Diastereoselective Methylations of Enolates Derived from Pyridyl Amides

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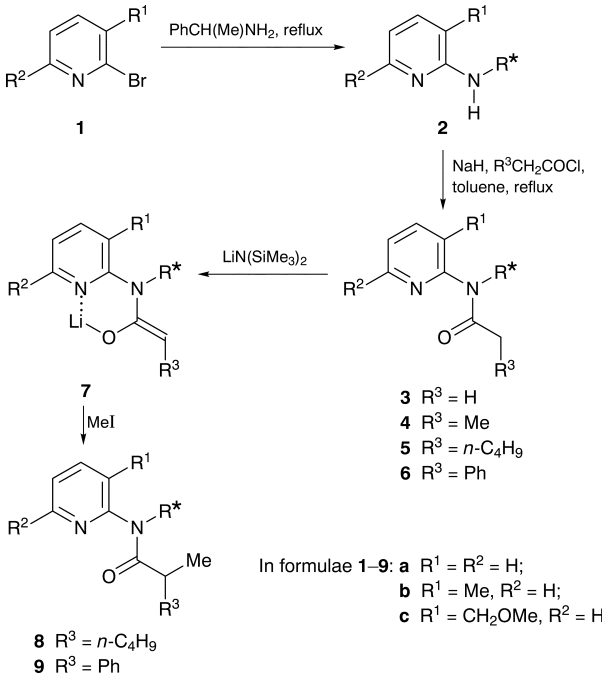
The diastereoselective methylations of chiral pyridyl amide enolates **7** is described which gave products **8** and **9** in moderate diastereoisomeric excesses.

Chiral enolates which have been prepared by deprotonation of chiral amides[1,2] and chiral lactams[3] have found extensive use in asymmetric synthesis as a method for introducing a substituent at the amide α-position. We have been interested in preparing enolates of general structure **7** (Scheme 1) by treatment of suitable amide precursors such as compounds **5** and **6** with lithium hexamethyldisilazane (LiHMDS).[4] The pyridine nitrogen lone-pair in structure **7** would be expected to coordinate to the lithium atom and hence restrict rotation of the enolate moiety. Subsequent addition of an electrophile such as methyl iodide might then yield alkylated products such as compounds **8** and **9** in which a new chiral centre has been generated at the amide α-position because the chiral substituent R* would be expected to direct alkylation preferentially at the less hindered face of the enolate **7**. To ascertain whether chiral enolates **7** might be associated with useful facial selectivity in alkylation reactions, the synthesis of racemic enolates **7** and their subsequent methylations yielding diastereoisomers of compounds **8** and **9** are reported in this paper.



Scheme 1

The preparation of racemic compounds **2a**[4–6] and **2c**[4] have been described previously. Racemic compound **2b** was prepared in a similar manner to compounds **2a** and **2c** by heating 2-bromo-3-methylpyridine **1b**[7,8] with an excess of racemic α-methylbenzylamine at reflux. α-Methylbenzylamine was chosen as the chiral auxiliary because it can be used both as a reactant and the reaction solvent in the preparation of compounds **2** from bromopyridines **1** and both enantiomers and the racemic compound are commercially available. Racemic amines **2** were used in our preliminary studies to avoid a further purification step deemed necessary for their enantiomeric counterparts since (*R*)- or (*S*)-α-methylbenzylamines are not readily available in 100% optical purity. The presence of the pyridyl moiety is an important feature in the design of the proposed chiral auxiliaries because the pyridine lone pair would be available for coordination to electrophilic entities such as protons and Lewis acids which might assist in the future cleavage of the amides such as **8** and **9**. Additionally, if organometallic reagents such as Grignard reagents were used to cleave the amide bond, the pyridine nitrogen lone pair could provide a coordination site of the metal atom. Thus, the pyridine fragment's role is twofold, to assist both in the asymmetric induction process and any subsequent cleavage of the amide bond.

Table 1 Yield of amides **3**–**9**

Precursor	Product	Yield (%)	*de* (%)
2a	**3a**	75	–
2a	**4a**	55	–
2a	**5a**	90	–
2a	**6a**	25	–
2b	**5b**	97	–
2b	**6b**	25	–
2c	**5c**	95	–
2c	**6c**	33	–
5a	**8a**	83	29
5b	**8b**	11	80[a]
5c	**8c**	56	43
6a	**9a**	47	53
6b	**9b**	46	57
6c	**9c**	94	50

[a]Best of several runs.

