Tetrahedron Letters, Vol. 33, No. 8, pp. 1117-1120, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press plc

Bifunctional Chiral Auxiliaries 4: Alkylation of Enolates Derived from 1,3-Diacyl-*trans*-4,5-tetramethyleneimidazolidin-2-ones[1]

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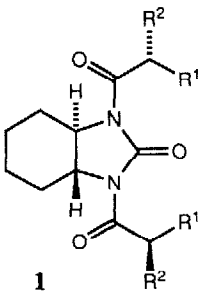
Abstract: Addition of alkyl halides to sodium and potassium enolates of 1,3-diacyl-*trans*-4,5-tetramethyleneimidazolidin-2-ones allows diastereoselective alkylation of both acyl sidechains with the latter enolates showing generally higher stereoselectivities. S-(-)-3-Phenyl-2-methylpropan-1-ol **6** was prepared in this way with a 93% enantiomeric excess.

The diastereoselective alkylation of chiral enolates is a powerful synthetic method which has been widely employed in natural product synthesis[2]. Typically such asymmetric alkylations are highly stereoregular, occurring *via* a specific enolate geometry and conformation and consequently, starting from an acetyl group, the configuration of the newly-formed stereogenic centre is determined by the order in which the substituents are introduced[3]. Evans has reported that lithium and sodium enolates of N-acyl oxazolidones undergo highly stereoselective alkylation reactions with the more reactive alkyl halides (methyl iodide, benzyl bromide, allyl bromide, etc.)[4]. We have already reported aldol reactions in which dibutylboron enolates derived from 1,3-diacylimidazolidin-2-ones reproduce the transition states of the corresponding N-acyl oxazolidone enolates so as to allow the stereoselective elaboration of both acyl sidechains[1,5]. In this communication we report the stereoselective alkylation of these bifunctional chiral auxiliaries *via* their sodium and potassium enolates.

As alkylation of both acyl sidechains may generate two new stereogenic centres, it might be expected that four possible diastereoisomers of the dialkylated product could, in theory, be formed. In fact, there are only three diastereoisomers (**1**-**3**) of this dialkylated material, two of which (**1** and **3**) have a C_2 symmetry element and one (**2**) which does not.



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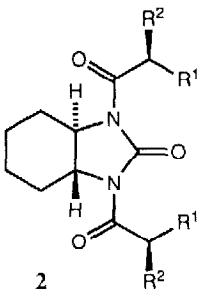

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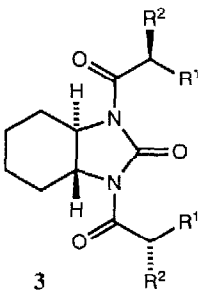

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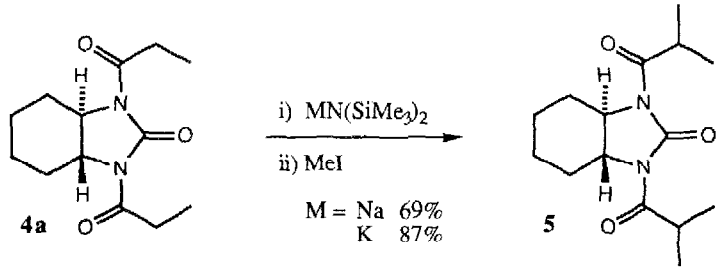
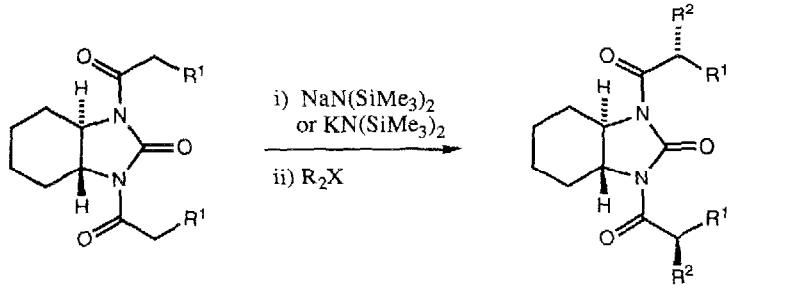
This phenomenon has been reported in a related system by Seebach during a synthesis of (+)-11,11'-di-O-methylelaiophylidene, in which the low stereoselectivity of the reaction ensured that the non-C_2 symmetric diastereoisomer was formed as the major product (as expected from a statistical product distribution)[6].

