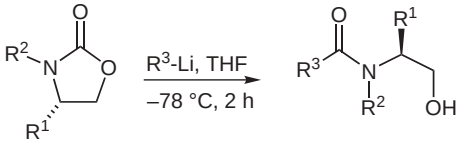
Table 1 Yields of *N*-Alkyl Oxazolidin-2-ones

Entry	R^1	R^2	Yield (%)[a]	$[\alpha]_D^{25}$ (*c* 1, $CHCl_3$)
1	*i*-Pr	Me	96	+40.8
2	Bn	Me	94	+65.1
3	*i*-Pr	Bn	97	–17.0

[a] Refers to crude yield.

Addition reactions were carried out at –78 ºC in THF over 2 hours (Scheme 2, Table 2).[5] It was found that organolithium reagents were essential in all of these reactions and that use of Grignard reagents led to recovered starting material. In all cases compounds were isolated using column chromatography that somewhat reduced the yield due to the polar nature of the functional groups and in most cases, these products existed as a mixture of rotamers, which is consistent with previous observations on similar classes of compounds.[6] Products were isolated in varied yields, with the addition of *n*-BuLi providing the most promising result (entries 2 and 9). In the case of addition of MeLi (Entry 1) the low yield was attributed to

increased water solubility of this product, since a higher yield was obtained for the *N*-benzyl analogue (entry 8). It is important to note that the formation of the amide derived from *N*-methyl imidazole (entries 5 and 12) by classical methods was not possible due to decomposition during the preparation of the imidazole acid chloride.



Scheme 2

Both *t*-BuLi (entries 3 and 10) and 9-lithioanthracene (entries 6 and 13) were essentially unreactive under the conditions described presumably due to their large steric bulk.

Of interest, reaction of *s*-BuLi with either oxazolidin-2-one (entries 7 and 14) gave rise to products with a low, but measurable diastereomeric excess. The diastereomeric ratio in each case was estimated to be approximately 3:2, although a more accurate determination was not possible due to overlapping signals from the individual rotamers of each diastereoisomer in the ^{1}H NMR spectra. Although, separation of the individual diastereoisomers was not possible in these cases, this methodology offers potential for a new approach to the synthesis of enantiomerically enriched α-substituted carboxylate derivatives. This method is particularly attractive since the organolithium reagent rapidly racemises, essentially leading to dynamic kinetic resolution.

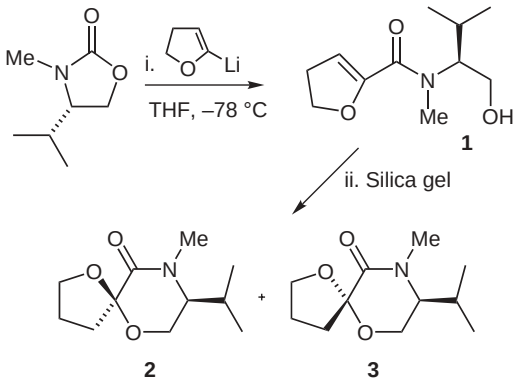
The second reaction of note involved ring opening with 2,3-dihydro-5-furyllithium[7] (entry 15) in an attempt to further demonstrate the use of this methodology in the synthesis of amides that would be otherwise difficult to prepare.

This reaction proceeded well, giving good mass return of the desired ring opened product **1** (Scheme 3). However, the crude reaction product underwent rapid rearrangement on silica gel to a diastereomeric mixture of spiroacetals **2** and **3** (dr, 4:1). The assignment of the major diastereoisomer is arbitrary at this time since the absolute configuration of each spiroacetal has not been determined. The ring

