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Stereoselective Michael Additions of Nitromethane Yielding 3R(1S N-Substituted Aminoethyl)Pyrrolidines

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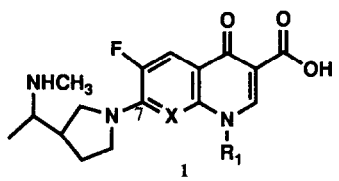
Abstract: The 1,4-addition of nitromethane to vinylogous esters of N-protected amino acids proceeded with good to excellent yields and with good diastereoselectivity.

Ongoing studies in our laboratories have determined that 3-[1-(methylamino)ethyl]pyrrolidines attached to the 7-position of fluoroquinolones result in compounds with potent broad spectrum antibacterial activity (figure 1). Due to their excellent biological activity[2] those quinolones containing the side chain with the 3R,1S configuration, **1a**, were desired. In pursuit of a diastereoselective synthesis of **1a** , we developed a route employing L-alanine as the starting material, which provides the correct stereochemistry at the 1 position in **1a**. The stereochemistry at the 3-position is set in a diastereoselective 1,4-addition of an "aminomethylene" equivalent to the appropriate olefin. This letter describes the synthesis of **1a**, the reaction conditions and the results of the diastereoselective conjugate addition.



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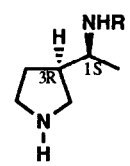
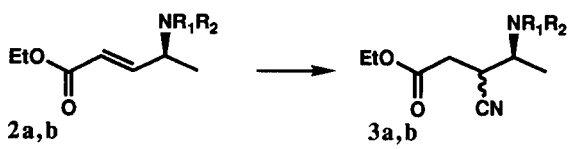


1a R=CH_3

Figure 1

Olefins **2** were prepared in high yields by a Horner -Emmons olefination of the corresponding aldehydes.[3] The amino protected aldehydes were made via their N,O dimethyl amides[4] according to literature procedures.

Table 1. Reaction Conditions for Addition of Cyanide Anion

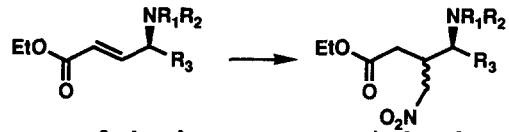


	Reaction conditions	Yield	Diastereomer ratio[a]
2a R_1=H, R_2=Boc	$(CH_3)_2C(OH)CN/KCN/CH_3CN$ 18 crown 6/ 24h/ RT	100%	1:1
	$KOAc/NCCO_2CH_3/Et_3N$/DMF/90C/6h	60	1:1
	Bu_4NCN/THF/2h	19	1:1
2b R_1=H, R_2=Bn_2	Et_2AlCN/THF/Et_3N/TMSCl/67C/72h	6	1:1
	$CsOAc/NCCO_2CH_3/Et_3N$/DMF/90C/6h	53[b]	1:1

a. Determined by ^{1}HNMR b.crude yield

Our first attempt to introduce an "aminomethylene" group to give **3** was with cyanide ion (Table 1). Obtaining a Michael addition product of cyanide ion with **2** proved difficult under standard conditions.[5] However, with acetone cyanohydrin/KCN, addition took place, but with no diastereoselectivity.

