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Stereoselective Synthesis of 2,6-Disubstituted Morpholines from Chiral Non-Racemic Lactams

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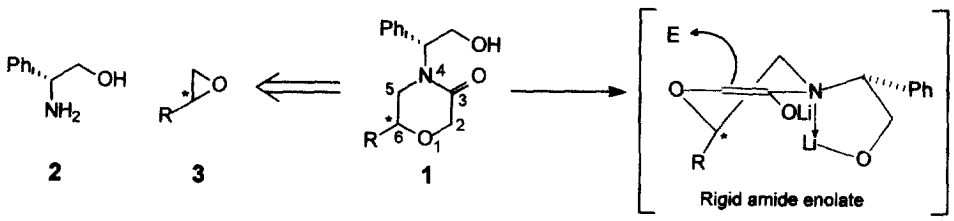
Abstract : Optically pure 2,6-disubstituted morpholines **11** have been obtained by diastereoselective alkylation of 6-substituted 3-oxo morpholines **1** derived from (*R*)-(-)-phenylglycinol and a series of chiral epoxides.

Keywords : Asymmetric synthesis, Lactam Alkylation, 1,4-oxazine, phenylglycinol

By targeting the synthesis of nitrogen containing compounds of biological interest we are developing new synthetic methods based upon the use of building blocks derived from both enantiomers of phenylglycinol as a source of chirality and nitrogen[1]. Among the impressive variety of transformations figures the diastereoselective alkylation of amide[2] and lactam enolates[3]. The high diastereoselectivity observed has been explained by a chelated controlling process[4]. In connection with our work in the piperidine[2] and piperazine[3] series we wish to report our results on the synthesis of optically pure 2,6-disubstituted morpholines.

Despite the importance of such polysubstituted compounds in medicinal chemistry[5], there is a lack of asymmetric routes for preparing them. Except the asymmetric construction of 2,5-disubstituted morpholines via palladium catalyzed cyclisation[7], the previous strategies resort to optically pure starting material[6]. Thus the choice of the potential substituents is restricted. Our lactam-alkylation process could circumvent this problem. For this purpose we designed lactam **1** (Scheme 1) as potential starting material as it could allow the introduction of an electrophile and a nucleophile at C-2 and C-3 positions respectively as demonstrated in the piperidine series[2,8].



Scheme 1

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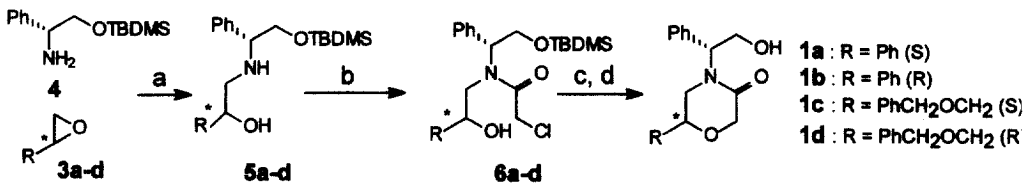
Furthermore the preparation of such a lactam would involve the condensation of (*R*)-(-) phenylglycinol **2** with epoxide **3**. Indeed, a great number of chiral epoxides are commercially available, and Sharpless or Jacobsen methodologies allow the preparation of functionnalized optically pure epoxides. Consequently, it is possible to introduce at will a first substituent at the C-6 position of the key intermediate **1**.

The presence of a heteroatom β to the carbonyl group has already been evaluated during our studies in the piperazine series and it was observed that there was no influence on the diastereoselectivity of the reaction. Furthermore the alkylation of non-chiral morpholine lactams has been previously described making us confident in the reactivity of compound **1**[9].

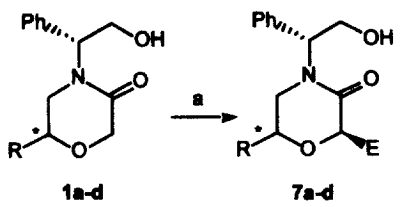
In this paper we describe the preparation of lactams **1** and the reactivity of their enolate forms towards various electrophiles. We were particularly interested in studying the influence of the orientation of the C-6 substituent on the diastereoselectivity of the alkylation as we thought that the results could furnish some indications on the validity of the chelated amide enolate intermediate. Our route to lactams **1** was exemplified by 2-phenylmorpholine **1a** derived from (*S*)-styrene-oxyde **3a** (Scheme 2).



