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Diastereoselectivity in the Alkylations of Bicyclic Piperidinones

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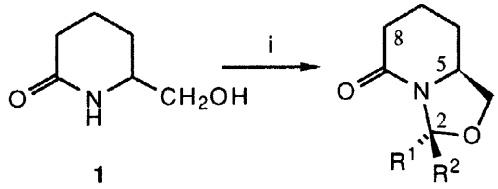
Abstract: The synthesis of substituted [4.3.0] bicyclic lactams derived from 6-oxo-2-hydroxymethylpiperidine is described. The enolate derived from these systems can be alkylated with a range of reactive electrophiles; the diastereoselectivity which can be achieved depends on the substitution pattern of the oxazolidine ring system and the nature of the alkylating reagent, and can vary from 1:1 to as much as 10:1.

Because of their widespread occurrence in nature, and their wide-ranging biological activity, there has been considerable interest in the development of synthetic routes to substituted piperidines, piperidinones and indolizidines.[1-4] In particular, the development of general methodology for the preparation of piperidines, substituted at any or all of the ring carbons, in a diastereoselective and enantioselective manner, has attracted considerable attention, principally due to the potent neuroexcitatory activity of this class of compound.[5-18] We have recently described that racemic or homochiral 6-oxo-2-hydroxymethylpiperidine **1** is readily available in 5 steps from lysine and in 60% overall yield.[19] Herein we describe the synthesis of a bicyclic lactam derived from this alcohol, and report on its diastereoselective functionalisation *via* the lactam enolate.

Reaction of lactam (±)-**1** or (*S*)-(+)-**1** with aldehydes, ketones or their equivalents gave the corresponding bicyclic *O,N*-hemiaminal ethers in moderate to good yield (Table 1).[20] Although the benzaldehyde adduct was obtained as the easily separable diastereomers **2** and **3** (Entry 1) in low yield, the acetophenone-derived *O,N*-hemiaminal ether **5** was exclusively one diastereomer; the stereochemistry of **2**, **3** and **5** was assigned by a series of n.O.e. experiments, and confirmed in the case of **5** by a single crystal X-ray analysis.[21] The synthetic application of some related bicyclic lactams by the "CNRS" approach is well documented.[22-24]



2 R^1=Ph, R^2=H
3 R^1=H, R^2=Ph
4 R^1=Me, R^2=Me
5 R^1=Me, R^2=Ph

(i) PhCHO, $MeC(OMe)=CH_2$, $PhCH(OMe)_2$, or $PhCMe(OMe)_2$, p-TsOH, toluene, 72h, reflux

Table 1: Reactions of Lactam **1**

Entry	Lactam	Reagent	Product(s)(% Yield)
1	(±)-**1**	PhCHO	(±)-**2** and (±)-**3** (22)
2	(±)-**1**	$CH_2=C(OMe)CH_3$	(±)-**4** (54)
3	*S*-(+)-**1**	$PhCH(OMe)_2$†	(+)-**2** (82)
4	*S*-(+)-**1**	$PhCMe(OMe)_2$†[25]	(-)-**5** (40)

† 1.1 equiv. of $B(OH)_3$ also added

Because the formation of the mixture of **2** and **3** (Entry 1) contrasted with the exclusive formation of the analogous *exo*-diastereomer for the [3.3.0] bicyclic system derived from L-pyroglutaminol and benzaldehyde,[26, 27] further investigations were made. Surprisingly the ratio of **2**:**3** was found to depend upon the purity of the starting lactam **1**. Thus, when crude **1** was used, a ratio of as much as **2**:**3** = 5:1 was

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obtained, although the exact value was noted to vary between batches of the starting material, but when lactam **1**, which had been carefully purified by column chromatography, was subjected to identical reaction conditions, an inverted ratio of **2:3** = 1:4 (based on isolated yield) was obtained. To determine if boric acid, which would arise from the work-up of the reduction step in the synthesis of **1**,[19] might be responsible for this interconversion, pure diastereomer **3** was refluxed in toluene with a mixture of benzaldehyde, *p*-toluenesulphonic acid and boric acid, and complete interconversion to **2** was observed, as determined by analysis of the ^{1}H NMR spectrum of the crude reaction mixture. No conversion of **3** to **2** was obtained under identical conditions but in the absence of boric acid. The kinetics of the formation of **2,3** were examined by conducting several reactions, using pure (in the absence or in the presence of boric acid) or crude lactam **1**; aliquots taken at regular time intervals over the course of the reaction were examined by ^{1}H NMR spectroscopy, and the results are indicated in Figure 1.