Simple acyl derivatives of *trans*-4,5-tetramethyleneimidazolidin-2-one are readily prepared in both racemic and homochiral form[7]. Thus, treatment of a THF solution of 1,3-dipropionyl-*trans*-4,5-tetramethyleneimidazolidin-2-one **4a** at -78°C with sodium bis(trimethylsilyl)amide (3eq) followed by addition of methyl iodide and further stirring at -78°C for 3 h, gave **5** in 69%, after work-up and chromatography. The reaction was repeated, using potassium bis(trimethylsilyl)amide which gave **5** in 87% yield under identical reaction conditions.



Whilst methylation of the butanoyl (**4b**) and hydrocinnamoyl (**4c**) derivatives of *trans*-4,5-tetramethyleneimidazolidine-2-one occurred cleanly at -78°C, repetition of these conditions would not allow alkylation with either allyl bromide or benzyl bromide. However, by allowing the reaction to warm to -30°C after addition of the alkyl halide, clean dialkylation could be achieved in good chemical yield.

In those cases where all three diastereoisomers could be detected, the distribution of these three diastereoisomers suggested that both alkylation steps proceeded with the same diastereoselectivity. If it is assumed that the selectivity of one of these alkylation steps is x:1, the expected ratio of **1**:**2**:**3** should be x^2:2x:1. Thus, x may be calculated from the ratio of **1**:**2** as this ratio is equivalent to x/2.



R^1 = CH_3 **4a**; CH_2CH_3 **4b**; CH_2Ph **4c**

R^1	R^2	
CH_3	C_3H_5	**a**
CH_3	CH_2Ph	**b**
CH_2CH_3	CH_2Ph	**c**
CH_2CH_3	CH_3	**d**
CH_2Ph	CH_3	**e**
CH_3	CH_2CH_3	**f**
CH_2Ph	CH_2CH_3	**g**

Table 1: Alkylation Reactions of Sodium Enolates

S. Material	R_1	R_2X	Product	1 : 2 : 3*	Selectivity#	Yield
4a	Me	BnBr	**a**	67 : 30 : 3	82 : 18	77%
4a	Me	C_3H_5Br	**b**	73 : 25 :(2)	85 : 15	52%
4b	Et	BnBr	**c**	84 : 15 :(1)	92 : 8	72%
4b	Et	MeI	**d**	64 : 32 : 4	80 : 20	59%
4c	CH_2Ph	MeI	**e**	81 : 18 :(1)	90 : 10	81%

* Values in parantheses are calculated assuming the same stereoselectivity for each alkylation step
\# Calculated from the ratio of **1** to **2**

The stereoregularity of these reactions should also be noted; thus, the third diastereoisomer formed in the methylation of **4b** is the major product in the ethylation of **4a**. Because of this stereoregularity, the assignment of product stereochemistry was made by analogy with the alkylation of N-acyl oxazolidones. Unambiguous assignment of this stereochemistry was later achieved with the asymmetric synthesis of **(S)-6** (*vide infra*).

It is clear that the level of diastereoselection in these reactions is lower than is observed in the analogous reactions of N-acyl oxazolidones: This may result from the higher temperatures required for reaction.

It was felt that a more reactive enolate might show higher stereoselectivity due to the reaction occurring at lower temperature and consequently the series of reactions was repeated using potassium bis(trimethylsilyl)amide. It was found that both allylation and benzylation occurred readily at -78°C with dramatically enhanced diastereoselectivities. Furthermore, alkylation with ethyl iodide was now possible although it required the reaction to be warmed to -30°C before being quenched and worked-up in the normal manner.

