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Efficient Synthesis of 3-Substituted Lactams Using Meerwein Eschenmoser Claisen [3,3] Sigmatropic Rearrangements.

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Abstract: 3-Allyl substituted five, six ,and seven membered ring lactams are readily available in good yields and reasonable selectivity by a formal Meerwein Eschenmoser Claisen [3,3] rearrangement, using the readily available N,N-dialkylalkoxymethylene iminium salts and lithium alkoxides derived from allyl alcohols

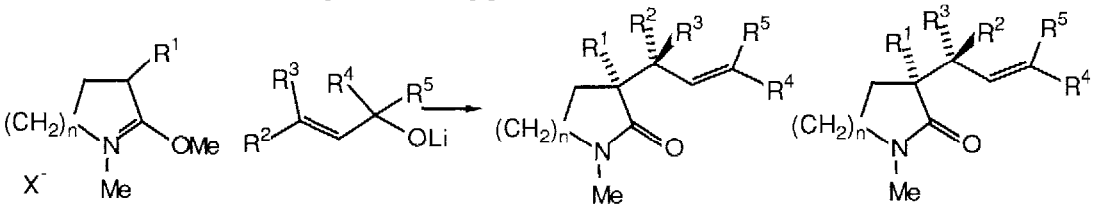
The stereoselective formation of new carbon carbon bonds β to a nitrogen atom is a process that is fundamental in alkaloid synthesis. To date Diels Alder reactions of acrylamides[1], alkylation of enamines[2] and anions derived from amides[3] and imides[4] have been the most popular methods for achieving this transformation. The Meerwein Eschenmoser Claisen rearrangement (**1**→**2**)[5] has also been used to a limited extent in acyclic systems but has the disadvantage that the starting ketene-N,O-acetals are difficult to obtain in all but the simplest of cases and to date it has not been possible to use endocyclic ketene-N,O acetals for these rearrangements. One example has recently appeared where exocyclic ketene-N,O-acetals have been rearranged with ring expansion to seven membered ring lactams[6].

(1) (2)

Recently Walsh[7] reported that formal Meerwein Eschenmoser Claisen rearrangements could be effected simply by treating N,N-diakylalkoxymethylene iminium salts with allyl lithium alkoxides at room temperature in THF as solvent. We now report that this chemistry can be extended to include cyclic substrates and the stereoselectivity of new carbon carbon bond formation ranges from poor to good, **Table1**.

The N,N-diakylalkoxymethylene iminium salts (**3**) are readily available by treating tertiary amides or imino ethers with either methyl triflate or dimethyl sulphate[8]. Treatment of the salts (**3**) with lithium allyl alkoxides (**4**) in boiling THF gave the substituted lactams (**5**) in good to excellent yield, **Scheme1**. The reaction is tolerant to secondary and even tertiary lithium alkoxides (enteries **e** and **d Table 1**), works well for ring sizes ranging from five to seven and is capable of producing quarternary chiral centres stereoselectively (enteries **c, h** and **k Table1**). In all cases small amounts (5 -20%) of the unsubstituted N-methyl lactam was formed as a by

product but this was easily separated using flash chromatography. When substituents are placed on the end of the double bonds then two new chiral centres are produced. In the case of (**3**, n=1) reacting with crotyl alkoxide the sterochemistry of the major product is consistent with the reaction proceeding by a chair like transition state. It is well known that in acyclic case the preferred transition state for [3,3] sigmatropic rearrangements are chair like[9]. However, when one or more of the double bonds is incorporated into a ring other factors come into play and the reaction can either proceed via a chair or boat transition state. Hence, Lythgoe[10] reported that the ketene acetal (**6**) rearranges via a boat transition state to give (**7**) as the major diastereoisomer. It appears that simply changing a oxygen atom in the ring for a nitrogen atom is enough to reverse the diastereoselectivity of this reaction. In the case of (**3**, n=2) reacting with crotyl alkoxide the steroselectivity of the rearrangement appears to be poor. Stopping the reaction after 10% consumption of starting material showed an isomer ratio of 10:1 (**5gA**):(**5gB**), which progressively got worse as the reaction proceeded. In the case of (**5h**) when there was no hydrogen on the chiral centre after rearrangement the stereoselectivity of the rearrangement was good confirming that epimerisation under the reaction conditions is a problem in the piperidinone series.



(3) (4) (5A) (5B)

