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Asymmetric Synthesis. XXXIII.[1] Diastereoselective Alkylation of N,N-substituted Amides.

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Key-words : Asymmetric synthesis, diastereoselective alkylation of amides, phenylglycinol derivatives.

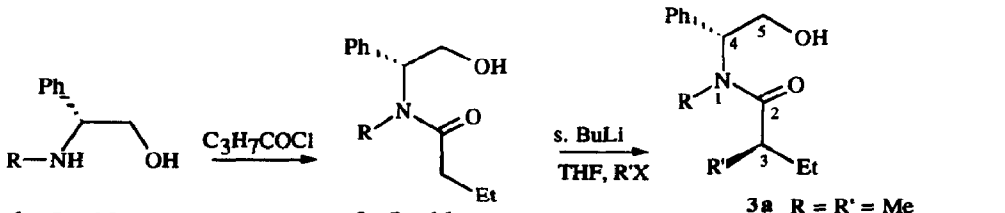
Abstract : A series of α-substituted amides **3** and **7-9** has been synthesized in enantiomerically pure form by diastereoselective alkylation of N-alkyl phenylglycinol amides **2** and **4-6** respectively. A rigid amide enolate has been postulated to explain the observed diastereoselectivity.

Non-racemic chiral molecules play an important role in the context of biological activity.[2] The creation of asymmetric centres via the formation of carbon-carbon σ-bonds provides one of the main methods for asymmetric synthesis. Especially attractive is the diastereoselective and enantioselective synthesis of α-substituted carbonyl compounds.[3] Alkylations of acyclic enolates possessing a chiral auxiliary group have been used successfully for the asymmetric synthesis of a large variety of compounds. Alkylations of (1R,2S)-(-)-ephedrine amides have been reported by Larchevêque[4] but modest yields and diastereoselectivities were observed.[5] Two years later Sonnet[5] and Evans[6] reported the reaction of amides derived from (S)-prolinol. Finally imides derived from chiral 2-oxazolidones have proved to be versatile auxiliaries for diastereoselective enolate alkylations.[7]

In connection with our work[8] dealing with the diastereoselective alkylation of chiral non-racemic lactams derived from (R)-(-)-phenylglycinol we decided to investigate the ability of phenylglycinol amides to afford alkylated products diastereoselectively.

In a first series of experiments N-methyl and N-benzyl phenylglycinol (**1a** and **1b**) were condensed with butyryl chloride to furnish amides **2a** and **2b**.[9] These compounds were submitted to classical enolate forming conditions [s.BuLi (2.5 eq), HMPA, THF, -78°C],[10] then reacted with various alkyl halides. High diastereoselectivities were observed for N-methyl amides (Table I) leading to substituted products **3** as the only isomer detected in the ^{1}H and ^{13}C NMR spectra and HPLC (entry 1). When the reaction was performed with N-benzyl derivatives (entries 3 and 4) reduced diastereoselectivity was observed. These results constitute a major improvement to the previously described alkylation of ephedrine derivatives where the observed diastereoselectivity was no better than 70 %.[4,5]

NMR studies did not allow the determination of the configuration of the newly created asymmetric center. This problem was solved by an X-ray analysis (Figure) of compound **3a**[11] which indicated a (R) configuration for C-3.



