Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 23 Sep 2006.

To cite this article: A. Atmani , A. El Hallaoui , S. El Hajji , M. L. Roumestant & Ph. Viallefont (1991) From Oxazolines to Precursors of Aminoacids, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 21:22, 2383-2390, DOI: 10.1080/00397919108021599

To link to this article: http://dx.doi.org/10.1080/00397919108021599

SYNTHETIC COMMUNICATIONS, 21(22), 2383-2390 (1991)

FROM OXAZOLINES TO PRECURSORS OF AMINOACIDS

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Abstract : After optimization of the reaction conditions, action of nucleophiles on the tosyl derivatives of 4-hydroxymethyl oxazolines 1 and 2 afforded precursors of α and ß aminoacids.

Oxazolines have been used in a great number of synthesis of functionalized organic compounds [1,2,3,4,5,6]. They are precursors of α-aminoacids[4] lactones[4,5] aldehydes[6], ketones[4] orthosubstituted aromatic acids[4,6]. They are inert to largely used reactives in

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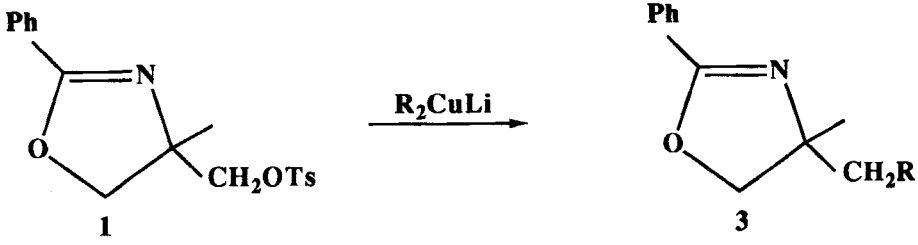
organic synthesis like aluminium lithium hydride[4,5], diisopropylaluminium hydride at low temperature, organomagnesium compounds[2,4,5,6] or organocuprates. They can be manipulated in an acidic (pH = 5,6) as well as in a basic medium[4]. Oxazolines can be prepared via different pathways, among them condensation of aminoalcohols with acids in refluxing toluene or benzene[7] or with imidates[3] in dichloromethane at room temperature.

We report here the first results concerning modification of the lateral chain of oxazolines by action of a nucleophile on the O-tosyl derivatives prepared from 2-phenyl 4-carboxymethyl oxazoline[1,3] and 2-phenyl 4-methyl 4-hydroxymethyl oxazoline[7]. After hydrolysis and oxydation, α-aminoacids can be obtained.

The tosyl derivatives 1 and 2 were classicaly prepared by action of tosyl chloride in pyridine at 0°C in 85% yield. The reactivity of different nucleophiles was studied by controlling several parameters : temperature, solvent, presence of cosolvents. With diorganocuprates which are good nucleophiles[8,9] the best results were obtained with the following reaction conditions :

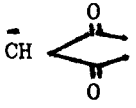
- solvent : Ether + Toluene (cosolvent)
- reaction temperature : - 30° to - 20°C during 15 h
- 4 equivalents of R_2 CuLi



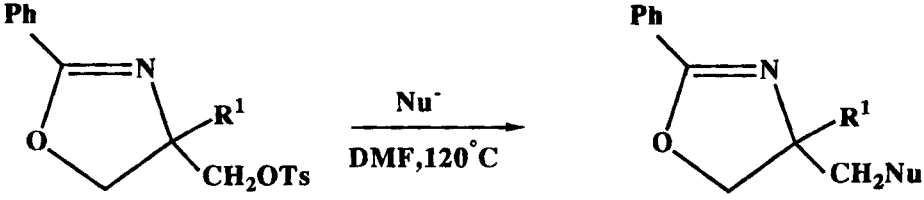
1 3

3a	R = CH_3	Yield : 71%
3b	R = n-Bu	Yield : 76%
3c	R = CH_2-Ph	Yield : 73%

Table I

Product	R^1	Nu^-	Yield %
4a	CH_3	CN^-	60
4b	CH_3	N_3^-	77
4c	CH_3		30
5a	H	CN^-	60
5b	H	N_3^-	65

The reaction of other nucleophiles(CN^-,N_3^-,$CH_3-\overset{\overset{O}{\|}}{C}-CH-\overset{\overset{O}{\|}}{C}-CH_3$) on 1 and 2 was examined. A systematic study showed that these compounds were inactive to CN^- when solvent acetone was used even to reflux. With dimethyl sulfoxyde at room temperature, the starting compounds were recovered, at reflux a complex mixture was obtained. However, when dimethylformamide was used at 120°C the desired products were obtained in satisfactory yields. (Table I).

