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Conjugate Addition of Nitrogen Nucleophiles to an α, β-Unsaturated Pyrrolidinone

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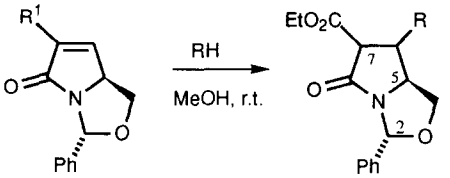
Abstract: The conjugate addition of nitrogen nucleophiles to α,β-unsaturated lactam **1b** under very mild conditions occurs in good yield with high diastereoselectivity. Deprotection provides a simple access to β-aminopyrrolidinones in excellent overall yield. © 1997 Elsevier Science Ltd.

Because of their wide ranging biological activity, functionalised pyrrolidines are of considerable importance.[1-3] We[4] and others[5-7] have recently reported that a bicyclic lactam[8] derived from pyroglutamic acid provides a useful template for the preparation of variously functionalised pyrrolidinones by simple alkylation and cycloaddition reactions. A related bicyclic lactam, extensively investigated by Meyers, has been shown to undergo conjugate addition with a variety of carbon and heteroatom nucleophiles under mild conditions.[9] We report here that the α,β-unsaturated lactam **1b**[10, 11] is a useful template for conjugate additions of nitrogen nucleophiles, giving the corresponding β-aminated products **2a-f** in good yield with high diastereocontrol. This provides a simple route to conformationally well-defined β-amino-γ-lactams, compounds which are now recognised to be of some biological importance, and whose synthesis has recently attracted considerable attention.[12] Although the conjugate addition of amines, azides, amine equivalents, and more recently chiral amines[13, 14] is relatively well known for acyclic systems[15, 16] and for unsaturated lactones,[17] these reactions are less common in pyrrolidine substrates.[18] Heteroatom functionalisation β- to a lactam carbonyl has, however, been achieved using 1,3-dipolar cycloadditions.[19]

We found that the enone **1a** was unreactive with benzylamine and *O*-benzylhydroxylamine under the reported reaction conditions for closely related substrates.[20, 21] However, we were pleased to observe that the activated enone **1b**[10, 11] gave a very rapid reaction with a variety of substituted hydroxylamines and hydrazines to give the corresponding adducts in excellent yield (Scheme 1); in all cases one diastereomer was obtained predominantly but not exclusively.[22, 23] The stereochemistry for the major adducts **2a-f** was shown to be (6*S*, 7*S*) by a series of n.O.e. experiments (Table), corresponding to *exo*- (less hindered) approach of the heteroatom nucleophile followed by protonation to give the C-6/C-7 *trans*- product; all of the major adducts are expected to possess this stereochemistry.



1a R^1 = H
1b R^1 = CO_2Et

2a-f

Scheme 1

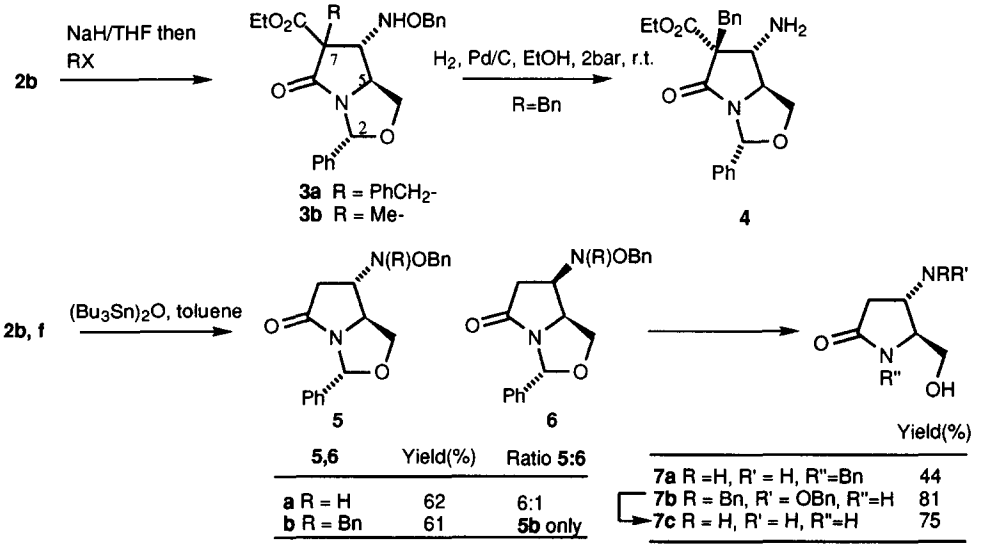
Compounds **2a, c-e** were found to be unstable to silica and aqueous conditions, undergoing β-elimination, and the phenylhydrazine adduct **2c** was found to be prone to aerial oxidation, and readily converted to the azo derivative **2** (R = -N=NPh) on standing. Believing the incomplete diastereoselectivity to be due to the relatively small bulk of the nucleophile, we examined the reaction of *O,N*-dibenzylhydroxylamine, and were gratified not only to find that the adduct **2f** was obtained in 99% yield as only two diastereomers in a ratio of 9:1, but was also stable.