Table 2. Reaction Conditions for the Addition of Nitromethane



2a,b,c,d **4a,b,c,d**

Compound	Base	Conditions[h]	Yield	Diastereomer ratio[i]
2a R^1=H, R^2=Boc R^3=CH_3	DBU[a]	neat 5eq. CH_3NO_2/4h	95	20:80
	DBN[b]	neat 5eq. CH_3NO_2/1h	95	16:84
	TMG[c]	neat 5eq. CH_3NO_2/1h	84	20:80
	Triton B[d]	Dioxane/ 1.1 eq CH_3NO_2	67[e,g]	18:82
	DBU	1.1eq CH_3NO_2/DMF/20h	41[e]	12:88
	DBU	1.1eq CH_3NO_2/CH_3CN/2h	95	16:84
2b R^1= R^2=Bn R^3=CH_3	DBU	neat 5eq. CH_3NO_2/8h	78	19:81
	DBN	neat 5eq. CH_3NO_2/24h	NR	
	TMG	neat 20eq. CH_3NO_2/7d	47	
	DBU	1.1eq CH_3NO_2/CH_3CN/4d	70[e,g]	19:81
	DBU	1.1eq CH_3NO_2/DMF/4.5d	66[e,g]	14:86
2c R^1=H, R^2=Boc R^3=$CH(CH_3)_2$	DBU	neat 5eq. CH_3NO_2/2.5h	98	14:86
	DBU	1.1eq CH_3NO_2/DMF/3d	70	16:84
	DBU	1.1eq CH_3NO_2/CH_3CN	98	14:86
2d R^1=H, R^2=Boc R^3=CH_2Ph	DBU	neat 5eq. CH_3NO_2/2.5h	83	20:80[j]
2e R^1=Boc, R_3=CH_2 R^2= $(CH_3)_2COR^3$	DBU	neat 5eq. CH_3NO_2/2.5h	89	20:80

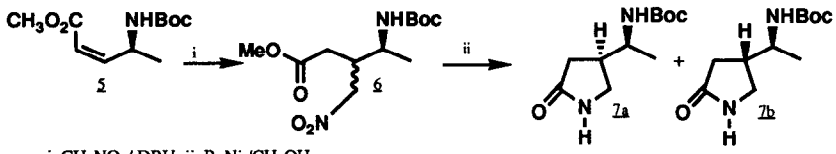
a.DBU, 1,8 Diazabicyclo[5.4.0]undec-7-ene b. DBN, 1,5 Diazabicyclo[4.3.0]non-5-ene c.TMG 1,1,3,3-Tetramethylguanidine d. Triton-B, N-Benzyltrimethylammonium hydroxide e. Crude yields f. 70%conversion g. 50% conversion h.All reactions at RT unless otherwise noted i. Determined by Chiralcel OJ HPLC j. Determined by ^{1}HNMR of a cyclic derivative.[8]

Our second approach employed the use of nitromethane as the "aminomethylene" synthon. The reaction of nitromethane with olefin **2** in the presence of a variety of bases (Et_3N, Hunigs' base, LDA or Triton B) yielded either no reaction or unidentifiable products. However, when the bases DBU, DBN or TMG were used, the reactions gave analytically pure products in good yields.[6] The ratio of stereoisomers of **4** was determined on a Chiralcel OJ column by examining the crude reaction mixtures.[7] Variations in the steric bulk geminal to the amino group did not significantly change the selectivity of the addition, as evidenced by changing the methyl group in **2a** to an isopropyl group (**2c**) or a benzyl group (**2d**).

In an attempt to reverse the selectivity of the 1,4 addition we spectulated that the Z- olefin would give rise to 1,3 allyl strain and postulated that the 1,4 addition would proceed with the opposite sense. The Z-olefin **5** was prepared in high yields using a literature procedure.[9] In the event, however, reaction of **5** with nitromethane and DBU resulted in the desired addition product **6,** in high yield (Scheme 1). Compound **6** was

analyzed on the Chiralcel OJ column and was found to be a 1:1 mixture of diastereomers.