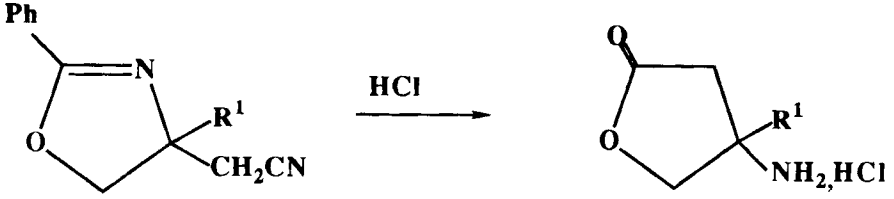


1 $R^1=CH_3$

2 $R^1=H$

4

It is worthnoting that reactions with 1 give only substituted compounds without any trace of dehydro product. Compounds 4a and 5a after hydrolysis with 6N HCl were converted to ß-amino γ-butyrolactones 6 and 7 which are good precursors of ß-amino γ-hydroxy acids. These last compounds can be easily transformed in ß-aminoacids[8] differently substituted in position α to the amino group.



4a $R^1=CH_3$

5a $R^1=H$

6 $R^1=CH_3$

7 $R^1=H$

From compounds 4b and 5b cycloadditions reactions are now under active investigation in order to obtain heterocyclic amino acids.

Experimental

Reagents and solvents were purified in the usual way. Melting points were not corrected. ^1H NMR spectra were recorded on a Varian (60 MHz).

2-phenyl 4-hydroxymethyl oxazoline.

To a suspension of $LiALH_4$ (4,2 mmol) in anhydrous ether (10ml) the ester[3] (4,9 mmole) dissolved in anhydrous ether (30 ml) was added dropwise. The mixture was stirred during 5 H at room temperature. After hydrolysis by ice-water, the organic layer was dried ($MgSO_4$) evaporated and the residue chromatographed over silica gel (eluent : ether/ethanol 9/1).

Yield : (68%) m.p. = 81°C (ether/ethanol 9/1).^{1}H NMR ($CDCl_3$) : 3.33-4 (m,3H); 4.33-4.66 (m,2H); 7.16-8.18 (m,5H).

O-Tosylated derivatives **1** and **2**.

They are prepared by the method described by HARDEGGER[11].

1 : (85%), m.p. = 104°C (ether-chloroform 9/1) ^{1}H NMR (CCl_4): 1.33 s(3H); 2.43 (s,3H); 3.93(s,2H); 4.19 (q, 2H, J = 8Hz); 7.17-8 (m,9H).

2 : (83%) m.p. = 109°C (ether-chloroform 9/1). ^{1}H NMR ($CDCl_3$) : 2.46 (s,3H); 3.93-4.86 (m,5H); 7.23-8.20 (m,9H).

Reaction of diorganocuprates on **2** : Synthesis of **3**.

To a suspension of CuI (20 mmol) in anhydrous ether (40 ml) at 60°C under N_2, the organolithium compound (40 mmol) dissolved in anhydrous ether was added via a syringe. Stirring was continued at this temperature during 30 min. The temperature of the mixture was raised to the desired one and the tosylated compound **2** (5mmol) dissolved in ether-toluene (2/1) (30 ml) was added. The mixture was stirred at this temperature during 15 h and hydrolysed with a saturated solution of ammonium chloride. After decantation, the aqueous layer was extracted with ether (3 x 15 ml), the organic layers were dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The residue was chromatographed on silica gel (eluent : ether-hexane).

3a :(71%) ^{1}H NMR (CCl_4) :0.91 (t,3H, J = 7Hz) ; 1.33 (s,3H); 1.59 (q, 2H, J = 8Hz); 4.1 (q, 2H, J = 2Hz); 7.23-8.16 (m,5H).

