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Stereoselective synthesis of *trans*-2,3-disubstituted pyrrolidines via addition to *N*-acyliminium ions

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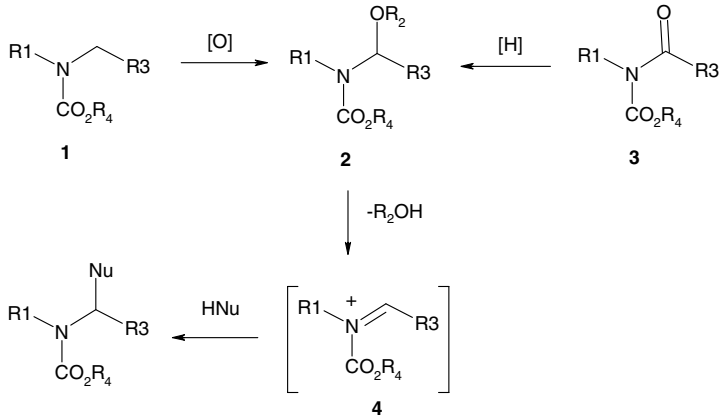
Abstract—An efficient and stereoselective synthesis of *trans*-2,3-disubstituted pyrrolidines is described. The intermolecular alkylation of racemic *N*-acyliminium ions generated in situ from the corresponding 3-substituted lactams proceeds stereoselectively and in high yield.

1. Introduction

Pyrrolidine derivatives are an important class of organic compounds due to their frequent occurrence in nature and their use as intermediates in the synthesis of natural products and pharmaceuticals.[1] Several polysubstituted pyrrolidines have shown very potent activities as enzyme inhibitors, or as agonists or antagonists of receptors. In addition to pharmaceutical applications, the pyrrolidine moiety has also seen wide use as a chiral auxiliary for asymmetric synthesis.[2] Accordingly, development of efficient general methods for the preparation of pyrrolidines is of significant value. There are numerous reports of syntheses of 2,3-disubstituted pyrrolidines in the literature in which the pyrrolidine ring is constructed by the formation of various different bonds from acyclic precursors.[3]

One of the most useful ways to obtain functionalization at the α position of amines is nucleophilic addition to *N*-acyliminium ion intermediates **4** (Scheme 1), which have been shown to have great synthetic potential.[4] *N*-Acyliminium ions can be generated from α-alkoxycarbonyl amines **2**, obtained either from the corresponding amines **1** by electrochemical oxidation[5] or from lactams **3** by partial reduction to the hemiaminal.[6]



Scheme 1.

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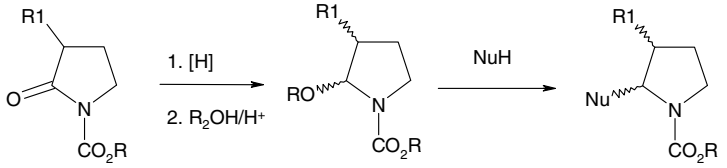
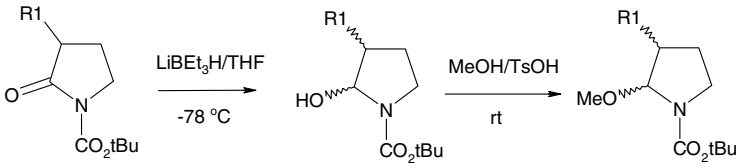


Scheme 2.



5a R_1= Me
5b R1= Ph

6a R_1= Me
6b R1= Ph

7a R_1= Me
7b R1= Ph

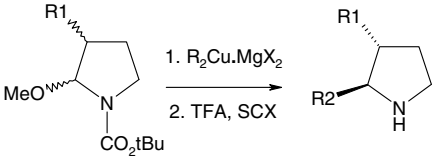
Scheme 3.

Intermediates **4** have been reacted with various nucleophiles or trapped intramolecularly by alkenes, alkynes, arenes, or heteronucleophiles, in the presence of Lewis acids.[4] In particular, additions of carbon nucleophiles to non-substituted cyclic five-membered iminium ions have been described, and this has been applied to the synthesis of a natural product.[7] Furthermore, additions to the corresponding substituted *N*-acyliminium ions to give 2,5 disubstituted pyrrolidines or prolines have been described with various stereochemical outcomes.[8] However, the intermolecular addition[9] of a nucleophile to the 3-substituted[10] *N*-acyl pyrrolidinium ion has not been reported to date.

In our quest for 2,3-*trans*-pyrrolidines we envisioned a straightforward synthesis from suitable 3-substituted lactams by addition of the corresponding nucleophiles to the *N*-acyl pyrrolidinium generated in situ (Scheme 2).

2. Discussion

The required aminals **7a**,**b**, precursors of the reactive *N*-acyliminium intermediates, were prepared from the corresponding substituted lactams **5a**[11] and **5b** (Scheme 3).[12] Selective partial reduction of the lactam group was accomplished using superhydride in THF at −78 °C.[13] Subsequent reaction of the hemiaminals **6a**,**b** in methanol in the presence of a catalytic amount of *p*-toluenesulfonic acid gave the corresponding aminals in quantitative yields. These compounds were used without further purification. The reaction of **7a**,**b** with 4 equiv of $R_2Cu{\cdot}MgX_2$ gave, after deprotection of the nitrogen, a mixture of 2,3-disubstituted pyrrolidines (Table 1) in good yields. The organocopper reagent was generated in situ from stoichiometric amounts of a Grignard reagent and copper(I) bromide–dimethyl sulfide complex at −40 °C with stirring for 45 min. The reaction mixture was cooled to −78 °C, and $BF_3{\cdot}OEt_2$ was added. After 30 min, the aminal **7a** or **7b** was added and the mixture allowed to react as it warmed from −78 °C to room temperature. Finally, hydrolysis of the carbamate group with TFA gave rise to the free pyrrolidines (Scheme 3). The diastereomeric ratio of the crude reaction mixture was determined by NMR, the major isomer being *trans*.



