Acta Chemica Scandinavica, 1994: 48: 367–371
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ACTA
CHEMICA SCANDINAVICA
ISSN 0904–213X

Stereoselective Addition of Organocopper Reagents to Cyclic *N*-Acyliminium Ions

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Ludwig, C. and Wistrand, L.-G., 1994. Stereoselective Addition of Organocopper Reagents to Cyclic *N*-Acyliminium Ion. – Acta Chem. Scand. 48: 367–371
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Addition of alkylcopper reagents to the chiral *N*-acyliminium ion **2a** occurs with a high degree of *trans* selectivity, in contrast with the addition of π-nucleophiles, where *cis* selectivity has been observed. A mechanism involving the formation of a pre-complex has been proposed in order to account for this selectivity.

N-Acyliminium ions have been shown to be versatile intermediates in the synthesis of naturally occurring alkaloids and amino acids.[1–6] In particular, intramolecular reactions using chiral *N*-acyliminium ions have been reported to display a high degree of stereoselectivity.[7,8] Varying degrees of stereoselectivity have been reported using the corresponding intermolecular approach. The problem with the intermolecular reaction is the relative insensitivity of the selectivity to the nucleophile; i.e., the selectivity is determined largely by the structure of the cation. Thus for example, Shono and coworkers have reported that the non-racemic *N*-acyliminium ion **1a** (prepared *in situ* from the corresponding α-methoxy compound **1** by treatment with a Lewis acid) derived from natural (*S*)-proline, reacts with various nucleophiles, e.g., allyltrimethylsilane, vinyl acetate and malonic ester derivatives[9,10] with essentially identical stereoselectivity (*cis*:*trans* ~ 7:3, see Scheme 1).[11]

On the other hand, reaction of the *N*-acyliminium ion **2a** with nucleophiles occurs with a high degree of *cis* selectivity.[12,13] This has been attributed to stereoelectronically controlled attack on the conformation with an axial ester group, which is the thermodynamically preferred conformation due to $A^{1,3}$ strain.[14,15] We recently reported that treatment of **1** with alkyl- and alkenyl-copper reagents in the presence of $BF_3 \cdot Et_2O$ gives a reversed and increased stereoselectivity.[16–18] For example, treatment of **1** with two equivalents each of heptylcopper and $BF_3 \cdot Et_2O$ gives the corresponding *trans*-5-heptylproline (*cis*:*trans* = 3:97). A mechanism involving nucleophilic attack on the least hindered face of a sterically biased *N*-acyliminium ion–copper complex was suggested.

Results and discussion

In this report, we present results from the addition of organocopper reagents to the corresponding six-membered ring, i.e., the non-racemic *N*-acyliminium ion **2a**. The precursor to **2a**, the α-methoxylated pipecolic acid derivative **2**, was prepared from L-lysine using a modification of the procedure reported in the literature.[19,20] Thus, *N*-acylation and esterification of L-lysine gave the protected intermediate **3**, which upon anodic methoxylation (4.5 F mol^{-1}, MeOH–Bu_4NBF_4) furnished the α-methoxy compound **4**. Finally, treatment with *p*-toluenesulfonic acid gave the desired pipecolic acid derivative **2** (Scheme 2). These four steps were carried out without purification of any of the intermediates with an overall yield of 39%.

When **2** was reacted with 4 equivalents each of PrCu and $BF_3 \cdot Et_2O$, the formation of two propylated isomers in a 96:4 ratio was observed. In order to identify these isomers, the *cis* compound **6a** was prepared independently by allylation of **2** (allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, −78 °C) followed by hydrogenation (H_2, Pd–C, EtOH). Allylation of **2** has been reported to give exclusive *cis* substitution;[12,13] in our hands, a *cis*:*trans* ratio of 95:5 was observed. Gas chromatographic separation of the reaction mixtures established the major isomer in the propylation reaction as the *trans* isomer, **6b** (Scheme 3).

Similar selectivities were observed on butylation and heptylation of **2** using the corresponding alkylcopper reagent in combination with $BF_3 \cdot Et_2O$ (Table 1). Thus, alkylation of **2** using alkylcopper reagents gives a reversed selectivity compared with π-nucleophiles, behavior which parallels that of the corresponding proline derivative, **1**.

