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Asymmetric Synthesis with Chiral Hydrogenolysable Amines. ω-Imino Esters Reduction : A Diastereoselective Route to ω-Alkyl Lactams

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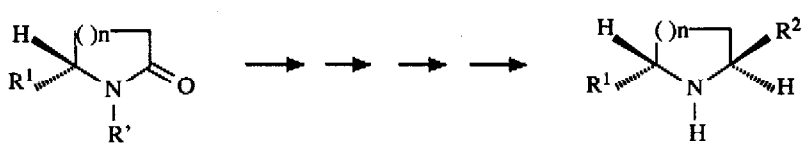
Abstract : Chiral methylbenzylamine is used to prepare ω-amino esters which are then transformed into ω-alkyl lactams with good diastereoselectivity.

A large number of substituted pyrrolidines and piperidines have been reported as constituants from the venoms of ants in the related genera *Monomorium* and *Solenopsis*, such as 2-(5-hexenyl)-5-nonylpyrrolidine **1a** and 2-methyl-6-undecylpiperidine **1b** which display significant insecticidal activity[1]. The use of chiral ω-alkyl lactams as a tool for enantioselective synthesis of alkaloids is a good strategy; pyrrolidine **1a** have been prepared from (R)-5-nonylpyrrolidinone **2b** (n=1; R^1= n-C_9H_{19}), easily obtained from a commercial (S)-pyroglutamic acid[2]. However, synthesis of Solenopsine A **1b** via 6-methylpiperidin-2-one **2b** (n=2; R'= CH_3) requires to start from a six membered ring amino acid not readily available and the literature reports only a long and uneasy preparation of 6-methylpiperidin-2-one by deracemization of 2-methylpiperidine and subsequent oxidation[3]. Only one asymmetric lactam synthesis has been described[4] by intramolecular Michael addition of a chiral amide anion to α,β-unsaturated ester to give (S)-(+)-2-oxo-6-piperidineacetic acid **2b** (R'= H, n= 2, R^1= CH_2CO_2H).

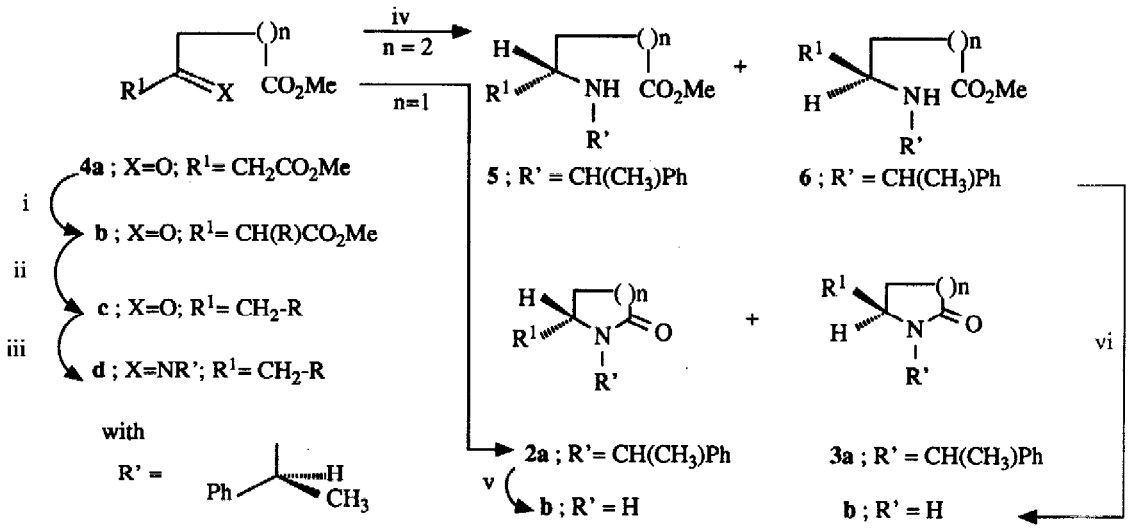


2b ; R'= H

1a ; n=1; R^1= n-C_9H_{19}; R^2= $(CH_2)_4$-CH=CH_2
1b ; n=2; R^1= CH_3; R^2= n-$C_{11}H_{23}$

We report preliminary results concerning a general strategy which permits a diastereoselective synthesis of ω-alkyl lactams **2b**, via asymmetric reduction of ω-imino esters **4d** obtained by reaction of ω-keto esters **4c** with hydrogenolysable cheap (R) or (S)-α-methylbenzylamine. Both amines have been widely used in the course of asymmetric imines alkylation with excellent enantiomeric excesses[5,6]. This

synthesis is based on a simple and general preparation of ω-oxoalkanoates **4b** (n=1,2; R^1=CH_3, n-C_9H_{19}, n-$C_{11}H_{23}$, $(CH_2)_2$-Ph,...) which can be obtained by mono C-alkylation of β-keto diesters **4a** with alkyl halides and potassium carbonate in acetone[7] followed by a chemoselective monodecarbomethoxylation using boric acid[8]. This method introduces more than one carbon unit, as compared to other general syntheses[9,10] (Scheme 1).



