

Studies on the Niobium Pentachloride-Mediated Nucleophilic Additions to an Enantiopure Cyclic *N*-acyliminium Ion Derived from (*S*)-malic acid

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A adição nucleofílica de vários nucleófilos (alilsilano, silil enol éter da acetofenona, indol e *N*-sulfonilindol) ao íon *N*-acilimínio enantiopuro **1a**, derivado do ácido (*S*)-málico, promovida por pentacloreto de nióbio é descrita. Os produtos foram obtidos em bons rendimentos e em diastereosseletividades variáveis dependendo do volume estérico do nucleófilo. Os melhores resultados foram obtidos com a adição de indóis.

The nucleophilic addition of several nucleophiles (allyltrimethylsilane, silyl enol ether from acetophenone, indole and *N*-sulfonylindole) to the enantiopure cyclic *N*-acyliminium ion **1a**, derived from (*S*)-malic acid, promoted by niobium pentachloride is described. The products were obtained in good yields and in variable diastereoselectivities depending on the steric bulkiness of the nucleophile. The best results were obtained with the addition of indoles.

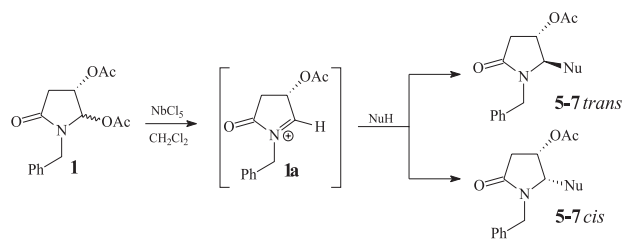
Keywords: *N*-acyliminium ions, niobium pentachloride, nucleophilic additions, diastereoselectivity

Introduction

The search for new Lewis acids that effectively promote the formation of *N*-acyliminium ions has been the subject of many studies.¹ These ions are very important in organic synthesis since they are reactive intermediates involved in the synthesis of many compounds with interesting biological properties, especially alkaloids.^{2,3}

Recently, the use of niobium pentachloride as a novel and efficient Lewis acid in nucleophilic additions to cyclic *N*-acyliminium ions was reported by us.^{4,5} Now we wish to report our preliminary results on the diastereoselectivity control in these reactions.⁶

The enantiomerically pure substrate **1** was prepared in 3 steps, as a diastereomeric mixture, from commercially available (*S*)-malic acid, according to a known procedure.^{3,7} In the presence of 0.6 equiv. of NbCl₅ in CH₂Cl₂, at 0°C, the presumed *N*-acyliminium ion **1a** was formed in 20 min (Scheme 1), as evidenced by the consumption of **1** by TLC. Next, the nucleophiles were added and the reactions were followed by TLC, affording the respective compounds **5-7** (Scheme 1).

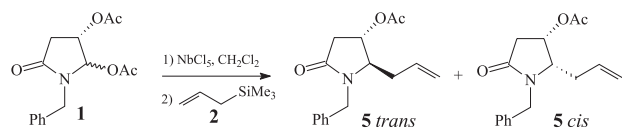


Scheme 1. Nucleophilic additions to the *N*-acyliminium ion **1a**.

Three classes of nucleophiles were investigated: allyltrimethylsilane (**2**), silyl enol ether (from acetophenone) (**3**), and indoles (indole **4a** and *N*-sulfonylindole **4b**).

The addition of allylsilane **2** (Scheme 2) was used as a model and the results are summarized in Table 1.

The reaction did not work with a 25 mol % amount of NbCl₅ (entry 1). On the other hand, a substoichiometric



Scheme 2. NbCl₅-mediated addition of allylsilane **2** to the substrate **1**.

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Table 1. Conditions and results for the synthesis of compound **5**

Entry	NbCl ₅ (equiv.)	2 (equiv.)	Temp. (°C)	time (h)	5 <i>cis:trans</i> ^c	Yield (%) ^d
1	0.25	1.3	rt ^a	16	-	-
2	0.60	1.3	0	1.5	-	25
3	0.60	1.3	0	3	-	48
4	0.60	2.0	rt ^a	13	1 : 2	68
5	0.60	3.0	rt ^a	16	1 : 2	80
6	0.60	3.0	rt ^b	18	1 : 2	86

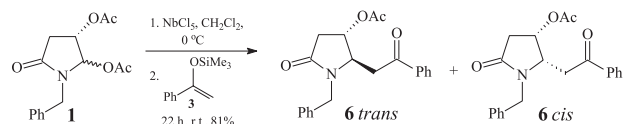
^a 2 hours at -78 °C, then rt; ^b 2 hours at 0 °C, then rt; ^c Determined by ¹H-NMR integration of the hydrogen attached to the α-nitrogen carbon; ^d Isolated yield of the chromatographically pure products.

amount of NbCl₅ (0.6 equiv) was enough to generate the *N*-acyliminium ion from substrate **1**.