The identity of **7b** and **8b** was established from their ^1H NMR spectra. In addition to the resemblance to the spectrum of **6b**, the spectra showed the presence of one equatorial proton α to the ester group and one axial proton α

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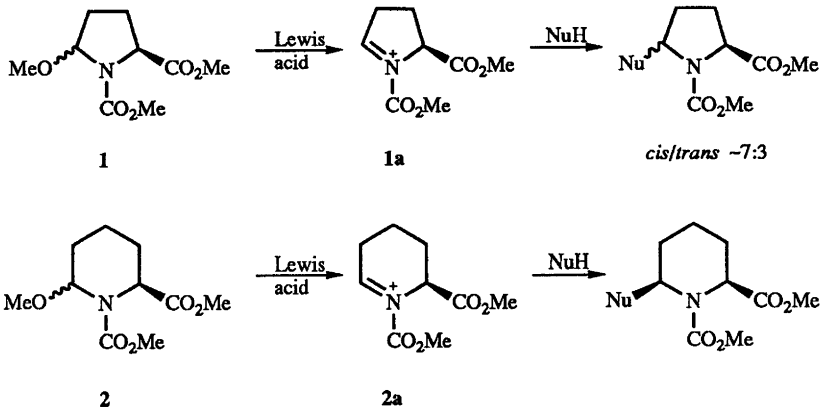


Scheme 1.

to the alkyl group as determined by the vicinal coupling constants, consistent with a relative *trans* stereochemistry.[21] Thus, an intermediate *N*-acyliminium ion–copper(I) complex similar to that suggested for the corresponding proline derivative, shown in Scheme 4, can be invoked in order to rationalize the stereoselectivity of the reaction between **2a** and alkylcopper reagents.

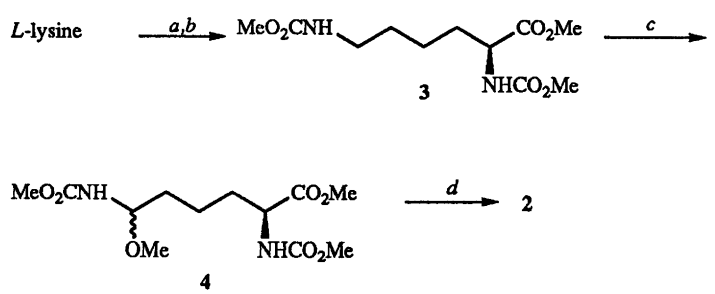
Intermediate copper–alkene π-complexes have been observed[22] and isolated[23] in the conjugate addition of organocuprates to α,β-unsaturated esters. Intramolecular coordination of cuprate reagent to oxygen in the conjugate addition of Me_2CuLi to an *ortho*-methoxymethyl cinnamic ester has been suggested.[22] One of the resonance forms of *N*-acyliminium ions is actually a cationic aza analogue of an α,β-unsaturated carbonyl compound and thus, an intermediate copper(I)–olefin d–π* complex should be energetically favorable owing to the electron-poor double bond.

In order to clarify the role of the ester group for coordination in the intermediate complex, we have also investigated the racemic *N*-acyliminium ion precursor **10** which was prepared by a regioselective anodic methoxylation of the corresponding racemic 2-methylpiperidine.[24] Reaction of **10** with allyltrimethylsilane in the presence of $TiCl_4$ gave a 97:3 diastereomeric mixture in favor of the *cis* isomer (in analogy with **2** and as indicated by the ^1H NMR spectrum). Catalytic hydrogenation of **11a** then gave **12a**. Reaction of **10** with PrCu in the presence of $BF_3 \cdot Et_2O$ at −78 °C produced a mixture of **12a** and **12b** in a ratio of 24:76 (Scheme 5). This decrease in selectivity, compared with that observed for **2**, indicates the importance of the ester group for the formation of an intermediate face-selective complex.

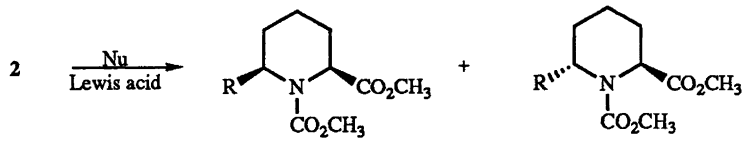
In conclusion, we have shown that addition of organocopper reagents to the chiral *N*-acyliminium ion **2a** occurs with a high degree of *trans* selectivity. The possibility of controlling the stereoselectivity by appropriate choice of nucleophile should extend the usefulness of *N*-acyliminium ions in synthetic applications.

