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Reaction of the Lithio-derivative of Methoxy allene with SAMP-Hydrazones : Access to Enantiopure 3-Pyrrolines

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Abstract : α-Lithio methoxy allene reacts with SAMP-hydrazones to give α-allenyl hydrazines **5** or 3-methoxy-3-pyrrolines **6** depending on the nature of the solvent. Both compounds have been obtained with d.e. ≥ 99 %. Hydrogenolysis of the N-N bond of **6** affords the pyrroline **7** in enantiopure form.
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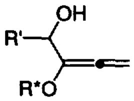
There is still continued interest in the development of new and efficient methods for synthesising nitrogen heterocycles which form important structural motifs in many biologically active molecules. However, few synthetically useful routes exist to functionalised 3-pyrrolines,[1] which are potentially interesting building blocks for the multi-step preparation of more complex molecules.

We have recently shown that the lithio derivative of enantiopure alkoxy allenes **1** react with aldehydes to give, in good yield, α-allenic alcohols **2,** with diastereoselectivities up to 85%.[2] These alcohols may be converted, without racemisation, to α-hydroxyenones **3**, the usefulness of which has been illustrated by synthesis of the cytotoxic styryllactone, (+)-goniodiol **4**.[3]

1



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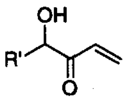

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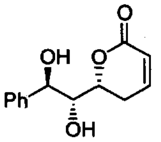

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R* = Chiral group

As a part of a program aimed at developing new applications for alkoxy allenes, the amination of their lithio derivatives has also been studied. However, results with electrophiles such as silyl imines have been disappointing due to the instability of these compounds and/or condensation products under the reaction conditions. Attention was then focussed on hydrazones, which have been used extensively in the last decade as reagents for electrophilic amination, mainly in enantioselective syntheses.[4]

The lithio derivative of methoxy allene was reacted with the SAMP-hydrazone of benzaldehyde. This electrophile was reported by Enders *et al.*[4b] to give a high degree of stereodifferentiation during the amination of organometallic reagents. When 6 equivalents of the allenic organometallic reagent were used and the reaction was carried out **in diethyl ether** (-78°C, for 2h then –20°C overnight), hydrazine **5a** was obtained as a single diastereomer[5, 6, 7] in 85% yield. If fewer equivalents of the organometallic reagent were employed, then the starting hydrazone was not entirely consumed regardless of the reaction time.[8]

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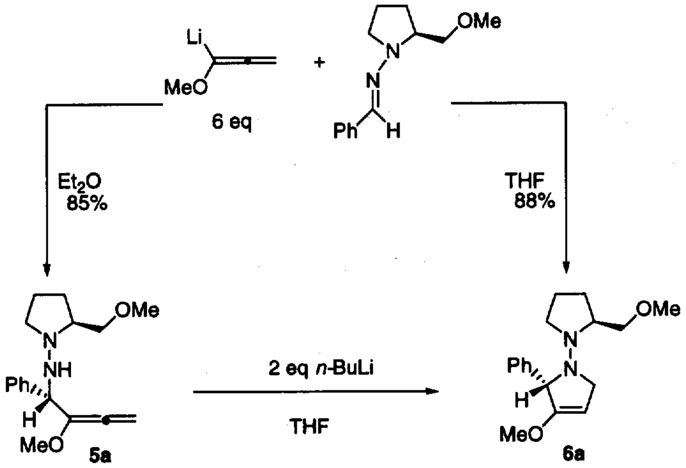


Scheme 1

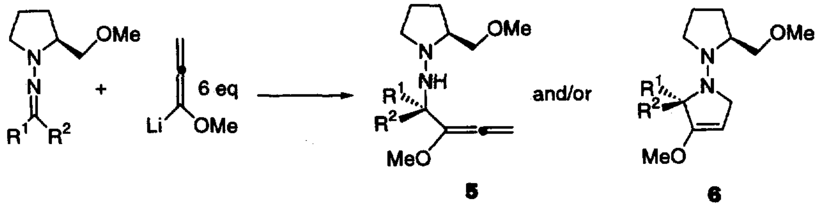
Although surprising, it is interesting to note that when the reaction was run **in THF** under the same conditions the hydrazine **5a** was not observed; rather the pyrroline **6a**[6,7] was obtained exclusively as one diastereomer. This appears to be the result of intramolecular cyclisation of the lithium hydrazide on the allenic moiety in **5a**.[9] This assumption is supported by the clean transformation of **5a** into **6a**, when **5a** is treated with 2 equivalents of *n*-BuLi **in THF**(-78°C, for 2 h; then -20°C, 16 h)(Scheme 1).