A mixture of compounds **5 trans** and **5 cis** were obtained in better yields when 3 equiv. of the allylsilane were used (entries 5 and 6) in a relative ratio of 2:1 favoring the **5 trans** isomer and this ratio remained unchanged regardless of the experimental conditions used. The ratio of isomers and their relative stereochemistry were determined by ¹H-NMR integration of the hydrogen attached to the α-nitrogen carbon and by its chemical shift, respectively, comparing to literature data for similar compounds.^{3,8,9}

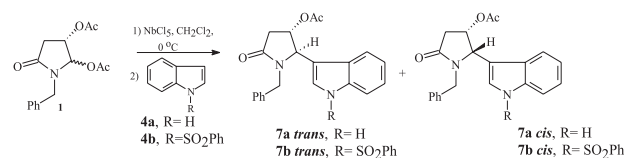
Although the *N*-acyliminium ion **1a** can be generated at -78 °C, the reactions did not proceed at this temperature (even after 2 h the products could not be detected by TLC). However, when the reaction was warmed up to room temperature the products were obtained in good yields after stirring for 13-16h (entries 4 and 5).

A similar level of diastereoselectivity was obtained in the addition of the silyl enol ether of acetophenone **3** (2 equiv.) to the cation **1a**. The 2:1 mixture of compounds **6 trans** and **6 cis**, respectively, was obtained in 81% yield (Scheme 3). The ratio of isomers and their relative stereochemistry were determined as above comparing with literature data for the same compounds.⁸

**Scheme 3.** NbCl₅-mediated addition of silyl enol ether **3** to the substrate **1**.

This low diastereoselectivity was unexpected in view of the better results with other Lewis acids such as InCl₃ which gave a *trans: cis* ratio of 10:1.⁸

Next, we investigated the indole compounds **4a** and **4b** as nucleophiles, which are not so commonly used in nucleophilic additions to *N*-acyliminium ions (Scheme 4).¹⁰ The results obtained were noteworthy and are summarized in Table 2.

**Scheme 4.** NbCl₅-mediated addition of indoles **4a** and **4b** to the substrate **1**.

The addition of indole **4a** to the *N*-acyliminium ion **1a** gave a mixture of compounds **7a trans** and **7a cis** (80-90% yield) in a **7a trans: 7a cis** = 6:1 ratio (entries 1 and 2). As expected, the major isomer showed a *trans* configuration. This was confirmed by the analysis of the ¹H-NMR spectrum of **7a trans** and **7a cis**. The hydrogen attached to the α-nitrogen carbon of the major **7a trans** isomer appears as a doublet with a small coupling constant (*J* 1.4 Hz) at 4.76 ppm whereas the same proton of the **7a cis** isomer appears also as a doublet at 5.03 ppm but with a larger coupling constant (*J* 6.2 Hz). This difference in *J* values is in agreement with the reported data for the *trans* and *cis* isomers in similar compounds.^{3,8,9} The ratio of isomers was measured by ¹H-NMR integration of these signals.

Table 2. Conditions and results for the synthesis of compounds **7a** and **7b**

Entry	Indole(equiv.)	Temp. (°C) ^a	time (h)	7a,b cis:trans ^b	Yield (%) ^c
1	4a (1.2)	rt	20	7a 1 : 6	80
2	4a (2.0)	rt	18	7a 1 : 6	90
3	4b (2.0)	rt	36	7b 1 : 15	75

^a 2 hours at 0°C, then rt; ^b Determined by ¹H-NMR integration of the hydrogen attached to the α-nitrogen carbon; ^c Isolated yields of the chromatographically pure products.

The reaction of the bulkier *N*-sulfonylindole **4b** showed a high level of diastereoselectivity with a ratio of 94:6, favouring the **7b trans** isomer in 75% isolated yield (entry 3).

On the other hand, probably due to the strongly electron withdrawing sulfonyl group attached to the indole nitrogen, the reaction with compound **4b** was slower as compared to indole **4a** (see entries 2 and 3).

The stereochemistry of the isomers was once more assigned based on spectroscopic data. Similar to the data for compounds **7a trans** and **7a cis**, the hydrogen attached to the α -nitrogen carbon of the major isomer in compound **7b trans** appears at 4.61 ppm (broad singlet) whereas in the *cis* isomer **7b** it appears at 4.90 ppm (doublet, *J* 7.0 Hz).

The preference for *anti* addition can be rationalized by previously reported *antiperiplanar* and *synclinal* models shown in Figure 1 in which the preferential approach of the nucleophile occurs at the opposite face of the acetoxy group in the cyclic *N*-acyliminium ion.⁸ This explains the increase in the diastereoselectivity with an increase in the steric bulkiness of the nucleophile when indoles **4a** and **4b** were used.