1a R = Me
1b R = CH_2Ph

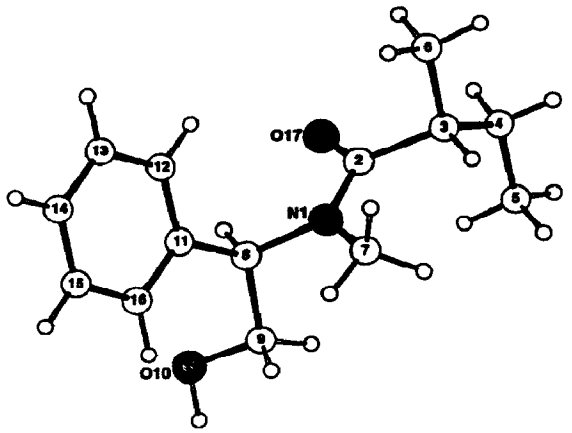
2a R = Me
2b R = CH_2Ph

3a R = R' = Me
3b R = Me, R' = CH_2Ph
3c R = CH_2Ph, R' = Me
3d R = R' = CH_2Ph

Table I

Entry	Amide 2	R'X	Compound	Yield[a] (%)	de (%)	$[\alpha]_D$ ($CHCl_3$)
1	**2a**	CH_3I	**3a**	66	≥ 98[b]	-125 (c=1.0)
2	**2a**	$PhCH_2Br$	**3b**	75	≥ 95[c]	- 2 (c=1.5)
3	**2b**	CH_3I	**3c**	68	88[b]	n.d.
4	**2b**	$PhCH_2Br$	**3d**	40	80[c]	n.d.

a) Based on isolated products ; b) Determined on crude material by HPLC and NMR ; c) Determined on crude material by ^1H and ^{13}C-NMR.

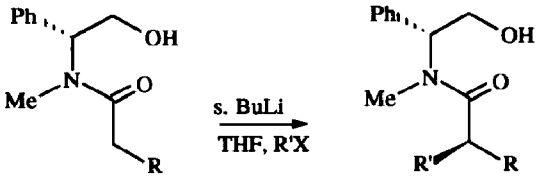


FIGURE

We then appplied this method to the alkylation of phenyl acetyl amide **4**. In this case the diastereoselectivity was slightly less (compare entries 1 and 2 of table I and II). This could be due to the greater acidity of proton α to the carbonyl group which is expected to be removed by the excess of base.

Particulary interesting is the reactivity of nitrogen derivatives **5** and **6** {mp. = 103-105°C; $[\alpha]_D$: -94 ($CHCl_3$, c=0.79)} obtained by condensation of N-methylphenylglycinol with glycine derivatives in the presence of isobutyl chloroformate and N-methylmorpholine. Methylation occurred with poor yield but high diastereoselectivity (de ≥ 95 %). Yields were improved when N-Boc derivatives were used. Methylation

proceeded with very high diastereoselectivity furnishing compound **9a** (R = N(Me)Boc, R' = Me) as the only isomer detected by HPLC {mp. = 141-143°C; $[\alpha]_D$: -174, ($CHCl_3$, c=0.62)}. Although it has been impossible to obtain suitable crystals for X-ray analysis, it is likely that the configuration is the same as in compound **3a**.



4 R = Ph
5 R = $N(CH_2Ph)_2$
6 R = N(Me)Boc

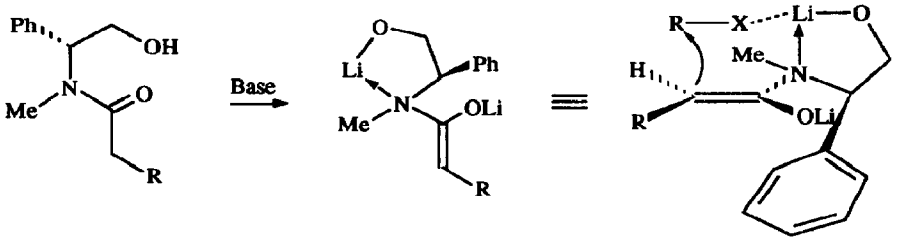
7a R = Ph, R' = Me
7b R = Ph, R' = CH_2Ph
8 R = $N(CH_2Ph)_2$, R' = Me
9a R = N(Me)Boc, R' = Me
9b R = N(Me)Boc, R' = CH_2Ph

Table II

Entry	Amide	R'X	Compound	Yield[a] (%)	de %	$[\alpha]_D$ ($CHCl_3$)
1	**4**	CH_3I	**7a**	70	80[b]	- 140 (c=0.79)
2	**4**	$PhCH_2Br$	**7b**	75	90[c]	n.d.
3	**5**	CH_3I	**8**	27	≥ 95[c]	n.d.
4	**6**	CH_3I	**9a**	84	≥ 99 [b]	-174 (c=0.62)
5	**6**	$PhCH_2Br$	**9b**	58	≥ 95 [c]	-137 (c=0.54)

a) Based on isolated products ; b) Determined by HPLC and NMR ; c) Determined by ^1H and ^{13}C NMR.