Experimental

General. All chemicals used were of highest commercial quality and used without further purification, except as noted. Light petroleum (b.p. 60–80 °C) and ethyl acetate, used for chromatography, were distilled before use. $BF_3 \cdot Et_2O$ was distilled from CaH_2 before use and stored under an atmosphere of argon. $CuBr \cdot Me_2S$ was prepared according to the method described by House.[25] The alkyllithium reagents were prepared from the corresponding alkylbromide and lithium powder in Et_2O at −10 °C, and the concentration of the alkyllithium solution (usually around 0.5 M) was determined by titration as described by Watson and Eastham.[26] Reaction mixtures were analyzed by capillary GC using a Varian 3400 chromatograph equipped with a Varian 4270 integrator on a



Scheme 2. *a*, $ClCO_2Me$–NaOH; *b*, HCl–MeOH; *c*, −2e, MeOH–Bu_4NBF_4; *d*, TSOH.



5a, R= allyl
6a, R= C_3H_7
7a, R= n-C_4H_9
8a, R= n-C_7H_{15}
9a, R= n-$C_{11}H_{23}$

5b, R= allyl
6b, R= C_3H_7
7b, R= n-C_4H_9
8b, R= n-C_7H_{15}
9b, R= n-$C_{11}H_{23}$

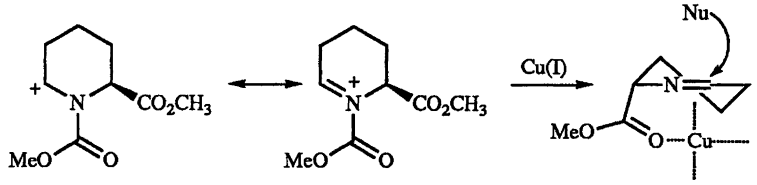
Scheme 3.

25 m × 0.25 mm OV 1701 column and by TLC on commercially available silica gel/aluminium foil plates. Flash chromatography was performed on TLC grade gel according to Taber.[27] ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian XL 300 instrument unless otherwise stated, δ being given in ppm downfield from $SiMe_4$ and coupling constants in hertz. Optical rotations were determined on a Perkin-Elmer 141 instrument. High resolution mass spectra [MS(hr)] were obtained using a Jeol SX 102 instrument, with direct inlet.

(2S)-Dimethyl 6-methoxypiperidine-1,2-dicarboxylate **2**. The *N*-acyliminium ion precursor **2** was prepared in four steps without purification of the intermediates. To a stirred solution of L-lysine (0.1 mol, 18.2 g) in 2 M aq. NaOH (100 ml) was added simultaneously methyl chloroformate (0.2 mol) in toluene (25 ml) and 100 ml of 2 M aq. NaOH. After being stirred for 1 h, the mixture was cooled to 0 °C and acidified with 4 M aq. HCl. The mixture was extracted with EtOAc which was then dried ($MgSO_4$) and evaporated, giving 23 g of crude product.

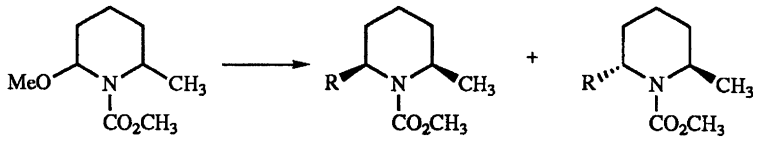
The *N*-protected L-lysine was then dissolved in MeOH (1000 ml), cooled to 0 °C and the solution was saturated with HCl (g). The mixture was stirred overnight and then evaporated. The residue was dissolved in CH_2Cl_2 and anhydrous K_2CO_3 was added with stirring. The mixture was filtered and evaporated to give **3** (21.8 g) as a white solid. Anodic oxidation of the crude product (40 mmol, 11.0 g) in MeOH–Bu_4NBF_4 (0.05 M) using an undivided cell and graphite electrodes was then carried out. The reaction was monitored by TLC and was interrupted after 4.5 F mol^{-1}. The solution was evaporated and triturated with diethyl ether which was filtered and evaporated to give 11.6 g of crude product. The product was dissolved in MeOH and *p*-toluenesulfonic acid (5.9 g, 31 mmol) was added. The reaction was monitored by TLC and, after 35 min, the reaction was complete and CH_2Cl_2 was added. The mixture was extracted with aq. satd. $NaHCO_3$, H_2O, dried ($MgSO_4$) and evaporated. Purification by column chromatography (silica gel, light petroleum–ethyl acetate 3:2) gave **2** (4.57 g, 39% from L-lysine) as a colorless liquid. ^{1}H NMR (300 MHz): δ 5.44 (s, 0.5 H), 5.26 (s, 0.5 H), 4.89 (s, 0.5 H), 4.7 (s, 0.5 H), 3.76, 3.74 (2 s, 3 H), 3.70 (s, 3 H), 3.30, 3.27 (2 s, 3 H), 2.12–2.38 (m, 1 H), 1.68–1.98 (m, 2 H), 1.4–1.68 (m, 3 H).