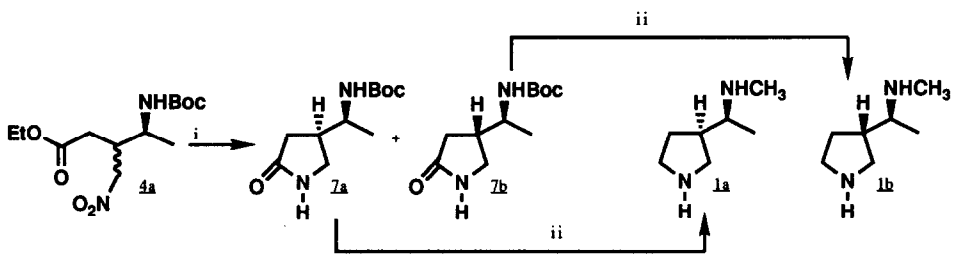
Scheme 1



i. CH_3NO_2/ DBU, ii. RaNi /CH_3OH

Having determined the selectivity of the 1,4-addition of nitromethane to olefin **2**, we completed the synthesis of **1a** and separated the diastereomers. Reduction of the nitro group of **4a**, with Raney nickel, followed by spontaneous ring closure yields two compounds, **7a** and **7b** as a 80: 20 mixture (90%). The desired diastereomer, **7a**, was successfully crystallized (EtOH) from the mixture to give pure 3R, 1S pyrrolidinone **7a** (50%) (Scheme 2). Reduction of the Boc group and the amide carbonyl of **7a** with LAH yielded the desired N-methylaminoethyl pyrrolidine **1a** (80%).

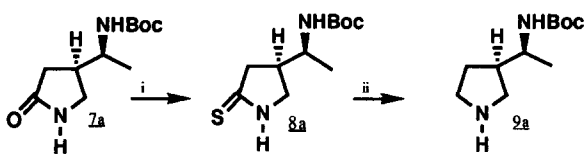
Scheme 2



i. RaNi/ CH_3OH, ii. LAH, THF reflux

Also of interest were the quinolones whose side chains had a primary amine at the 1 position. Selective reduction of the amide in **7a** in the presence of the Boc group using LAH, was not straight forward.

Scheme 3



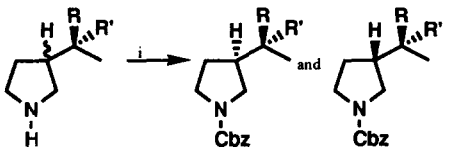
i. Lawesson's reagent/THF, ii. $NiCl_2$ $6H_2O$/ $NaBH_4$/THF-MeOH

To obtain the primary amine at the 1 position, the thioamide **8a** was prepared using Lawesson's reagent. Reduction of the thioamide with $NiCl_2.6H_2O$/ $NaBH_4$ gave the protected 1- amine **9a** [10] (Scheme 3).

To ensure the chiral integrity of the final pyrrolidine **1a**, the dibenzyloxycarbonyl derivatives **11a** and **11b** were prepared by conventional methods (Scheme 4). The stereochemistry of the final pyrrolidines **1a** and **1b** was confirmed to be the 3R,1S and 3S,1S respectively when **11a** and **11b** were compared by HPLC with derivatives previously prepared by an alternate route in which X-ray structures were assigned.[11] Also by comparing the products of the antipode derived from D-alanine we confirmed that no racemization had occured

at the 1 position in **1**.

Scheme 4



1a,b R= $NHCH_3$; R'= H **11a** R= NCH_3Cbz; R'= H **11b**

i. $ClCO_2CH_2Ph$, Et_3N, CH_2Cl_2

We have demonstrated a facile route to 3R-(1S-N-methylaminoethyl) pyrrolidines. The success of the 1,4 addition reaction is very dependent on the base used; DBU and DBN being optimal. The protecting group on the nitrogen influences the rate of the 1,4 addition reaction (Table 2), but the size of the substituent at the gamma position in **2** does not appear to influence the diastereoselectivity of the 1,4 addition reaction.

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5. Reagents tried included Et_2AlCN, Bu_4NCN, KCN, LiCN, $NCCO_2CH_3$. These reagents gave either poor yields and no diastereoselectivity or no reaction.
6. Silverman, R.B.; Andruszkiewicz, R. *Synthesis*, **1989**, 953-954.
7. HPLC conditions: Chiralcel OJ column, 98.5/1.5 hexane/ isopropyl alcohol 1ml/min, 214nm. Our thanks to Dr. S. Priebe and Mr. E. Charles for their assistance with the chiral HPLC studies.
8. The product **4d** was treated with dry HCl then base to yield the cyclic derivative. The ratio of diastereomers could be determined by ^1H NMR. The other products **4a-4c** were also treated in the same way. In all cases the diastereomeric ratios observed were 20:80; which correlates with the ratios observed from the chiral HPLC studies.
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