The excellent diastereoselectivity observed can best be explained by a chelation controlled process as suggested by Evans [6] and which we previously proposed for lactams.[8]



The N-lone pair in the amide enolate allows the chelation with lithium leading to a rigid intermediate. During the alkylation, the alkyl halide approaches the lactam enolate from its less hindered side when chelation is possible, leading to the observed stereochemistry. This hypothesis is supported by the loss of reactivity observed when the alkylation was performed with O-substituted derivatives. The diminution of diastereoselectivity observed with N-benzyl phenylglycinol amides is possibly a result of the steric hindrance of the benzyl group

which is anticipated to preclude the formation of the rigid intermediate as well as the approach of the electrophile. In contrast to the case of lactams, creation of a quaternary center by a second alkylation failed.

In conclusion the efficiency of our method provides a new access to substituted optically active amides precursors of acids, aminoacids and amines. Preliminary experiments have shown that reduction of the carbonyl group can be realized without any epimerisation of C-3, thus providing a practical route to optically pure β-substituted amines. Moreover it is known that such amides are smoothly hydrolyzed to acids without epimerization.[5,6]

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9. All new compounds were fully characterized by IR, MS, ^{1}H and ^{13}C NMR spectroscopy and exhibit satisfactory combustion analyses for C, H, and N.
10. Preparation of **3a**, is typical. To a solution of amide **2a** {$[\alpha]_D$: -116 (c=0.76, $CHCl_3$)}, (321 mg, 1.45 mmol), HMPA (0.6 mL) in THF (17 mL) was added s.BuLi (2.5 eq) at -78°C under nitrogen. The mixture was stirred for 20 min and MeI (271µl, 3eq) was then added dropwise. After stirring at -78°C for 3h, the mixture was treated with saturated NH_4Cl, extracted with CH_2Cl_2, washed with brine and concentrated to give a colorless oil which was purified by chromatography on silica gel with ethyl acetate as eluent. Crystallization from cyclohexane-ethyl acetate, furnished **3a** as white crystals (mp : 108°C) (226 mg, 66 %).
11. **X-ray structure analysis** : Crystal data . $C_{14}H_{21}NO_2$, M_w = 235.33, monoclinic, space group $P2_1$, Z = 2 , a = 6.976 (3), b = 12.378 (5), c = 8.218 (4) Å, β = 101.68 (4) °, V = 694.9 (5) $Å^3$, d_c = 1.12 g cm^{-3}, F(000) = 256, λ (Cu Kα) = 1.5418 Å, µ = 0.56 mm^{-1} ; 1865 Nonius diffractometric intensities measured, 1273 unique of which 907 with I > 3.0 σ(I) considered as observed. The structure was solved by direct methods using *SHELXS86* [12] and refined by full matrix least-squares with *SHELX76*[13] minimizing the function $\Sigma w (Fo-|Fc|)^2$. All the hydrogen atoms, located in difference Fourier maps, were replaced at theoretical positions (d C-H = 1.00 Å) and assigned an isotropic thermal factor equivalent to that of the bonded carbon atom, plus 10%. Convergence was reached at R = 0.046 and R_w = 0.067 (with $R_w = \{\Sigma w(Fo-|Fc|)^2 / \Sigma wFo^2\}^{1/2}$ and $w = 1/[\sigma^2(Fo) + 0.004650\ Fo^2]$. No residue was higher than 0.11 e $Å^{-3}$ in the final difference map. In the crystal structure, the molecules are linked in chains through hydrogen bonds established between the hydroxyl group O10-H (x,y,z) of one molecule and the oxygen atom O17 (1-x, 0.5+y-1,1-z) of the neighbouring one (distances O10...O17 = 2.73(1), HO10...O17 = 1.74 Å, angle O10H...O17 = 170.2°). Lists of the fractional atomic coordinates, thermal parameters, bond distances and angles have been deposited at the Cambridge Crystallographic Data Centre, U.K., as supplementary material.
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