Scheme 2. *Reagents and conditions* : a) MeOH, 40 °C, 10h, 78%. b) Chloroacetyl chloride, THF, NaOH 50% aq. (1 eq.), 2h, 76%. c) NaH (1 eq.), THF, 10h, 90%. d) THF, TBAF, 0 °C then 2h at r.t., 96%.

In order to avoid side reactions due to the presence of a free hydroxyl group we decided to start with O-protected (*R*)-(-) phenylglycinol. The *tert*-butyldiphenylsilyl ether **4** was reacted with **3a** in methanol at 40 °C to furnish **5a** as a single isomer in 78 % yield along with the N,N-disubstituted derivative in small amounts. Subsequent condensation with chloroacetyl chloride was achieved in 76% yield in the presence of NaOH. Cyclisation of the resulting chloroamide **6a** (NaH, THF) followed by deprotection of the hydroxyl group furnished the required 3-oxo-morpholine **1a** in 86% yield. The same sequence was applied to the synthesis of lactams **1b-d** in quite similar overall yields from epoxides **3b-d** (30-51%).

We then investigated the substitution at the C-2 position in the conditions previously described for piperidine and piperazine lactams[2,3]. The amide enolate was generated in THF at –78 °C by treatment with *sec*-BuLi in the presence of HMPA followed by addition of a series of electrophiles at the same temperature (Scheme 3). Reactions were complete in 3-4 hours. In every case the reaction was highly diastereoselective (d.e.>95%). Products **7a-f** were all obtained with the same C-2 configuration.

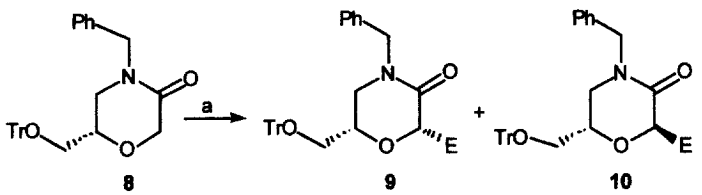


R	EX	Yield [a] (%)	d.e.[b] (%)	$[\alpha]_D^c$
1a : Ph (*S*)	MeI	**7a** : 74	>95	+46 (c = 0.47)
1b : Ph (*R*)	MeI	**7b** : 79	>95	+41 (c = 1.32)
1b : Ph (*R*)	BnBr	**7c** : 56	>95	+42 (c = 1.10)
1b : Ph (*R*)	$BrCH_2CO_2t$-Bu	**7d** : 76	>95	+45 (c = 1.85)
1c : $PhCH_2OCH_2$ (*S*)	MeI	**7e** : 32	>95	-38 (c = 0.80)
1d : $PhCH_2OCH_2$ (*R*)	MeI	**7f** : 53	>95	+10 (c = 0.50)

a) Based on isolated product
b) Determined by ^1H NMR and GC-MS on crude material
c) Measured at 25 °C in $CHCl_3$

Scheme 3. *Reagents and conditions* : a) *sec*-BuLi 1 eq., HMPA 2.5 eq., THF, -78 °C 30 min, EX 3 eq., 3 to 5h at -78 °C.

Contrary to our previous experiments, the presence of HMPA was necessary to obtain good yields in alkylated products. The use of DMPU or LiBr did not allow to obtain the desired products in better yields. In order to evaluate the influence of the chiral appendage and/or the C-6 substituent, we also realised the same alkylation experiments with lactam **8**[10] derived from benzylamine (Scheme 4).



