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Highly Diastereoselective Alkylation of 6-Methylperihydropyrimidin-4-ones Directed Towards the Synthesis of α-Substituted β-Amino Acids

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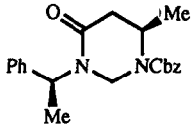
Abstract *: The highly diastereoselective alkylation of 6-methylperihydropyrimidin-4-ones 1 and 2 has been reported. The corresponding lithium enolates have been alkylated under a variety of conditions with good trans selectivity and all the reaction products have been easily separated and characterised.*

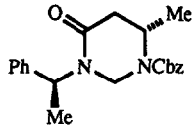
Recently the enantioselective synthesis of β-amino acids has attracted considerable interest. In fact β-amino acids are components of natural biologically active peptides [1] and are useful starting materials in the synthesis of β-lactam antibiotics.[2]

Several diastereoselective syntheses of β-amino acids have been reported and high diastereoselectivity has been achieved for substrates containing chiral auxiliaries.[3] In the development of chemical methods for the production of enantiomerically pure β-amino acids, high 1,4-trans selectivity has been recently obtained in the alkylation of 2-(*tert*-butyl)-perihydropyrimidin-4-ones, which provides protected forms of α-substituted β-amino acids,[4] and high 1,3-trans selectivity has been achieved in the Pd-catalysed addition of aryl iodides to enantiomerically pure 2-(*tert*-butyl)-dihydropyrimidin-4-ones in the synthesis of β-aryl β-amino acids.[5]

In a program of our laboratory direct towards the synthesis of α- and β-amino acids,[6] we wish to report herein the high 1,2-trans selectivity [7] achieved in the alkylation of (1'*S*,6*R*)- and (1'*S*,6*S*)-6-methyl-perihydropyrimidin-4-ones **1** and **2**. These compounds can be easily prepared [8] and show versatile applicability to the synthesis of polyfunctionalised amino derivatives.



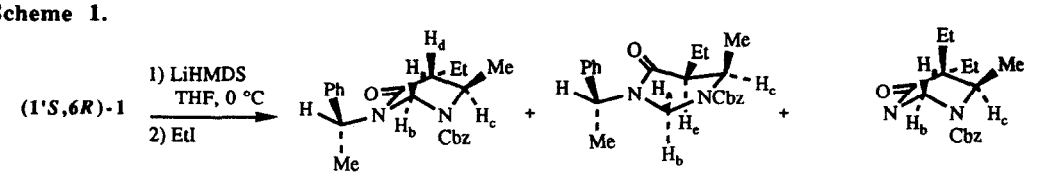
(1'*S*,6*R*)-**1**



(1'*S*,6*S*)-**2**

The alkylation of **(1'*S*,6*R*)-1** was performed by treatment of the corresponding lithium enolate,[9] generated with lithium hexamethyldisilazide (LiHMDS) in dry THF,[10] with ethyl iodide as depicted in Scheme 1.

Scheme 1.



(1'*S*,5*R*,6*R*)-3 **(1'*S*,5*S*,6*R*)-4** **(1'*S*,6*R*)-5**

The addition of ethyl iodide (1.1 equivalents) was made under a variety of conditions and the diastereomeric ratios were determined by means of GLC and GC/MS (gas chromatography - mass spectrometer) analysis. After aqueous work up the products were separated by silica gel chromatography and the trans compound **3** was obtained in 70-75% yield.[11] The 5,6-trans and 5,6-cis relationships of products **3** and **4** have been determined by means of ^{1}H NMR analysis and NOEDIF experiments.[12] The results are reported in Table 1.

Table 1.

Entry	Reaction temp. (°C)	Reaction time (h)	equiv. LiHMDS	Unreacted **1** (%)	Yield **3+4** (%)	Dialkylated **5** (%)	Trans/cis ratio [a]
1	0	2	0.9	15.8	84.2	-	87 : 13
2	0	2	1.1	10.3	78.3	11.4	96 : 4
3.1	-20	1	1	45.4	53.2	1.4	91 : 9
3.2	-20	4	1	7.6	89.3	3.1	91 : 9
4	-78 - r. t.	14	1	4.5	85.8	9.7	94 : 6

[a] Determined by GLC analysis.