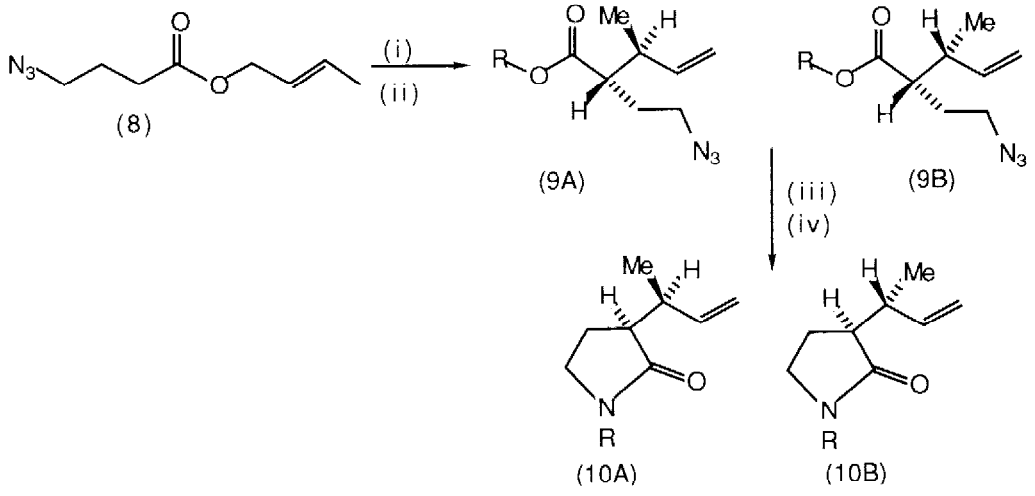
Scheme 1

Table 1

5	n	R^1	R^2	R^3	R^4	R^5	Ratio A:B	Time (hr)	Yield (%)
a	1	H	H	H	H	H	-	12	65
b	1	H	Me	H	H	H	5.5:1	12	64
c	1	Allyl	Me	H	H	H	6:1	12	85
d	1	H	H	H	Me	Me	-	12	68
e	1	H	H	Et	H	Me	1:5	12	64
f	2	H	H	H	H	H	-	12	83
g	2	H	Me	H	H	H	1:1	12	71
h	2	Allyl	Me	H	H	H	5:1	24	84
i	3	H	H	H	H	H	-	12	78
j	3	H	Me	H	H	H	5:1	12	63
k	3	Ally	Me	H	H	H	5:1	12	78
l	3	H	Ph	H	H	H	4:1	12	61

(6) (7)

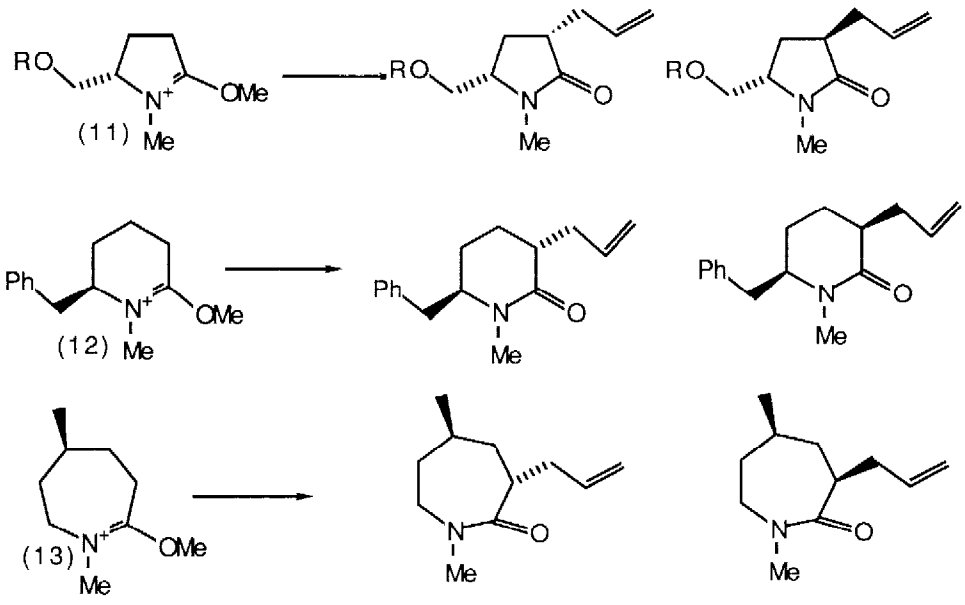
The relative stereochemistry of (**5A**) and (**5B**) was assigned by synthesising authentic samples, **Scheme2**. It is well documented that Ireland Claisen rearrangements in acyclic systems of E-silyl ketene acetals and E-alkenes proceed via chair like transition states to give erythro isomers as the main product[10]. Hence Ireland Claisen rearrangement of (**8**) (under conditions which are known to give the E-enolate) give a 3:1 mixture of diasteroisomers (**9A**, R=H) and (**9B**, R=H). This rearrangement itself is worthy of comment. It is well known that ester enolates react with with azides to give triazolinones[11]. However this reaction proceeded cleanly without giving any of that side reaction and is the first example of an Ireland Claisen rearrangement proceeding in the presence of azide functionality. Esterification using Shaw's procedure[12] give the methyl esters (**9A,B,** R=Me, 3:1) without any epimerisation. Reduction of the azide with triphenyl phosphine and water[13] give an amino ester (not isolated) which cyclised when heated in THF at 60°C for two hours to give the lactams (**10A**, R=H) and (**10B**, R=H) agin in a 3:1 ratio. Finally N-methylation gave authentic samples of (**5B**) and (**5A**). Since the major lactams derived from the unambiguous synthesis and that derived from the Meerwein Eschenmoser Claisen rearrangement are different the transition states for the two rearrangements must be the same since the ketene acetals for the two cases are of opposite configuration.



Reagents: (i) LDA, trimethylsilyl chloride, THF -80 - 60°C, (ii) Sodium hydroxide, methyl iodide, DMSO 25°C overnight, (iii) triphenylphosphine, water, THF 25°C one day then 2hr 60°C; (iv) NaH, MeI, DMF 25°C 1 day.

Scheme2

When additional substituents are present on the ring of the salt the stereoselectivity of new carbon carbon bond formation is good for 5-substituted pyrollidones (**11**, R=Me) where a *trans:cis* ratio of 4.4:1 was obtained. However for the 6-substituted piperidinone salt (**12**) and the 5-methyl-2-azacycloheptanone salt (**13**) the sclectivity was of new carbon carbon bond formation was poor, (56:44 and 53:47 *trans:cis* respectively, **Scheme3**). Again it is suspected that epimerisation under the reaction conditons is a problem with the substituted piperidone



Scheme3

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