Table: Reaction of Enone **1b** with Nitrogen Nucleophiles (Scheme 1), and n.O.e. data for the major diastereomers of the products **2**.

Nucleophile RH	Product	Yield (%)	Diastereomer Ratio[a]	n.O.e Enhancements (%)		
				C-2/C-4$_{endo}$	C-4$_{endo}$/C-6	C-5/C-7
$HONH_2$	**2a**	93	16:7:4:1	-	-	-
$PhCH_2ONH_2$	**2b**	96	20:2:2:1	1.8	26	2
$PhNHNH_2$	**2c**	93	12:1:1:1	3.2	8.8	√[b]
$PhCONHNH_2$	**2d**	90	10:1:1	2.2	3	√[b]
$NH_2NHCONH_2$	**2e**	92	12:2:1:1	-	-	-
$PhCH_2ONH(CH_2Ph)$	**2f**	99	9:1	1.9	7.4	5

[a]Estimated from the ^1H NMR spectrum; [b] nOe enhancement not integrated

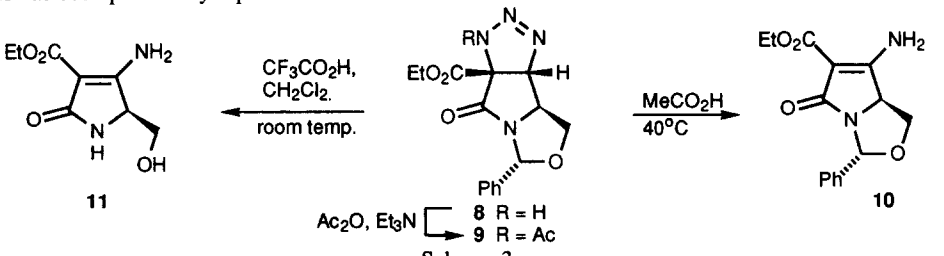
Reasoning that the instability of some of these adducts could be due to a facile β-elimination process, we examined their alkylations at C-7 in order to prevent this process (Scheme 2). Good yields of the alkylated adducts **3a,b** could be achieved by treating **2b** (mixture of diastereomers) with NaH and then benzyl bromide or methyl iodide (61 and 58% respectively) but with poorer diastereoselectivity than in the simple conjugate additions (43:24:4:1 and 8:8:1:1 respectively); in contrast to their precursor **2b**, the products **3a,b** were indeed stable. Presumably the increased proportion of the second major isomer in both cases is due to a smaller steric bias in the intermediate enolate, leading to a reduced steric selectivity for *exo-* versus *endo-* attack of the alkylating agent. However, the adduct **2f** was found to be unreactive to alkylation, probably due to the steric bulk of the C-6 substituent.