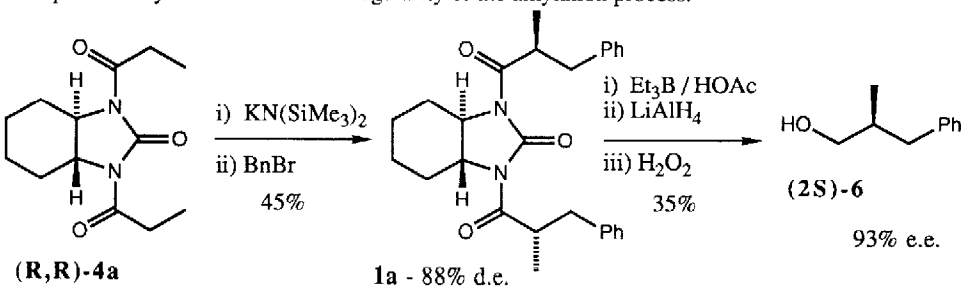
Table 2: Alkylation Reactions of Potassium Enolates

S. Material	R_1	R_2X	Product	1 : 2 : 3*	Selectivity#	Yield
4a	Me	BnBr	**a**	94 : 5 :(1)	97 : 3	72%
4a	Me	C_3H_5Br	**b**	>96 : <3 :(0)	>98 : 2	81%
4b	Et	MeI	**d**	76 : 22 :(2)	88 : 12	66%
4c	CH_2Ph	MeI	**e**	85 : 14 :(1)	92 : 8	72%
4a	Me	EtI	**f**	85 : 14 :(1)	92 : 8	64%
4c	CH_2Ph	EtI	**g**	76 : 22 :(2)	88 : 12	71%

* Values in parantheses are calculated assuming the same stereoselectivity for each alkylation step
\# Calculated from the ratio of **1** to **2**

To confirm the assignment of stereochemistry of the products of these reactions, the potassium enolate derived from **(R,R)-4a** was quenched with benzyl bromide in the manner already described to give a 94:5:(1) mixture of the diastereoisomers **1a**, **2a** and **3a**, consistent with a facial selectivity of 97:3. This mixture of dialkylated products was treated with lithium aluminum hydride at -20°C to give 3-phenyl-2-methylpropan-1-ol **6** as a colourless oil, after work-up and chromatography. The specific rotation of this material was found to be $[\alpha]_D^{20}$ -10.2 (c 1.1, benzene) corresponding to an enantiomeric excess of 93% based on the literature value of $[\alpha]_D^{20}$ +11.0 (c 1.1, benzene) for the homochiral R enantiomer[4,8]. Thus, reductive cleavage proceeds without

detectable epimerisation, as the 94:5:(1) mixture of diastereoisomers should give a product with an enantiomeric excess of 94%, and confirms the configuration of **1a**. This is as expected after consideration of the results obtained with N-acyl oxazolidones and allows assignment of the relative stereochemistries within all the dialkylated products by virtue of the stereoregularity of the alkylation process.



It is proposed that the transition state models for these alkylation reactions parallel those previously described for the analogous reactions of N-acyl oxazolidone enolates[4]. Thus, the sense of asymmetric induction is consistent with the reaction occurring *via* a *syn* enolate which is conformationally restrained by chelation between the enolate counterion and the imidazolidin-2-one carbonyl group. Of the two possible approach trajectories which an electrophile may adopt, one is sterically hindered by the cyclohexyl methylene group and reaction occurs predominantly on the face of the enolate *exo* to this group. The reduced diastereoselection observed with methyl and ethyl iodide may then be ascribed to the small size of these electrophiles which makes them less sensitive to this differential shielding of the two faces of the enolate.

The greater stereoselectivities shown by potassium enolates may be rationalised by the greater reactivity of these species which allows alkylation to occur at lower temperature, where the enolate is more conformationally restricted by chelation. For the corresponding sodium enolates, which are somewhat less reactive, alkylation requires higher temperatures and reaction may occur *via* both the chelated *syn* and open *anti* enolates, causing a marked reduction in the stereoselectivity of alkylation.

Acknowledgements. We thank BP International, Sunbury for a Research Studentship (to AAM) and a Venture Research Award.

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(Received in UK 9 December 1991)