A series of amides **3**–**6** (Table 1) were therefore synthesised by heating the appropriate racemic compounds **2a**–**c** with sodium hydride to form the corresponding sodium salt and then adding the relevant acid chloride and heating under reflux in toluene. The yields shown in Table 1 are not optimised and are generally moderate to good with the exception of amides **6a**–**c** which were produced in poor yield. An interesting feature of the ^{1}H NMR spectra of heterocycles **5b** and **6b** was that two signals were observed for the methine proton of the α-methylbenzyl moiety. This was attributed to the existence of the two rotamers **10a** and **10b** as depicted for the *R* enantiomer in Fig. 1.

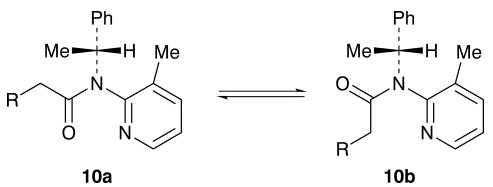


Fig. 1

*To receive any correspondence.

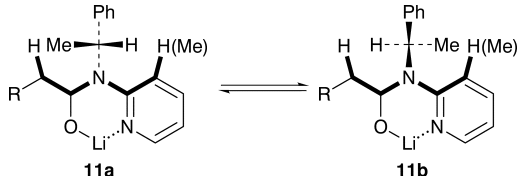


Fig. 2

To establish a useful methylation procedure the synthesis of amide **4a** from amide **3a** *via* enolate **7** ($R^1 = R^2 = R^3 = H$) was initially investigated. Treatment of compound **3a** with LiHMDS in THF at −47 °C under a nitrogen atmosphere, followed by dropwise addition of an excess of methyl iodide gave, after work-up, compound **4a** (89%) (identical with an authentic sample prepared from amine **2a** and propionyl chloride) together with a small quantity of starting amide **3a** and some dimethylated product by GLC-MS Other disilazanes (Na HMDS and KHMDS) and LDA did not give such good yields of the required amide **4a** as LiHMDS.

We next turned our attention to diastereoisomeric methylations of compounds **5a**–**c** and **6a**–**c** (Table 1). The presence of the 3-methyl group in amides **5b** and **6b** might be expected to hinder rotation of the α-methylbenzyl moiety and thus afford greater facial selectivity, and the oxygen atom of the methoxymethyl substituent in amides **5c** and **6c** could also provide an additional coordination site for the lithium atom in the corresponding enolate **7** and hence further restrict any rotation of the enolate moiety. We were therefore interested in discovering whether there would be any significant advantage in using these methyl- and methoxymethyl-substituted compounds over the parent unsubstituted compounds. Compounds **5a**–**c** and **6a**–**c** were converted into their corresponding enolates **7** by treatment with LiHMDS under the standard conditions described above. The formation of the kinetic *Z* enolate has been assumed and methylation of the enolates **7** gave amides **8a**–**c** and **9a**–**c** in the isolated yields and diastereoisomeric excesses (de) indicated in Table 1. The chemical yields of products were generally moderate to good with the exception of amide **8b** which was formed in poor yield. The de values were generally in the region of 43 to 57% and in the case of amide **5b**, de values up to 80% were obtained on some runs.

Although the relative stereochemistry at the new chiral centre is not known with absolute certainty, it is possible to propose a tentative assignment (Fig. 2, *R* stereochemistry shown). Assuming planarity of the pyridyl and enolate fragments, the bold lines illustrate that there is little steric differentiation between these two fragments when the 3-position of the pyridyl group is unsubstituted. Thus, in structure **11a** an interaction between the methyl substituent of the α-methylbenzyl group and the enolate hydrogen atom is depicted. Rotation of the α-methylbenzyl group of **11a** by 180° gives conformation **11b** in which an interaction between the methyl substituent of the α-methylbenzyl group and the hydrogen atom at the pyridyl 3-position is shown. It is difficult to rationalise which of these two methyl–hydrogen interactions is the most important and hence deduce the lowest energy conformation. However, when the pyridyl group bears a 3-methyl substituent, it is apparent that conformation **11a** is favoured over **11b** and that methyl iodide would be delivered from the top-face of the enolate, giving the *R* stereochemistry at the amide α-position. It is interesting to note that this model suggests that a 3-methyl substituent on the pyridyl ring is a desirable structural feature of the chiral auxiliary.

In all of the diastereoselective methylations described in this paper, the less polar diastereoisomer in the reaction mixture was always the major product as determined by GLC-MS. As we have tentatively assigned the relative stereochemistry of the new chiral centre in the methylation of amides **5b** and **6b** (Fig. 2), the relative retention times of the major/minor diastereoisomers in the other methylation reactions would suggest that they might possess the same relative stereochemistry.

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Techniques used; ^{1}H NMR, IR, GLC-MS

References: 8

Schemes: 1

Figures: 2

Tables: 1

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