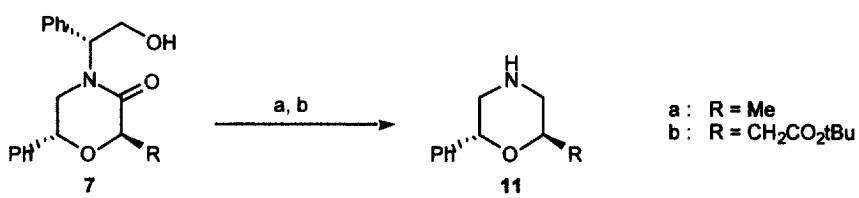
EX	Yield* 9+10	Ratio* 9+10
MeI	35%	69/31
BnBr	26%	68/32
CH_2=CH-CH_2I	27%	77/23

* Based on HPLC separation

Scheme 4. *Reagents and conditions* : Same experimental procedure as for **1a-d**.

Comparison of these results with those in the phenylglycinol series clearly indicated that the substituent at C-6 does not allow good diastereoselectivity for the alkylation of the C-2 centre. The same ratios with C-5 substituted morpholinones have been reported[9]. These results reinforced the hypothesis of a rigid chelated intermediate to explain the very high diastereoselectivity observed in the first series.

The transformation of 2,6-disubstituted morpholinone derivatives to disubstituted morpholines has been achieved for compounds **7a** and **7b** which were reduced with $LiAlH_4$ followed by hydrogenolysis of the chiral appendage to furnish the desired derivatives **11a** and **11b** in 50% overall yield (Scheme 5)[11].



Scheme 5. *Reagents and conditions* : a) THF, $LiAlH_4$, 0 °C then 3h at 60 °C ; b) H_2, $Pd(OH)_2/C$, MeOH, 24h, 50%.

In conclusion our methodology allows an easy route to a large variety of 2,6-disubstituted morpholines[8]. Application to the synthesis of natural products or biologically active compounds are under investigation and will be reported in due course.

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[10]. Lactam **8** was prepared by the same sequence as lactams **1** starting from benzylamine.

[11]. Compound (+)**11a**. Colorless oil. $[\alpha]_D$ = +6 (c = 0.75, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) (δ, ppm; J, Hz) : 1.29 (3H, d, J = 6.6, CH_3), 2.69 (1H, dd, J = 5.0, 12.5, H_{3a}), 3.00 (1H, dd, J = 3.5, 12.5, H_{3b}),), 3.06 (1H, dd, J = 6.6, 12.9, H_{5a}), 3.13 (1H, dd, J = 3.5, 12.9, H_{5b}), 3.94 (1H, m, H_2), 4.82 (1H, dd, J = 3.5, 6.6, H_6), 7.24-7.40 (5H, m, H_{arom}) ; ^{13}C NMR (75.43 MHz, $CDCl_3$, δ, ppm) : 17.6 (CH_3), 50.8, 51.0 (C_3, C_5), 67.8 (C_6), 72.2 (C_2), 127.0, 128.0, 128.9, 140.9 (C_{arom}). ; HRMS Calcd 177.1154 (M^+), found 177.1160.

The reduction of the ester function was not observed when **7b** was treated with $LiAlH_4$ at rt.

Compound (+)**11b**. Colorless oil. $[\alpha]_D$ = +10.5 (c = 2.35, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) (δ, ppm; J, Hz) : 1.35 (9H, s, tBu), 1.95 (1H, s, NH),), 2.56 (1H, dd, J = 6.7, 14.5, H_{7a}), 2.66-2.75 (2H, m, H_{3a}, H_{7b}), 2.92-3.10 (3H, m, H_{5a+b}, H_{3b}), 4.19 (1H, m, H_2), 4.74 (1H, dd, J = 3.2, 7.0, H_6), 7.19-7.33 (5H, m, H_{arom}) ; ^{13}C NMR (75.43 MHz, $CDCl_3$, δ, ppm) : 28.46 ($3CH_3$), 38.3 (C_7), 49.1, 51.2 (C_3, C_5), 69.4 (C_6), 72.6 (C_2), 81.5 (C_{-tBu}), 126.9, 127.8, 128.8, 140.4 (C_{arom}), 171.0 ($C_{carbonyl}$). ; HRMS Calcd 277.1678 (M^+), found 277.1680.