Scheme 2

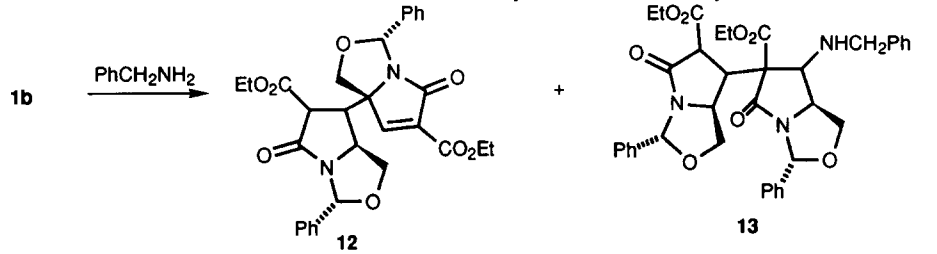
Deprotection of a mixture of two of the four diasteomers of **3a** (87% d.e.) was readily achieved under catalytic hydrogenolysis conditions with 10% Pd/C as catalyst and ethanol solvent, to give the product **4** in good yield (53%), with the major diastereomer having the stereochemistry shown (Scheme 2). Alternatively, ester hydrolysis[24] and decarboxylation of **2b,f** gave the lactams **5, 6** in 62 and 61% yield respectively; that the C-6(H) stereochemistry in both cases was *endo* as shown followed from n.O.e. studies, consistent with the initial addition of the nitrogen nucleophile to the *exo-* (less hindered) face of **1b**. Hydrogenolysis of **5b** with 10% Pd/C as catalyst using HOAc (4bar, 2days)[25] as solvent gave the N-benzyl lactam **7a** in 44% yield after ion exchange (Dowex 50W-X8). Alternatively, initial acidic deprotection of **5b** gave alcohol **7b** in 81% yield, and subsequent hydrogenolysis (10% Pd/C) gave the aminolactam **7c** in 75% yield after ion-exchange. Determination of the enantiopurity of **7b** from the MTPA derivatives (prepared with either (-)- or (±)-MTPA chloride[26]) indicated an e.e. of at least 95%.

Sodium azide addition to **1b** gave pyrazoline **8** as a single diastereomer in excellent yield (80%)(Scheme 3). This latter compound could be converted to the N-acetyl derivative **9** in 70% yield (Ac_2O, Et_3N, -5°C), whose structure was confirmed by ^1H NMR long range coupling experiments (pulsed field gradient HQMC (5:3:4)). Decomposition of the pyrazoline under carefully controlled conditions with acetic acid gave the enamine **10** in low yield (18%); alternatively, treatment with TFA/CH_2Cl_2 gave the pyroglutaminol **11** directly in 40% yield. The conjugate addition of azides to give similar adducts in related systems has been previously reported.[27, 28]



Scheme 3

The reaction of simple amines was more problematic; for example, treatment of **1b** with benzylamine gave 60% of dimer **12**, along with 30% of the coupled product **13**, both as single diastereomers whose relative stereochemistry could not be assigned (Scheme 4). Similar dimerisations have been reported in the conjugate additions of thiols to unsaturated lactones[29] and more recently in a related enone system.[30]



Scheme 4

Thus, we have shown that although conjugate addition of simple amines to an α,β-unsaturated pyrrolidinone is problematic, the addition of more reactive nitrogen nucleophiles gives good yields of the expected adducts with high diastereoselectivity. These can be selectively deprotected under standard conditions to give good yields of β-aminolactams.

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22. Sample procedure: To a solution of *O*-benzylhydroxylamine.HCl (86mg, 0.54mmol) in MeOH (5ml) at room temperature was added NaOAc (44mg, 0.54mmol) whilst stirring. The enone **1b**[10, 11] (134mg, 0.49mmol) dissolved in MeOH (5ml) was then added slowly dropwise to the reaction mixture and allowed to stir for 30 min. Brine (20ml) was added to the reaction mixture and extracted with EtOAc (3x20ml). The combined organic layers were then washed with water (2x20ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. This gave the product **2b** as a yellow gum (187mg, 96%). The reactions using the hydrazine nucleophiles were not subjected to aqueous work-up.
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