Table 2 Ring Opening Reaction of Oxazolidin-2-ones with Organolithium Reagents

Entry	R^1	R^2	R^3	Yield (%)[a]	Rotameric ratio	$[\alpha]_D^{25}$
1	*i*-Pr	Me	Me	30[d]	1.7:1	–44.8 (*c* 1, $CHCl_3$)
2	*i*-Pr	Me	*n*-Bu	93	1.7:1	–23.1 (*c* 2.5, $CHCl_3$)
3	*i*-Pr	Me	*t*-Bu	0	NA	NA
4	*i*-Pr	Me	Ph	49	1.2:1	–24.8 (*c* 2.6, $CHCl_3$)
5	*i*-Pr	Me	NMI[b]	35	16:1	–46.9 (*c* 1.4, $CHCl_3$)
6	*i*-Pr	Me	ANT[c]	0	NA	NA
7	*i*-Pr	Me	*s*-Bu	60	2.1:1	–25.3 (*c* 0.9, $CHCl_3$)
8	Bn	Me	Me	70[d]	1.4:1	–36.0 (*c* 3.9, $CHCl_3$)
9	Bn	Me	*n*-Bu	82	2.5:1	+3.6 (*c* 2.7, $CHCl_3$)
10	Bn	Me	*t*-Bu	0	NA	NA
11	Bn	Me	Ph	39	1.1:1	–75.4 (*c* 0.4, $CHCl_3$)
12	Bn	Me	NMI[b]	59	NA[e]	–31.8 (*c* 0.3, $CHCl_3$)
13	Bn	Me	ANT[c]	0	NA	NA
14	Bn	Me	*s*-Bu	58	2.5:1	–41.2 (*c* 2.0, $CHCl_3$)
15	*i*-Pr	Me	VF[f]	51[g]	NA[e]	Not determined
16	*i*-Pr	Bn	NMI	70	NA[e]	–12.0 (*c* 1.0, $CHCl_3$)

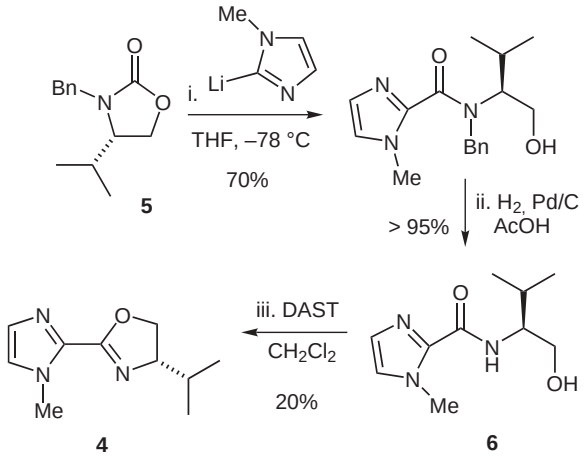
[a] Refers to isolated yield.
[b] 2-*N*-Methyl imidazole.
[c] 9-Anthryl.
[d] 2 equiv of MeLi used.
[e] Only 1 rotamer was observed.
[f] 2,3-Dihydro-5-furyl.
[g] Isolated yield of spiroacetals **2** and **3**.



Scheme 3

opening reaction was repeated and spiroacetal formation confirmed by treatment of the crude reaction product **1** with a catalytic quantity of TFA in CH_2Cl_2 giving an identical mixture of the spiroacetals **2** and **3** in 68% isolated yield. Separation of each of these diastereomeric compounds was not possible at this time.

In order to demonstrate the use of this methodology in the synthesis of an otherwise problematic target, the oxazolinyl imidazole **4** was prepared (Scheme 4). The *N*-benzyl oxazolidinone **5** was ring opened, followed by hydrogenolysis giving the hydroxy-amide **6** in near quantitative yield. Final cyclisation using diethylamino sulfurtrifluoride (DAST)[8] proved to the be the more problematic step only affording the desired oxazoline **4** in 20% isolated yield. Although the yield in the last step was poor, the synthesis of hydroxy amide **6** by more classical methods (e.g. DCC coupling, acid chloride formation) proved problematic and never gave the desired product. The route described provides an effective route to this compound.



