



Regio- and stereochemical aspects in the functionalisation of a lithiated 2-(3-chloro-2-methyl-1-propenyl)-2-oxazoline: electrophile and temperature effects

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ARTICLE INFO

Article history:

Received 26 May 2015

Received in revised form 5 June 2015

Accepted 9 June 2015

Available online 19 June 2015

This paper is gratefully dedicated to the memory of Professor Alan Roy Katritzky

Keywords:

Allyl carbanion
Organolithiums
Stereoselectivity
Heterocycles
DFT calculations

ABSTRACT

4,4-Dimethyl-2-(3-chloro-2-methyl-1-propenyl)-2-oxazoline has been synthesized and deprotonated with LDA in THF to give the corresponding lithiated species, which has been found to react α -regioselectively with NH_4Cl and alkyl halides, and γ -regioselectively with carbonyl compounds to afford α -protonated (or α -alkyl-substituted) regioisomers and vinyl epoxides, respectively. The *Z* diastereoselectivity of both the protonation and the alkylation reactions was usually found to increase with the temperature. *Ab initio* calculations, performed on both the naked lithium salt and the corresponding solvated form, support the observed regioselectivity.

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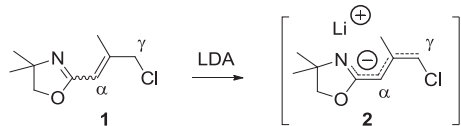
1. Introduction

Allyl carbanions, which are more stable than alkane anions for resonance reasons, are of considerable synthetic interest due to their ambident nucleophilic nature, and considerable efforts have been devoted to control the regiochemistry (α - or γ -) of their coupling reactions with electrophiles. Even more stable are heterosubstituted allyl carbanions due to the stabilising contribution of the heterosubstituent. Extensive work has been carried out in particular on the latter including a number of O-, N-, S-, P- and Si-linked derivatives,¹ the sulphur- and phosphorus-stabilised allyl anions being the most important from the synthetic point of view. Halogenoallyl carbanions have been studied much less² and found only limited synthetic application mainly due to their bias to

undergo 'homocoupling' reactions.³ Moreover, steric effects,⁴ electron density, solvation,⁵ reaction temperature, nature of the electrophile⁶ and the counterion,⁷ beside their potential 'carbenoidic' nature,⁸ proved to influence very much the regio- and stereoselectivity of their reactions.

Some years ago we reported the lithiation of *trans*-cinnamyl-^{9a} and 2-benzothiazolylallyl chloride^{9b} and the reactions of the resulting lithiated species with electrophiles. These chloroallyllithiums were found to react with non-enolizable ketones and aromatic aldehydes at the CCl terminus exclusively to give styryl epoxides and benzothiazolylvinyl oxiranes. The interesting outcome of that work has encouraged us to study the lithiation of 2-(3-chloro-2-methyl-1-propenyl)-2-oxazoline **1** and the regio-¹ and stereoselectivity of the coupling reactions of the resulting vinyl-ogous 1-azaenolate **2** with electrophiles (Scheme 1). The multi-dentate nature of such an anion, with the possibility of obtaining α - and/or γ -adducts with *Z* and/or *E* geometry around the C–C double bond, sounded appealing to us. We also considered that an investigation of the stereo- and regioselectivity of the reactions of **2**

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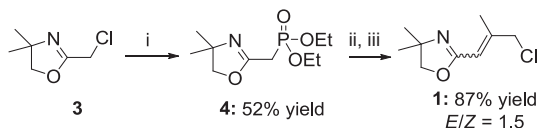
Scheme 1. Deprotonation of 2-(3-chloro-2-methyl-1-propenyl)-2-oxazoline **1** to give organolithium **2**.

with electrophiles, with special reference to the temperature influence, was of interest.

With reference to this last point, it might be useful to stress that the temperature effect on the stereoselectivity of a given process is often not uniform: the stereoselectivity may decrease upon increasing the reaction temperature but it may also be constant or even increase. The temperature effect on the diastereoselectivity of the addition of nucleophiles to carbonyl compounds and derivatives has been extensively studied by Cainelli.¹⁰ As part of our program aimed at elucidating the stereochemical behaviour of chiral functionalised organolithiums with temperature,¹¹ we started an investigation on the regioselectivity of coupling reactions of organolithium **2** with alkyl halides and carbonyl compounds.

2. Results and discussion

2-(3-Chloro-2-methyl-1-propenyl)-2-oxazoline **1** was prepared in a good yield starting from 2-chloromethyl-2-oxazoline **3**. The latter was treated with (EtO)₃P (Arbuzov's reaction) to furnish the phosphonate **4**,^{12a} which was subsequently deprotonated with *s*-BuLi in THF at -78 °C, and finally coupled with chloroacetone (the Horner–Wadsworth–Emmons olefination)^{12b} (Scheme 2). The *E* and *Z* isomers of **1** were separated by preparative HPLC and fully characterised.¹³



Scheme 2. Synthesis of 2-(3-chloro-2-methyl-1-propenyl)-2-oxazoline **1**. Reagents and conditions: (i) P(OEt)₃, 140 °C, 22 h (ii) *s*-BuLi, -78 °C, THF (iii) chloroacetone.

With the chloroallyloxazoline **1** in hand, we first studied its deprotonation-reprotonation sequence. Deprotonation of a diastereomeric mixture of **1** (*E/Z*=1.5) with LDA at -98 °C in THF, followed by quenching (20 min) at the same temperature with satd aq NH₄Cl, afforded a mixture of two α regioisomers **5**¹³ (*Z/E*=55/45) (entry 1, Table 1) suggesting that at low temperature the reaction proceeds with complete α -regioselectivity and no or extremely poor diastereoselectivity.