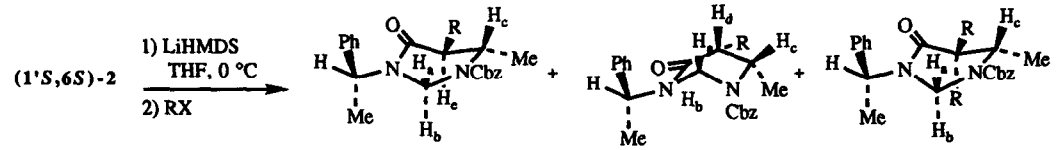
As shown in Table 1 both the trans/cis ratio and the amount of dialkyl derivative **5** increase if the reaction temperature decreases, moreover, when more than 1 equivalent is present (entry 2), the diastereomeric ratio and the amount of **5** increase. Both results suggest that the dialkylation occurs faster on the cis diastereoisomer **4** than on the trans **3**.[13]

In fact when the reaction is performed at -78 °C and slowly warmed up at room temperature (entry 4), a good trans/cis ratio is observed, although in the presence of an appreciable amount of dialkylated compound **5**. Under these conditions the reaction is complete after 14 hours.

Furthermore if the alkylation is carried out at -20 °C, a 91:9 trans/cis ratio is observed both after 1 hour (entry 3.1) and after 4 hours, when the reaction is complete (entry 3.2). This temperature seems to be the temperature of choice because a good trans/cis ratio is obtained and only traces of dialkylated derivative **5** are present.

In a similar way the lithium enolate of the perihydropyrimidin-4-one (1'*S*,6*S*)-**2** was generated with LiHMDS in dry THF.[10] The alkylation was performed by adding different alkylating agents (1.1 equivalents) at different temperatures (Scheme 2).

Scheme 2.



Some preliminary results where the effects of the reaction temperature, of the employed amount of LiHMDS and of the nature of the alkylating agent are reported in Table 2.[11] The trans/cis ratios have been determined by means of GLC and GC/MS analysis. Products **6**, **7** and **8** have been easily separated by silica gel chromatography and their structures have been assigned by means of ^{1}H NMR spectroscopy and NOEDIF experiments.[12]

Table 2.

Entry	Reaction temp. (°C)	Reaction time (h)	equiv. LiHMDS	Alkylating agent	Unreacted **2** (%)	Yield **6**+**7** (%)	Dialkylated **8** (%)	Trans/cis ratio[a]
1	0	21	0.8	EtI	23.2	76.8	-	85 : 15
2	0	2	1.1	EtI	-	92.1	7.9	94 : 6
3.1	-78 - r.t.	4	1	EtI	6.6	87.2	6.2	94 : 6
3.2	-78 - r.t.	14	1	EtI	1.5	88.5	10.0	97 : 3
4	0	50	1	i-BuI	43.9	56.1	-	87 : 13
5	0	5	1	BnBr	10.2	89.8	-	93 : 7

[a] Determined by GLC analysis.

It is worth noting that the diastereomeric ratio increases with the use of a bulkier substituent (entries 1, 4, 5). Furthermore in the presence of more than 1 equivalent of LiHMDS, both the trans/cis ratio and the amount of dialkylated compound **8** increase, confirming that the dialkylation occurs faster on the cis derivative than on the trans one (entries 1 and 2).[13] Moreover when the alkylation is carried out at -78 °C and the reaction is slowly warmed up, a good trans/cis ratio is obtained, both after 4 hours (entry 3.1) and after 14 hours (entry 3.2), despite the presence of a considerable amount of **8**.

In conclusion this paper describes preliminary results for the synthesis of enantiomerically pure α-substituted β-amino acids, useful starting materials in the synthesis of β-lactams. In fact, after acid hydrolysis of the heterocycles,[6,8a] the desired β-amino acids can be obtained.

Acknowledgement

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10. In a typical run, to the perihydropyrimidin-4-one **1** or **2** (100 mg, 0.284 mmol) in dry THF (5 ml), LiHMDS (sol. 1M in THF) is added at 0 °C. After 1 hour the reaction mixture is cooled to the required temperature and the alkylating agent is added (1.1 equiv.). When the reaction is complete, water is added and the mixture is extracted with ethyl acetate. The organic layer is dried, concentrated and chromatographed on silica gel (cyclohexane/ethyl acetate 9:1 as eluant).
11. All new compounds reported herein gave satisfactory spectral and microanalytical data.
12. The relative configuration of the stereogenic centre at C_6 of **1** and **2** has been established by means of ^1H NMR spectroscopy and NOEDIF experiments. In the same way the configuration and the conformation of the alkyl derivatives has been determined. While the trans derivatives **3** and **6** have both the methyl and the alkyl substituent in the equatorial position, the cis derivatives **4** and **7** have the alkyl at C_5 in the equatorial position and the methyl at C_6 in the axial position.
13. The conformation of the alkyl derivatives may account for the preferential alkylation of the cis derivative.

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