Scheme 4

In conclusion an alternative synthesis of *N*-acyl-*N*-alkyl amino alcohols has been described which utilises *N*-alkyl oxazolidin-2-ones and a range of organolithium reagents. This methodology should overcome circumstances where the direct use of regulated amino alcohols is prohibited.

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References

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(4) Analytical samples were prepared by column chromatography and/or recrystallisation. All new compounds reported had satisfactory analytical data that will be reported in full in due course.

(5) **Typical Experimental Procedure:** *n*-BuLi (1.6 M, 0.44 mL, 0.70 mmol) was added to a solution of *N*-methyl 4(*S*)-*iso*-propyl oxazolidin-2-one (0.1 g, 0.70 mmol) at –78 °C. The reaction was warmed to 0 °C and after 2 h quenched with H_2O (2 mL) and extracted with EtOAc (5 × 10 mL). The organic extracts were combined and washed with NH_4Cl (5 mL), dried over $NaSO_4$ and the solvent removed under vacuum to give a pale yellow oil as the crude product (0.157 g) which was purified using flash column chromatography (EtOAc) to give a clear oil (0.131 g, 93%); $[\alpha]_D^{25}$ –23.1 (*c* 2.5, $CHCl_3$); ratio of rotamers A/B = 1.7:1. Rotamer A: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.80 (d, *J* = 6.4 Hz, 3 H, C*H*$_3$CH), 0.86 (t, *J* = 7.3 Hz, 3 H, C*H*$_3$CH$_2$), 0.93 (d, *J* = 6.4 Hz, 3 H, C*H*$_3$CH), 1.29 (m, 2 H, CH$_3$C*H*$_2$), 1.55 (m, 2 H, CH$_3$CH$_2$C*H*$_2$), 1.84 [m, 1 H, (CH$_3$)$_2$C*H*], 2.33 (m, 2 H, CH$_3$CH$_2$CH$_2$C*H*$_2$), 2.84 (s, 3 H, NC*H*$_3$), 3.24 (s, br d, 1 H, O*H*), 3.97–3.42 (range of multiplets, 3 H, HOC*H*$_2$C*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.7 (*C*H$_3$CH), 27.6 [(CH$_3$)CH$_2$*C*H$_2$], 27.7 [(CH$_3$)$_2$*C*H], 34.1 [CH$_3$(CH$_2$)$_2$*C*H$_2$], 61.9 (HO*C*H$_2$), 65.6 (HOCH$_2$*C*H), 175.4 [*C*(O)N]. Rotamer B: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.77 (d, *J* = 6.7 Hz, 3 H, C*H*$_3$CH), 0.85(t, *J* = 7.3 Hz, 3 H, C*H*$_3$CH$_2$), 0.91(d, *J* = 6.4 Hz, 3 H, C*H*$_3$CH), 1.68 [m, 1 H, (CH$_3$)$_2$C*H*], 2.28 (m, 2 H, CH$_3$CH$_2$CH$_2$C*H*$_2$), 2.68 (s, 3 H, NC*H*$_3$), 3.24 (s, br d, 1 H, O*H*), 3.97–3.42 (range of multiplets, 3 H, HOC*H*$_2$C*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0 (*C*H$_3$CH), 26.8 [(CH$_3$)$_2$*C*H], 27.3 (CH$_3$CH$_2$*C*H$_2$), 32.1 (N-*C*H$_3$), 33.4 [CH$_3$(CH$_2$)$_2$*C*H$_2$], 60.8 (HO*C*H$_2$), 63.3 (HOCH$_2$*C*H), 175.1 [*C*(O)N]. MS (EI): *m*/*z* calcd [M$^+$] for $C_{11}H_{23}NO_2$: 201.1729; found: 201.1719. MS (EI): *m*/*z* (%) = 201 (1) [$C_{11}H_{23}NO_2^+$], 183 (2), 170 (1) [$C_{10}H_{20}N^+$], 86 (100), 74 (44).

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