3b : (76%) ^{1}H NMR (CCl_4) : 0.66-1.66 (m,11H); 1.33 (s,3H); 3.99 (q, 2H, J = 8Hz); 7.16-8.0(m,5H).

3c :(73%)^{1}H NMR (CCl_4) : 1.33 (s,3H); 2.26 (s,3H); 2.83 (s,2H); 4.06 (q, 2H, J = 8Hz); 7.03 (s,5H); 7.26-8.06 (m,5H).

Action of nucleophiles N_3^- and CN^- on O-tosylated derivatives 1 and 2.

To 1 or 2 (5.8 mmol) dissolved in DMF (60 ml), the nucleophile (2.9 mmol) was added in small portions and under stirring. The mixture was heated to 120°C during 48 h. The solution was evaporated to 30 ml and extracted by ether (3 x 10 ml). The residue was chromatographed on silica gel (eluent: ether-hexane).

4a : (60%) m.p. = 86°C (eluent : ether-hexane 60/40)
$C_{12}H_{12}N_2O$ Calc. C 72.0, H 6.02, N 14.01
found. C 71.96 H 6.02 N 14.10.
^1H NMR (CCl_4) : 1.50(s,3H); 2.50 (s,2H); 4.22 (q,2H, J = 8Hz); 7.26-8.06 (m, 5H).

4b : (77%) (eluent : ether-hexane 30/70).^1H NMR (CCl_4) : 1.40 (s,3H); 3.36 (q, 2H, J=12 Hz) ; 4.18 (q, 2H, J = 8Hz), 7.33-8.20 (m,5H).
M S : m/z = 217 $[M + H]^+$

5a :(60%) m.p. = 71°C (Eluent : ether-hexane 60/40).
$C_{11}H_{10}N_2O$ Calc. C 70.96 H 5.37 N 15.05
Found C 71.22 H 5.35 N 15.01
^1H NMR ($CDCl_3$) : 2.53 (q,2H) ; 4.20-4.66 (m,3H); 7.23-8.10 (m,5H).

5b :(65%) (eluent : ether-hexane 50/50) ^1H NMR (CCl_4) : 3.38(d,2H, J = 6Hz); 4.06-4.53 (m,3H) ; 7.20-8.13 (m,5H).
M S : m/z = 203 $[M + H]^+$

Synthesis of 4c

To absolute ethanol (15 ml) was added sodium (28 mmol) ; after complete dissolution of sodium, acetylacetone (29 mmol) was added

in small portions. After stirring (5 min.) at ambient temperature, the solution was evaporated to dryness and the solid added to compound **1** dissolved in DMF (60 ml). The mixture was heated to 120°C under stirring during 48 h. The solvent was evaporated, the residue extracted by ether. After evaporation of the solvent the crude product was chromatographed on silica gel (eluent : AcOEt/hexane 30/70).

4c : (30%) ^{1}H NMR ($CDCl_3$) : 1.36 (s,3H); 2.33 (s,6H); 2.5 (s,2H); 4.18 (q, 2H, J = 8 Hz); 7.26-8.06 (m,5H).
M S : m/z = 274 $[M + H]^+$

ß-amino ɣ-butyrolactones

To **4a** or **5a** (10 mmol) was added 6N HCl (10 ml), the mixture was refluxed during 1.5h. After cooling to room temperature, benzoic acid was extracted with methylene chloride. The aqueous solution was evaporated under reduced pressure ; the residue was recrystallised in absolute ethanol

6 :(60%) m.p. = 245°C ^{1}H NMR (DMSO-d_6) : 1.63 (s,3H); 3.0 (s,2H); 4.50 (q, 2H, J = 8Hz); 8.16 (m, NH_2).

7 : (68%) m.p. = 180°C $C_{10}H_{12}N_2O$ Calc. C 68.18 H 6.81 N 15.90
Found C 68.45 H 6.77 N 15.93
^{1}H NMR (DMSO-d_6) : 2.5-3.33 (m, 2H); 4.0-4.66 (m,3H) 8.26 (m, NH_2).

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(Received in The Netherlands 10 July, 1991)