General procedure for reaction of **2** *with alkylcopper reagents*. To a stirred solution of CuBr·Me_2S (12 mmol) in anhydrous diethyl ether (40 ml) was added dropwise a solution of the appropriate alkyllithium in diethyl ether (12 mmol) at −25 °C. After stirring for 30 min, the mixture was cooled to −70 °C and BF_3·Et_2O (12 mmol) was added dropwise. After 5 min, a solution of **2** (3.03 mmol) in anhydrous diethyl ether (5 ml) was added dropwise and after 10 min, the reaction mixture was allowed to reach ambient temperature. The reaction was quenched with a mixture of satd. aq. NH_4Cl and conc. NH_3 (1:1) and stirred for 1 h. The ether layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined phases were washed with satd. aq. $NaHCO_3$, dried ($MgSO_4$), filtered and evaporated.



2a

Scheme 4.



10 **11a**, R= allyl; **12a**, R= C_3H_7 **11b**, R= allyl; **12b**, R= C_3H_7

Scheme 5.

*(2S,6R)-Dimethyl 6-propylpiperidine-1,2-dicarboxylate (**6b**)* The crude product was purified by column chromatography (silica gel; light petroleum–ethyl acetate 7:3) to give **6b** as a colorless liquid. Yield: 58%. ^{1}H NMR (300 MHz, 40°C): δ 4.48 (t, *J* 5.9, 1 H), 4.06 (dddd, *J* 7.7, 5.2, 5.2, 2.6, 1 H), 3.73 (s, 3 H), 3.68 (s, 3 H), 1.84–2.03 (m, 2 H), 1.40–1.84 (m, 6 H), 1.21–1.40 (m, 2 H), 0.93 (t, *J* 7.3, 3 H). MS (hr): 200.0923, calc. for $C_{12}H_{21}O_4N - C_3H_7$: 200.0923. $[\alpha]_D^{25} = -41.6$ (*c* 0.6, MeOH).

*(2S,6R)-Dimethyl 6-butylpiperidine-1,2-dicarboxylate (**7b**)* The crude product was purified by column chromatography (silica gel; light petroleum–ethyl acetate 3:1) to give **7b** as a colorless liquid. Yield: 82%. ^{1}H NMR (300 MHz, 50°C): δ 4.19 (t, *J* 5.8, 1 H), 4.04 (dddd, *J* 8.2, 5.5, 5.5, 2.6, 1 H), 3.76 (s, 3 H), 3.68 (s, 3 H), 1.89–2.01 (m, 2 H), 1.78–1.85 (m, 1 H), 1.40–1.78 (m, 5 H), 1.21–1.40 (m, 4 H), 0.90 (t, *J* 6.9, 3 H). MS (hr): 257.1641, calc. for $C_{13}H_{23}O_4N$: 257.1627. $[\alpha]_D^{25} = -48.9°$ (*c* 1.0, MeOH).

*(2S,6R)-Dimethyl 6-heptylpiperidine-1,2-dicarboxylate (**8b**)* The crude product was purified by column chromatography (silica gel; light petroleum–ethyl acetate 3:1) to give **8b** as a colorless liquid. Yield: 78%. ^{1}H NMR (300 MHz, 50°C): δ 4.18 (t, *J* 5.9, 1 H), 4.03 (dddd, *J* 7.8, 5.3, 5.3, 2.8, 1 H), 3.73 (s, 3 H), 3.68 (s, 3 H), 1.82–2.11 (m, 2 H), 1.38–1.82 (m, 6 H), 1.18–1.34 (m, 10 H), 0.86 (t, *J* 6.6, 3 H). MS (hr): 299.2102, calc. for $C_{16}H_{29}O_4N$: 299.2097. $[\alpha]_D^{25} = -30.0°$ (*c* 1.0, MeOH).

