

Synthesis of 2 - (Chiral Alkyl) Oxazolines

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ملخص

يتناول البحث التالي استعمال طريقة فوربرغن المحسنة لتحضير ٢ - (كابرال الكيل) أوكسازولين بحلقة فنييل وفضالة حامض أميني . ولقد (فحصت) طرق أخرى لتحضير هذه المادة .

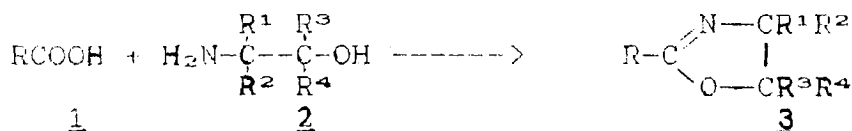
Abstract

A modified Vorbruggen method has been used to prepare 2 - (chiral alkyl) oxazoline with phenyl and aminoacid residue . Other methods of preparation have been tested .

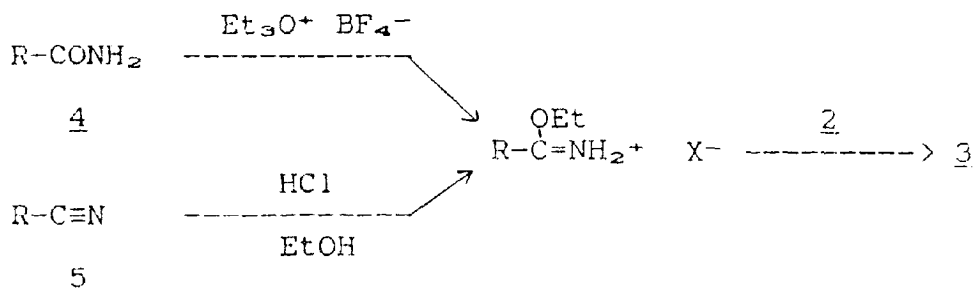
Introduction

Asymmetrical transformation of optically inactive carboxylic acids into optically active forms via oxazolines have been reported ^{1,2} Oxazolines are also used as protecting groups for the carboxylic acid moiety in organic synthesis ^{1,2} , and they can be used as intermediates in the transformation of carboxylic acids or nitriles to other functional groups .

Oxazolines 3 can be prepared by the reaction of carboxylic acids 1 , amides 4 , or nitriles 5 with aminoalcohols 2 by using various methods^{1,2}



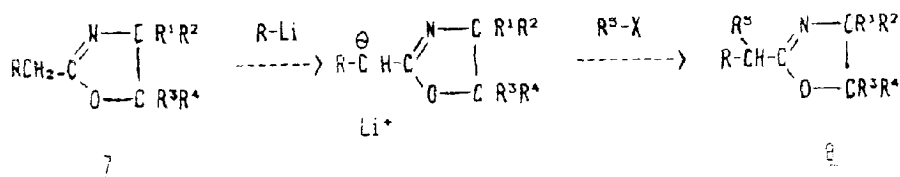
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Recently Vorbruggen described³ a facile synthesis of oxazolines, thiazolines and imidazolines by employing about three equivalents each of triphenylphosphine, triethylamine and excess of carbon tetrachloride in acetonitrile or an acetonitrile – pyridine mixture (1:1) for the condensation of carboxylic acids with aminoalcohols, mercaptoamines or diamines in one pot reaction under mild conditions affording good yields (50–75%).

Meyer et al reported⁴ that, the Vorbruggen method to generate heterocycles is one of a considerable utility which proceeds with high stereochemical control. When optically active aminoalcohols are employed, inversion of configuration takes place. Meanwhile, when diamines or mercaptoamines are used, retention of configuration is observed.

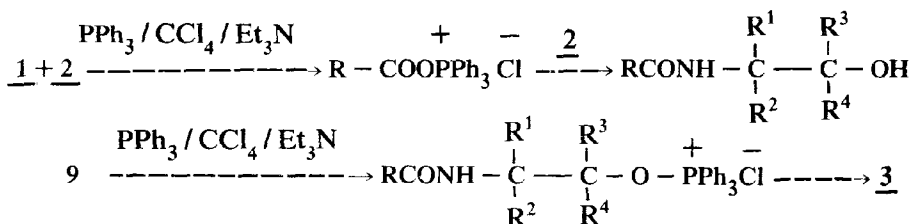
To our knowledge, no chiral carboxylic acids have been used in the Vorbruggen method in order to prepare oxazolines containing 2 – chiral alkyl group 8. Such chiral compounds were prepared by Meyer and others^{1,3,5-8} who used a multistep synthesis involving the metalation of oxazolines 7 with alkyl lithium at – 78°C followed by quenching the lithio oxazolines by the addition of alkyl halides.



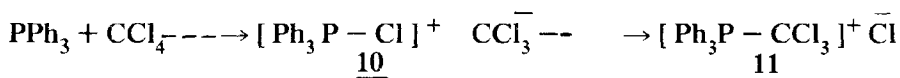
Results and Discussion

The above arguments prompted us to try to modify the Vorbruggen method and to prepare 2 - chiral alkyl oxazolines 8 by the modified method and by the alternative imidate method ⁹ as well . Another objective was to use the modified method to prepare 2 - Z - alanine oxazolines . These oxazolines were prepared in order to use them in asymmetric transformations to resolve chiral carboxylic and amino acids .

The proposed mechanism of the Vorbruggen method needs only two equivalents of each component of the reagent $\text{Ph}_3\text{P}/\text{CCl}_4/\text{Et}_3\text{N}$, which is called as Appel's reagent¹⁰ .