Similar reactions were observed for the SAMP-hydrazones of other **aromatic aldehydes**. In each case, the α-allenic hydrazine **5** was obtained when the reaction was performed in diethyl ether while the pyrroline **6** was exclusively formed when THF was employed. The diastereoselectivity is very high in each case studied: the ^{1}H and ^{13}C NMR spectra of all the products **5** and **6** show the presence of only one diastereomer. These results are collated in Table 1, they correspond to the use of 6 equivalents of the organometallic reagent, a quantity which gives the best yields of **5a** and **6a** as well.

In contrast, reaction of SAMP-hydrazones with **aliphatic aldehydes** affords, almost exclusively, the α-allenic hydrazines **5**, with low yields in THF, but quantitatively in diethyl ether.[5] These reactions are also highly diastereoselective, giving a single diastereomer of **5**.

Having established a totally diastereoselective synthesis of pyrrolines **6** from aromatic hydrazones, cleavage of the N – N bond was studied in order to obtain the pyrrolines **7** in an enantioenriched form. Many conventional reducing methods including Li/NH_3, hydroboration, SmI_2, were found to be unsuccessful. It was discovered that quaternisation of a nitrogen in the hydrazino group using methyl chloroformate followed by catalytic hydrogenation (Raney nickel, MeOH, 50 bar, 50°C, 48 hours) afforded the target pyrroline **7**. Under these conditions, the relatively unstable pyrrolines **7a-d** were obtained with 74 %, 68 % and 79 % yield respectively. No trace of the corresponding carbamates were observed. Although contaminated by 2-methoxymethyl pyrrolidine (SMP) resulting from the SAMP- auxiliary, these compounds may be purified by flash chromatography[10] and stored at -20°C under an inert atmosphere (Scheme 2).

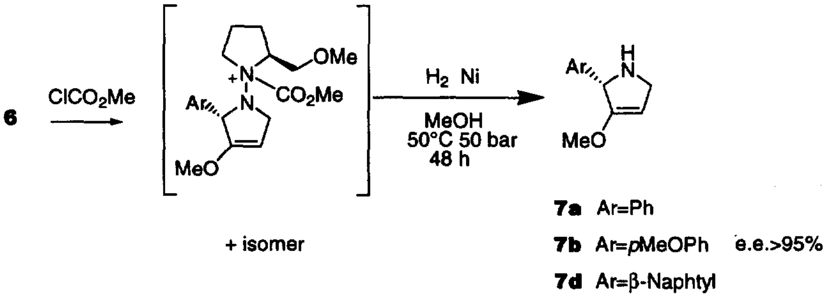
The enantiomeric excess of compound **7b** was determined by ^{1}H NMR using Eu(hfc)$_3$ as chiral shift reagent.[11] A racemic sample of compound **7b** was prepared, for comparison purposes, by reaction of lithiomethoxyallene with benzaldehyde morpholine hydrazone using an identical procedure to that detailed above.



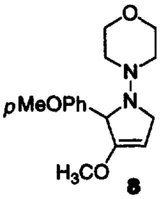
Solvent	R^1	R^2	5(%)	6(%*)	d.e %
THF	Ph	H	-	**6a** (88)	99
	p-MeOPh	H	-	**6b** (75)	99
	p-MePh	H	-	**6c** (79)	99
	β-naphtyl	H	-	**6d** (76)	99
	Ph	Me	-	**6e** (8)	99
	Ph	Ph		-	-
	Et	H	**5g** (38)	-	99
	t-Bu	H	**5h**	**6h** (8)	99
Et_2O	Ph	H	**5a** (> 95)	-	99
	β-naphtyl	H	**5d** (> 95)	-	99
	Et	H	**5g** (> 95)	-	93
	t-Bu	H	**5h** (> 95)	-	95

* Isolated yields : **6** were purified by flash-chromatography but **5** were unstable under chromatographic conditions; the NMR analysis shows the high purity of the crude product.