Reagents : (i) RX, K_2CO_3, acetone reflux; (ii) H_3BO_3, 110°C; (iii) $R'NH_2$, p.TsOH (cat.), toluene, azeotropic distillation, or $R'NH_2$, toluene, r.t., molecular sieves 4Å; (iv) reductions (Tables 1,2); (v) Na, liq. NH_3; (vi) H_2 (50 bar), Pd-C (10%); 50°C, 48h, AcOH.

Scheme 1

The best induction conditions were determined by the study of the reduction of ω-imino ester **4d** (n=1, R^1= CH_3) as a model easily prepared from common levulinic acid and (S)-α-methylbenzylamine .

After reduction, the resulting crude product was refluxed in toluene to give directly lactams **2a** and 3a (Table 1). Chemical reduction with sodium borohydride (run 10) and catalytic reduction (run 16) led to interesting results : chemical yields up to 60% and diastereoisomeric excesses closed to 70%. Catalytic hydrogenolysis was inefficient with lactams **2a** and **3a** but sodium in liquid ammonia led to a scalemic mixture of 5-methylpyrrolidin-2-one (52% yield) which showed a specific rotation value closed in magnitude and of opposite sign with that observed for the (R)-5-methylpyrrolidin-2-one **2a** prepared from (S)-pyroglutamic acid[11,12].

We can thus conclude that (S)-α-methylbenzylamine preferentially induces the formation of (S)-5-methylpyrrolidin-2-one **3a** by reduction of imino ester **4d** (n=1, R^1= CH_3).

Table 1 : Diastereoselective reduction of imino ester **4d** (n=1, R^1= CH_3)

Run	Conditions	Yield[a] %	d.e.[b] %	Run	Conditions	Yield[a] %	d.e.[b] %
1	$NaBH_3CN/CH_2Cl_2$	79	#0	9	$NaBH_4/CH_2Cl_2$	67	40
2	$NaBH_3CN/Et_2O$	19	#0	10	$NaBH_4/Et_2O$	61	65
3	KBH_4/MeOH	45	60	11	$NaBH_4$/THF	41	60
4	KBH_4/Et_2O	32	44	12	$NaBH_4$/THF (0°C)	47	70
5	KBH_4/THF	60	65	13	$NaBH_4$/HMPA	57	50
6	KBH_4/HMPA	58	60	14	H_2(1bar)/Pd-C/MeOH	66	40
7	$NaBH_4$/MeOH	47	50	15	H_2(1bar)/PtO_2/MeOH	78	50
8	$NaBH_4$/AcOH	69	20	16	H_2(100bar)/Ra.Ni/MeOH	63	70

[a] Calculated from lactam formation.

[b] Obtained by ^{1}H NMR (CH_3 doublet integration) of lactams **2a** and **3a** (n=1)

Based on the previous study, the best chemical and catalytic reduction conditions were applied to the 6-methylpiperidin-2-one precursor **4d** (n=2, R^1= CH_3). In that case, heterocyclization of amino esters **5a** and **6a** (n=2, R^1= CH_3) did not occur in refluxing toluene, not even without solvent at higher temperatures (Scheme 1). Diastereoisomeric excesses were measured at this stage (Table 2), and were nearly similar to those observed for the five-membered ring system. After catalytic debenzylation, ring closure was achieved, in acetic acid at 50°C with a 62% yield (Scheme 1).

The resulting scalemic mixture of lactams **2b** and **3b** (n=2, R^1= CH_3) presented a specific rotation value which permitted to conclude to the preferential formation of (S)-6-methylpiperidin-2-one **3b** by comparison with the literature value[10]. Extension to different six-membered lactams synthesis gave lower diastereoisomeric excesses and lower chemical yields (Table 2).

Table 2 : Diastereoselective reduction of imino esters **4d** (n=2) :

Run	R^1	Conditions	Yield[a] (%)	d.e. (%)
1	CH_3	H_2 (100bar)/Raney Ni/MeOH	80	64[b,c]
2	CH_3	$NaBH_4/CH_2Cl_2$	75	42[b,c]
3	CH_3	$NaBH_4/Et_2O$	67	50[b,c]
4	n-C_5H_{11}	$NaBH_4/Et_2O$	19	30[c]
5	n-$C_{11}H_{23}$	$NaBH_4/Et_2O$	35	16[c]
6	$(CH_2)_2$-Ph	$NaBH_4/Et_2O$	18	#0[c]
7	CH_2CO_2Me	$NaBH_4/Et_2O$	20	40[c]
8	CH_2CO_2Me	H_2 (100bar)/PtO_2/MeOH	32	56[c]

[a] Calculated from amino ester formation.

[b] Measured by ^{1}H-NMR (CH_3 doublet integration)

[c] Measured by ^{13}C-NMR (-CH(R)-N)

In conclusion, chiral methylbenzylamines are interesting amines for asymmetric synthesis of ω-alkyl lactams

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