Therefore , the Vorbruggen method is modified by using only 2.5 moles of Ph_3P , and 2.1 moles of each CCl_4 and Et_3N for each mole of carboxylic acid and aminoalcohol in acetonitrile - pyridine mixture (1:1) at room temperature for three days . Good yields were thus obtained . Appel's reagent consists of an excess of 20% of Ph_3P for each mole . This 20% excess of Ph_3P for each mole is needed due to the rearrangement of the reactive intermediate 10 to the more stable trichloro methyl - triphenylphosphonium chloride 11 ,



2 - (1 - Phenylethyl) - 4 , 4 - dimethyl - 2 - oxazoline 12 , 2 - (benzyl) - 4 , 4 - dimethyl - 2 - oxazoline 13¹¹ , 2 - (1 - benzyloxy carbonyl aminoethyl) - 4 , 4 - dimethyl - 2 - oxazoline 14 , and 2 - (1 - phenyl ethyl) benzoxazol 15 were prepared using this modification in good yield (> 75 %) . Compound 14 was prepared by this method , as a model for amino acid oxazoline . This preparation is easier than the multistep imidate synthesis⁹ in which the amino

Experimental

IR Spectra were recorded using a Perkin – Elmer IR 299 . NMR spectra were obtained by using a Jeol JNM — MHz– 100 and Bruker WM – 250 spectrometer . δ –Scale with tetramethylsilane as internal reference . Melting points are uncorrected .

Preparation of oxazolines :

1) General procedure for oxazoline's preparation from carboxylic acid (using PPh₃/CCl₄/Et₃N and aminoalcohol) :

In 100 ml of an acetonitrile – pyridine solution (1 : 1) at r . t . 0.25 mole of Ph₃P and 0.22 mole of Et₃N were added with stirring , followed by dropwise addition of 0.22 mole CCl₄ during a period of 30 min with good stirring . A white precipitate was formed , then the reaction mixture was stirred at r . t . for 3 days , filtered and the filtrate was evaporated to give an oil together with some solid residue . The residue was extracted with 3x50 ml n-hexane after boiling for 30 min . The n-hexane was evaporated , to give a viscous oil .

2 – (1 – Phenylethyl) – 4,4 – dimethyl – 2 – oxazoline 12 :

This compound was prepared from 2 – phenylpropionic acid and 2 – amino – 2 – methyl – 1 – propanol , yield 81 % ; H-NMR (CDCl₃) : δ = 1.30 (6H , s , CH₃-C) , 1.53 (3H , d , J = 7Hz , CH₃ – CH) , 3.72 (1H , m , CH₃CH) , 3.88 (2H , s , –CH–) and 7.31 (5H , m , C₆H₅) .

IR (CH₂Cl₂) ; 1650 cm⁻¹ (C = N) .

C₁₃H₁₆NO (202 . 3) calc . C = 77.20 , H = 7.97 , N = 6.92

found C = 77.31 , H = 7.92 , N = 6.88

2 – (Benzyl) – 4 , 4 – dimethyl – 2 – oxazoline 13 :

This compound was prepared from phenylactic acid and 2 – amino – 2 – methyl – 1 – propanol , yield . 86 % (lit . ¹¹) . 69 % and bp =155 – 160°C / 15mm) .

2 - (1 - Benzyloxycarbonylaminoethyl) -4 , 4- dimethyl -2-oxazoline 14

This compound was prepared from N - (benzyloxycarbonyl) alanine and 2 - amino - 2 - methyl - 1 - propanol) yield 83 % , H - NMR (CDCl₃) : δ = 1.31 (6H,s, (CH₃)₂ - C) ; 1.41 (3H , d , J = 7Hz, CH₃ - CH) , 3.89 (2H , s , - CH -) , 4.12 (1H , q , H = 7Hz , CH - CH₃) , 5.11 (2H , s , CH₂ - Ph) , 5.8 (1H , bd , NH) and 7.3 (5H , s , C₆H₅-) .
IR (Nujol) : 1670 cm⁻¹ (C = N) .

C₁₅H₂₀NO (230.3) calc . C = 78.22 , H = 8.75 , N = 6.08
found C = 78.33 , H = 8.78 , N = 6.15

2 - (1 - phenylethyl) benzoxazole 15 :

This compound was prepared from 2 - phenyl propionic acid and o - aminophenol , yield 76% .

H - NMR (CDCl₃) : δ = 1.84 (3H , d , J = 7Hz , CH₃ - CH -) , 4.41 (7H , q , J = 7Hz) , 7.28 (4H , m , C₆H₄) .

C₁₅H₁₂NO (222.3) calc . C = 81.06 , H = 5.44 , N = 6.30
found C = 81.16 , H = 5.44 , N = 6.33

2) From nitrile by using imidate method :

a) Preparation of ethyl - 2 - phenyl propioimidate hydrochloride 17 . Dry hydrochloric acid was passed through a cold stirred solution of 0.1 mole 2 - phenyl propionitrile 16 dissolved in absolute ethanol for a period until about 0.15 mole of HCl was dissolved .

The viscous solution was stoppered and kept in the refrigerator for 4 days . Then a 100 ml absolute ether was added , a colourless (white) precipitate was formed upon stirring , filtered and dried under nitrogen , yield 95 % , m.p. = 103 - 105 °C . IR (CH₂Cl₂) : 1645 cm⁻¹ (C = N) and 3200 cm⁻¹ (bd , NH) .

C₁₁H₁₆ClNO (213.7) calc . C = 61.83 , H = 7.55 , N = 6.88
found C = 61.88 , H = 7.53 , N = 6.86

b) A solution of 50 mmol of 17 and 50 mmol of aminoethanol in 50 ml. dichloromethane was refluxed for 3 hours . The starting material nitrile 16

was collected after evaporation of solvent and distillation of the residue .
The nitrile 16 was characterized by its boiling point (b . p.93 °C), and IR (2235 cm^{-1}).

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