Table 1



Scheme 2



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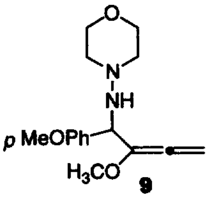

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Using THF as the solvent the cyclic hydrazine **8** and the allene **9** were obtained in 3:1 ratio but could be separated chromatographically. The NMR experiments show that no epimerisation occured during the transformation of **6b** into **7b**. It is therefore reasonable to assume that **7a** and **7d** were also obtained with an e.e.≥ 95 %.

In conclusion, this study has shown that pyrrolines **7** may be obtained in two high-yield steps from SAMP-hydrazones with almost complete enantioselectivity. The results herein described increase the synthetic potential of alkoxy allenes. We are presently trying to extend the cyclisation to aliphatic SAMP-hydrazines **5g** and **5h** and also transform these hydrazines **5** into enantiopure α-amino acids.

Ackwnoledgments : The authors wish to thank Mark Woods for his proof reading of this letter and V.D.B. thanks the Ministery of National Education (MENRT) for financial support .

Notes and references

1 – For recent preparations of 3-pyrrolines, see :

a) Hassner, A. ; Balasubramanian, T. *Tetrahedron Lett.* **1996**, *37*, 5755-5758.

b) Xu, Z ; Lu, X. *Tetrahedron Lett.* **1997**, *38*, 3461-3464 and *J.Org.Chem.***1998**, *63*, 5031-5041.

c) Ishii, K. ; Ohno, H. ; Takemoto, Y. ; Ibuka, T. *Synlett* **1999**, 228-230.

2 – Rochet, P. ; Vatèle, J.M. ; Goré, J. *Synlett* **1993**, 105-107.

3 – Surivet, J.P. ; Goré, J. ; Vatèle, J.M. *Tetrahedron* **1996**, *52*, 14877-14890.

4 – a) Enders, D. ; Schubert, H. ; Nübling, C. *Angew. Chem.Int.*Ed. **1996**, *25*, 1109-1114.

b) Enders, D. ; Nubling, C. ; Schubert, H. *Liebigs Ann./Recueil* **1997**, 1115-1123.

c) For a review on asymetric synthesis by addition of organometallic reagent to CN double bonds, see Enders, D. ; Reinhold, U. *Tetrahedron*: *Asymmetry* **1997**, *8*, 1895-1946.

5 – The SAMP-hydrazines **5** are unstable under chromatographic conditions. The isomeric pyrrolines **6** may be purified by flash-chromatography.

6 – Compounds **5** and **6** were fully characterised. The diastereomeric excess were determined by ^{1}H NMR and by gas chromatography.

7 – The configuration of compounds **5** and **6** given is in accordance with the stereochemistry proposed by Enders *et al.* for the addition of organolithium reagents to SAMP-hydrazones; see ref. 4b.The relative stereochemistry of **6a** has been confirmed by X-ray analysis of a single crystal.

8 – The use of large excess of organolithium reagent in their reaction with SAMP-hydrazones is commonplace, for example see Enders, D. ; Lochtman, R. ; *Synlett* **1997**, 355-356.

9 – The cyclisation of α-allenic amines to 3-pyrrolines has been previously decribed :
Claesson, A. ; Sahlberg C. ; Luthman K. *Acta Chem. Scand.* **1979**, 309-310.

10 – SMP may be quantitatively recovered allowing the chiral auxiliary to be recycled.

11 – At 200 MHz, two signals are observed for the vinylic proton of **7b** in the racemic sample. For the enantioenriched isomer **7b** ($[\alpha]^{20}_{D}= + 24$ (*c* 0.85,$CHCl_3$)) only one signal was observed.