7a R_1= Me
7b R1= Ph

8a-8g

Table 1. Study of the addition of organocopper reagents to the *N*-acyliminium ions generated from aminals **7a** and **7b**[a]

Entry	R1	R2	*Trans*/*cis*[b]	Yield (%)[c]
1	Me	*iso*-Bu	60:40	50
2	Me	Ph	88:12[3a,b,p]	82
3	Me	3-F–Ph	87:13	96
4	Me	3-Me–Ph	88:12	97
5	Ph	*iso*-Bu	74:26	87
6	Ph	Ph	91:9[3o]	97
7	Ph	3-F–Ph	88:12	92

[a] All the reactions were carried out according to the general procedure.
[b] Diastereomeric ratio and configurational assignment were determined by NMR analysis. Diastereomeric ratio by integration of respective protons at position 2 and configurational assignment by the observation of NOE effects between the methyl signal in position 3 and proton in position 2 for major isomer *trans* **8b** and between phenyl proton signals and proton in position 2 for major isomer *trans* **8g**. The remaining compounds follow the same pattern.
[c] Yields refer to isolated pure compounds after SCX chromatography.

Table 1 shows that a variety of Grignard reagents can be successfully used, demonstrating the general applicability of this organometallic species in this reaction. Use

of the readily available Grignard reagents to generate the alkylcopper makes these the reagents of choice compared with their alkyllithium counterparts. The stereoselectivity of the reaction is dictated by purely steric factors, *trans* attack by the organometallic species taking place preferentially. The *trans* diastereoisomer is obtained with higher stereoselectivity when the organocopper reagent is bulkier (compare entry 1 with 2–4 and entry 5 with 6 and 7). However, the nature of substituent R1 is not so important in the stereochemical outcome of the reaction when the organocopper reagent is of the aryl type (compare entries 2–4 with 6 and 7). Nonetheless, it is notably more important when an alkyl organocopper reagent is used (compare entry 1 with 5).

In summary, we have described a mild, versatile, and efficient method for the preparation of 2,3-*trans*-disubstituted pyrrolidines by the intermolecular addition of organocopper nucleophiles to *N*-acyliminium ions generated in situ from the corresponding 3-substituted lactams. The overall synthetic transformation from the corresponding 3-substituted lactam (easily accessible) is very efficient and straightforward. Four reactions are carried out with only one final purification.

3. Typical experimental procedure

To a stirred suspension of $CuBr{\cdot}Me_2S$ (4 mmol) in dry ether (8 mL), at −40 °C under N_2, was added dropwise a solution of the corresponding Grignard reagent (4 mmol). After stirring for 45 min, the mixture was cooled to −78 °C, and $BF_3{\cdot}OEt_2$ (4 mmol) was added dropwise. After 30 min, a solution of **7a** or **7b** (1 mmol) in dry ether (1.5 mL) was added dropwise. The mixture was stirred for 15 min and allowed to reach room temperature over a period of 3 h. After 1 h at room temperature, the reaction was quenched with a mixture of an aqueous saturated NH_4Cl solution and concentrated NH_3 (1:1) (5 mL) and the mixture stirred for 1 h. The organic layer was separated, and the aqueous layer was extracted with ether (3×10 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was dissolved in CH_2Cl_2 (20 mL) and TFA (10 mmol) was added. The resulting solution was stirred overnight. The reaction mixture was concentrated to dryness and the residue filtered through an ion-exchange column. The *trans*:*cis* diastereomeric ratio was determined by ^1H NMR from this mixture.[14] Chromatographic separation of the major diastereoisomer (except in the isobutyl cases, entries 2 and 5) yielded final products that were fully characterized.[15]

Acknowledgments

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References and notes

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14. *N*-Boc deprotection was required due to doubling of the ^{1}H NMR signals because of rotamers, which makes the proton assignment very complex.
15. ^{1}H NMR for **8c**, **8d**, and **8g** in $CDCl_3$ are respectively: 7.28–7.20 (m, 2H), 7.15–7.10 (m, 1H), 6.95–6.90 (m, 1H), 3.55 (d, *J*: 8.5 Hz, 1H), 3.30–3.00 (m, 2H), 2.20–1.85 (m, 3H), 1.60–1.40 (m, 1H), 1.10 (d, *J*: 6.5 Hz, 3H); 7.25–7.05 (m, 4 H), 3.45 (d, *J*: 8.5 Hz, 1H), 3.30–3.15 (m, 1H), 3.05–2.95 (m, 1H), 2.38 (s, 3H), 2.20–2.00 (m, 3H), 1.65–1.50 (m, 1H), 1.10 (d, *J*: 6.5 Hz, 3H); 7.30–7.10 (m, 6H), 7.05–6.85 (m, 3H), 4.14 (d, *J*: 8.8 Hz, 1H), 3.40–3.20 (m, 2H), 3.10 (dd, *J*: 17.7 and 8.8 Hz, 1H), 2.30–2.15 (m, 3H).