*(2S,6R)-Dimethyl 6-undecylpiperidine-1,2-dicarboxylate (**9b**)* The crude product was purified by distillation in a Kugelrohr apparatus followed by column chromatography (silica gel: light petroleum–ethyl acetate 4:1) to give **9b** as a colorless liquid. Yield: 86%. ^{1}H NMR (300 MHz): δ 4.11–4.21 (m, 1 H), 4.02–4.09 (m, 1 H), 3.72 (s, 3 H), 3.68 (s, 3 H), 1.91–2.02 (m, 2 H), 1.40–1.81 (m, 7 H), 1.22–1.33 (m, 17 H), 0.90 (t, *J* 6.6, 3 H). MS (hr): 355.2723, calc. for $C_{20}H_{37}O_4N$: 355.2723. $[\alpha]_D^{25} = -31.9°$ (*c* 1.0, MeOH).

*(2S,6S)-Dimethyl 6-allylpiperidine-1,2-dicarboxylate (**5a**).* To a stirred solution of **2** (0.70 g, 3.03 mmol) in CH_2Cl_2 (25 ml) at −70°C was added allyltrimethylsilane (0.96 ml, 6.06 mmol) and $TiCl_4$ (0.33 ml, 3.03 mmol). After 40 min, the reaction was complete as monitored by TLC and was allowed to reach ambient temperature. After being stirred with solid $Na_2CO_3 \cdot 10\ H_2O$, and dried ($MgSO_4$), the solution was filtered through Celite and evaporated. The product was used without further purification.

*(2S,6S)-Dimethyl 6-propylpiperidine-1,2-dicarboxylate (**6a**)* was prepared by hydrogenation at atmospheric pressure of **5a** in MeOH (25 ml) using palladium-on-carbon (10%, 100 mg) as the catalyst. The reaction mixture was filtered through Celite and the solvent was evaporated off. The product was purified by column chromatography (silica gel; light petroleum–ethyl acetate 4:1) to give a mixture of **6a** and **6b** in a ratio of 95:5 as determined by GLC analysis. Yield: 60% from **2**. ^{1}H NMR (300 MHz): 4.86 (br s, 1 H), 4.19 (m, 1 H), 3.71 (s, 3 H), 3.69 (s, 3 H), 2.2–2.35 (m, 1 H), 1.42–1.70 (m, 6 H), 1.21–1.40 (m, 3 H), 0.87 (t, *J* 7.1, 3 H). MS (hr): 200.0919, calc. for $C_{12}H_{21}O_4N - C_3H_7$: 200.0923. $[\alpha]_D^{25} = -69.1°$ (*c* 1.0, MeOH).

*Methyl 2-methyl-6-propylpiperidine-1-carboxylate (**12a**)* was prepared from **10** using the same method as for **6a**. The crude product was purified by column chromatography using light petroleum–ethyl acetate (7:3) as the eluent. Yield: 84% from **10**. ^{1}H NMR (300 MHz): δ 4.31 (p, *J* 6.3, 1 H), 4.10 (q, *J* 6.1, 1 H), 3.66 (s, 3 H), 1.21–1.80 (m, 10 H), 1.15 (d *J* 7.0, 3 H), 0.89 (t, *J* 7.2, 3 H).Reaction of **10** with PrCu was performed using the same procedure as described above and gave a mixture of **12a** and **12b** (24:76). Purification by column chromatography (silica gel; light petroleum–ethyl acetate 7:3) gave **12a**/**12b** in 37% yield. ^{1}H NMR (**12b**, 300 MHz): δ 3.81–3.97 (m, 2 H), 3.67 (s, 3 H), 1.27–1.93 (m, 10 H), 1.25 (d *J* 6.6, 3 H), 0.91 (t, *J* 7.2, 3 H). MS (hr): 199.1557, calc. for $C_{11}H_{21}O_2N$: 199.1573.

Acknowledgements. Financial support from the Swedish Natural Science Research Council and the Technical Research Council is gratefully acknowledged.

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Received November 3, 1993.