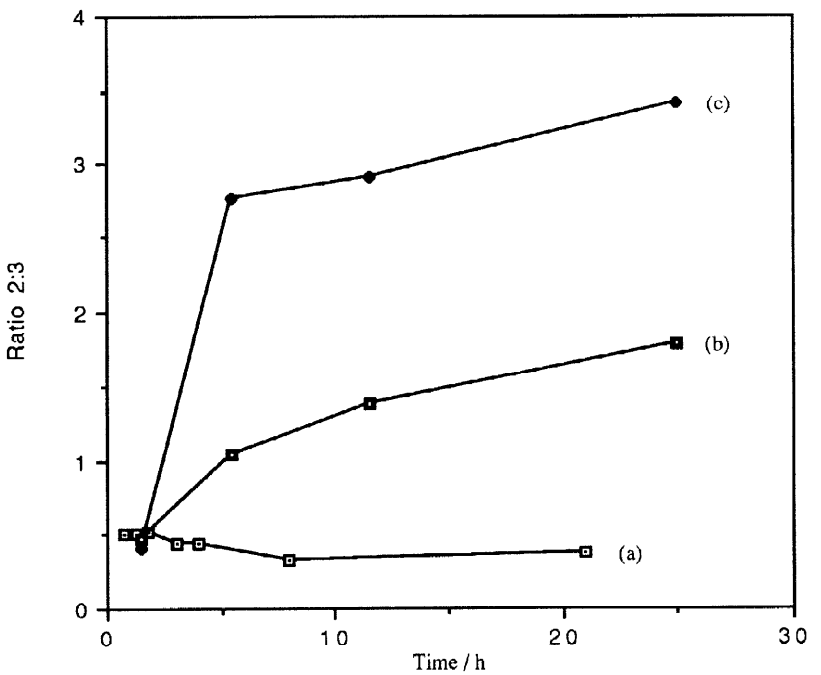

Figure 1: Distribution of products **2** and **3** from a solution of refluxing toluene, *p*-TsOH and benzaldehyde using (a) pure alcohol **1**; (b) crude alcohol **1**; and (c) pure alcohol **1** with boric acid.

Thus, the pure lactam produced a diastereomeric mixture in which **3** predominated, and the ratio was almost unchanged throughout the reaction (Fig. 1a). Whilst crude lactam **1** initially produced a similar ratio, equilibration over the course of the reaction led to a mixture in which **2** was favoured (Fig. 1b); pure lactam **1** in the presence of boric acid gave a mixture in which the diastereomeric ratio **2:3** was substantially higher (Fig. 1c). These results are consistent with **3** being the kinetic product, which can be equilibrated to **2**, the thermodynamic product, in a reaction catalysed by boric acid. The equilibration of epimeric oxazolidines via ring chain tautomerism has been recently investigated.[28]

That these hemiaminal ethers are useful intermediates for synthesis was demonstrated by their elaboration to substituted bicyclic piperidinone derivatives by generation of the lactam enolate.[29-33] Thus, treatment of lactam (±)-**2** with LDA in THF at -78°C, followed by the addition of *p*-nitrobenzyl bromide, gave the corresponding alkylated product as a separable mixture of two diastereomers **6a** and **7a** at the new chiral carbon (C-8), in a ratio of 5:1, with a total yield of 42%. The relative stereochemistry of these products was determined by a series of n.O.e. experiments. The predominance of the product **6a** is presumably due to steric factors, with the electrophile approaching from the *exo*- face of the bicyclic ring system. When methyl iodide was used as the electrophile in the above sequence, a yield of 60% of the methylated products **6b** and **7b** was obtained, in a 2:1 ratio, demonstrating that the diastereoselectivity was dependent on the bulk of the

incoming electrophile. A similar dependence has been observed in the alkylations of the corresponding [3.3.0] bicyclic system.[26] However, we could not extend the application of this compound to other less reactive electrophiles. Furthermore, the application of the corresponding *endo*- diastereomer (-)-**3** did not give lactam enolate formation, but instead decomposition by an oxazolidine ring opening reaction.