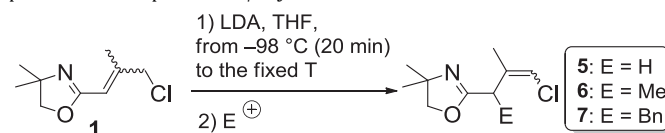
The lithio derivative **2** is quite stable and can be kept even for hours at room temperature but, like other allyllithiums,¹⁴ tends to undergo homocoupling in the presence of its precursor **1**. Indeed, when chloroallyloxazoline **1** was treated with 0.6 equiv of LDA, the reaction resulted in the formation of a mixture of four stereoisomers **8a–d** (56% overall yield) separable by column chromatography on silica gel in two fractions (**8a+8b/8c+8d**=40/60) (see Experimental Section) (Scheme 3). Moreover, isomers **8c** and **8d** could be further separated by preparative HPLC.

All these homocoupling products, which were fully characterized by NMR spectroscopy,¹³ derived from the α attack of the anion **2** on the γ position of the substrate **1** (*Z* + *E*) (junction α - γ' , Scheme 3).

Subsequently, in order to study the temperature effect on the stereocontrol of the deprotonation-reprotonation sequence, the anion **2** was generated at -98 °C starting from the isolated isomers (*E*)-**1** and (*Z*)-**1** and the trapping with NH₄Cl performed at temperatures ranging from -98 to $+20$ °C. The *Z/E* ratio of **5** was

Table 1

Influence of the temperature on the stereoselectivity of the deprotonation/reprotonation or deprotonation/alkylation of **1**



Entry	Substrate	E ⁺	T (°C)	Z/E 5–7 ^a
1	(<i>E</i> + <i>Z</i>)- 1 ^b	NH ₄ Cl	-98	5 : 55/45 ^c
2	(<i>E</i>)- 1	"	-98	5 : 85/15 ^c
3	"	"	-20	5 : 85/15 ^c
4	"	"	0	5 : 93/7 ^c
5	"	"	20	5 : 95/5 ^c
6	(<i>Z</i>)- 1	"	-98	5 : 9/91 ^c
7	"	"	-20	5 : 30/70 ^c
8	"	"	0	5 : 90/10 ^c
9	"	"	20	5 : 98/2 ^c
10	(<i>E</i>)- 1	Mel	-98	6 : 92/8 ^d
11	"	"	-20	6 : 94/6 ^d
12	"	"	0	6 : 97/3 ^d
13	"	"	20	6 : 98/2 ^d
14	(<i>Z</i>)- 1	"	-98	6 : 10/90 ^d
15	"	"	-20	6 : 30/70 ^d
16	"	"	0	6 : 87/13 ^d
17	"	"	20	6 : 97/3 ^d
18	(<i>E</i>)- 1	BnBr	-98	7 : 86/14 ^e
19	"	"	-20	7 : 96/4 ^e
20	"	"	0	7 : 91/9 ^e
21	"	"	20	7 : 70/30 ^e
22	(<i>Z</i>)- 1	"	-98	7 : 11/89 ^e
23	"	"	-20	7 : 58/42 ^e
24	"	"	0	7 : 90/10 ^e
25	"	"	20	7 : 95/5 ^e

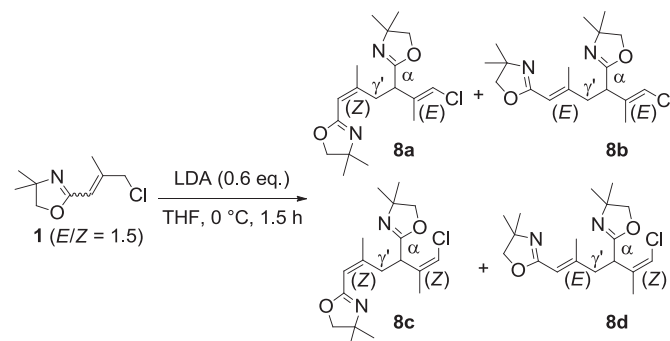
^a The *Z/E* ratio was determined by ¹H NMR analysis on the crude reaction mixture.

^b *Z/E* ratio=1.5.

^c Overall yields ranging from 64 to 95% (entry 9).

^d Overall yields ranging from 62 to 90% (entry 13).

^e Overall yields ranging from 22 to 70% (entry 25).



Scheme 3. Homocoupling products **8a–d** formed subjecting **1** to lithiation with 0.6 equiv of LDA.

measured by ¹H NMR analysis on the crude reaction mixture. These values are reported in Table 1.

From the data of Table 1, it is apparent that the diastereoselectivity of the deprotonation-reprotonation process carried out on either (*Z*)-**1** or (*E*)-**1** varies with the temperature: it increases with the temperature to become almost completely *Z* diastereoselective at 20 °C regardless of the *Z* or *E* geometry of the starting substrate **1** (entries 2–9, Table 1).

It is worth noting, in particular, that the treatment of (*Z*)-**1** with LDA leads to a very quick inversion of the diastereoselectivity even at -98 °C, with (*E*)-**5** being the most abundant isomer isolated at this temperature (ratio *Z/E*=9/91; entry 6, Table 1). This result can be rationalized assuming that the deprotonation reaction promoted by LDA takes place in a two-step process, the first one being the formation of the prelithiation complex **9**, which brings the reactive

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