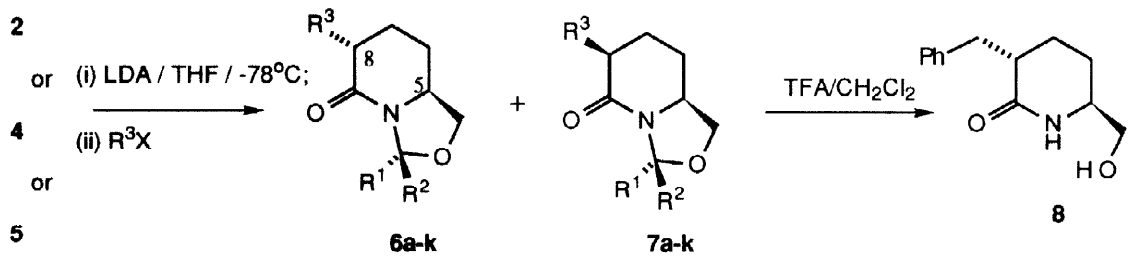

Table: Alkylations of Bicyclic Lactams **2**, **4** and **5**

Substrate	Electrophile	Product **6,7**	R^1	R^2	R^3	Yield (%)	**6:7**
(±)-**2**	*p*-$NO_2C_6H_4CH_2Br$	**a**	Ph	H	*p*$NO_2C_6H_4CH_2$-	42	5:1
(±)-**2**	MeI	**b**	Ph	H	Me-	60	2:1
(±)-**4**	*p*-$NO_2C_6H_4CH_2Br$	**c**	Me	Me	*p*$NO_2C_6H_4CH_2$-	28	1:1
(±)-**4**	MeI	**d**	Me	Me	Me-	43	1:1
5	*p*-$NO_2C_6H_4CH_2Br$	**e**	Me	Ph	*p*$NO_2C_6H_4CH_2$-	27	3:1
5	$PhCH_2Br$	**f**	Me	Ph	$PhCH_2$-	69	10:1
5	CH_2=$CHCH_2Br$	**g**	Me	Ph	CH_2=$CHCH_2$-	95	2:1
5	PhSeCl	**h**	Me	Ph	PhSe-	52	7:4
5	TsCl	**i**	Me	Ph	Cl-	46	4:3
5	MeI	**j**	Me	Ph	Me-	80	1:1
5	BnO_2CCl	**k**	Me	Ph	BnO_2C-	56	1:1

When the dimethyl derivative (±)-**4** was treated with LDA and either *p*-nitrobenzyl bromide or methyl iodide, derivatives **6c,7c** and **6d,7d** were obtained in yields of 28% and 43% respectively as inseparable mixtures of diastereomers at the new chiral centre (C-8). ^{1}H NMR spectroscopic analysis of the crude reaction mixture indicated that the *exo-/endo*- diastereoselectivity in these cases was approximately 1:1. A study has indicated that related bicyclo[4.3.0] heterocycles exhibit substantial conformational fluxionality, and this may account for the lack of diastereoselectivity observed in the alkylations of **4**.[34] In the case of **2**, the larger relative difference in the bulk of the C-2(H) and C-2(Phenyl) substituents may reduce such conformational mobility, causing an increased facial bias, and therefore higher diastereoselectivity, in the reactions of the lactam enolate.

However, compound **5** could not be reliably deprotonated under similar conditions, and it was eventually found that generation of the enolate at -30°C with *sec*-BuLi, followed by quenching with the electrophile at -78°C, was required for reproducible results. Using these conditions, good to very good yields of the products **6e-k** and **7e-k** were obtained, and these (except for **6,7jk**) were easily separated by column chromatography. Stereochemical assignment was made in the case of **6f,g,i** by careful n.O.e. experiments. In the case of **6-7i,k**, disubstitution proved to be competing reactions.

That these products are potentially useful synthetic intermediates was demonstrated by deprotection of **6f** with trifluoroacetic acid/dichloromethane to give the alcohol **8** in good yield.

This convenient synthesis and elaboration of these 6-oxopiperidines should be of potential application to a wide range of substituted piperidines and piperidinones, and further work in this regard will be reported in due course.

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