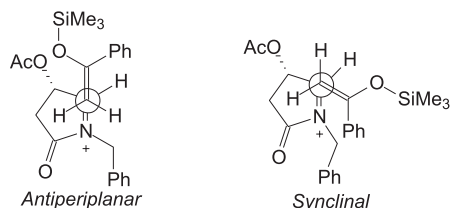


Figure 1. Proposed models for the nucleophilic attack on cyclic *N*-acyliminium ions.

Although the selectivities shown in this work are not superior to other common Lewis acids such as InCl_3 and TMSOTf some advantages associated with this methodology must be considered: NbCl_5 is solid and if handled and stored properly can be used without the need of purification; a substoichiometric amount of NbCl_5 is enough to generate the *N*-acyliminium ions; NbCl_5 is abundant in Brazil (Brazil accounts for 86% of total niobium production) and is less expensive than InCl_3 and TMSOTf (Aldrich catalog); and the reaction can be run in non-cryogenic temperatures. Besides, the results with indoles are promising and can be addressed in a future work.

In summary, NbCl_5 has proved to be an efficient Lewis acid in the formation of enantiopure *N*-acyliminium ions broadening even more the scope of this versatile reagent in organic synthesis.

The diastereoselectivity of this reaction proved to be dependent on the steric bulkiness of the nucleophile, at

least in the case of indoles. Studies towards the intramolecular version of this reaction are under investigation.

Experimental

All reactions involving Lewis acids were performed under argon in a flame-dried flask. CH_2Cl_2 was distilled from CaH_2 prior to use. NbCl_5 was supplied by Companhia Brasileira de Mineração e Metalurgia (CBMM). (*S*)-Malic acid was purchased from Aldrich.

IR spectra were recorded on a BOMEM Hartman & Braun – Michelson MB series 100 LASER FT-IR. NMR spectra were recorded on a Varian Mercury Plus 300 spectrometer. Chemical shifts are reported in ppm from tetramethylsilane as internal reference. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, td = triplet of doublets, ddd = doublet of doublets of doublets, m = multiplet, etc), coupling constant and integration.

Column chromatography was performed on silica gel (70-230 mesh).

General procedure for the nucleophilic attack to the *N*-acyliminium ions

To a NbCl_5 (0.6 mmol) suspension in CH_2Cl_2 (3 cm^3) at 0 °C, under an argon atmosphere, was added substrate **1** (1.0 mmol), diluted in CH_2Cl_2 (2 cm^3). After 20 min, the nucleophile (2.0 or 3.0 mmol) was added. After the time specified in the Tables, the reaction was quenched with sat. NaHCO_3 (4 cm^3), extracted with CH_2Cl_2 (2 x 10 cm^3), dried over Na_2SO_4 and concentrated at reduced pressure to furnish the crude products **5-7**, which were purified by silica gel chromatography (20% EtOAc in hexanes). The *cis* and *trans* isomers of compounds **5-7** were not separated during the chromatographic purification.

(2*RS*,3*S*)-2-Allyl-1-benzyl-5-oxopyrrolidin-3-yl acetate (**5**, mixture of *cis* and *trans* isomers)

5 trans. IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3065, 3030, 2931, 1740, 1694, 1443, 1237, 1033, 703; $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 1.98 (s, 3H), 2.20-2.40 (m, 2H), 2.44 (dd, *J* 18.0, 1.2 Hz, 1H), 2.87 (dd, *J* 18.0, 6.0 Hz, 1H), 3.45 (dd, *J* 6.6, 4.5 Hz, 1H), 3.98 (d, *J* 15.0 Hz, 1H), 5.00-5.20 (m, 2H), 5.25-5.40 (m, 2H), 5.51-5.60 (m, 1H), 7.22-7.40 (m, 5H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 20.9, 34.7, 37.7, 44.2, 62.3, 71.1, 119.7, 127.7, 127.8, 128.1, 132.0, 136.0, 170.3, 172.0.

5 cis. IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3065, 3030, 2931, 1740, 1694, 1443, 1237, 1033, 703; $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ

2.05 (s, 3H), 2.20-2.80 (m, 4H), 3.58 (dd, J 13.5, 6.0 Hz, 1H), 3.88 (d, J 15.0 Hz, 1H), 5.00-5.20 (m, 2H), 5.25-5.40 (m, 2H), 5.51-5.60 (m, 1H), 7.22-7.40 (m, 5H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 20.9, 32.0, 37.9, 44.2, 59.0, 68.2, 118.7, 127.7, 127.8, 128.1, 133.0, 136.0, 170.1, 172.0.

(2*RS*,3*S*)-1-Benzyl-5-oxo-2-(2-oxo-2-phenylethyl)pyrrolidin-3-yl acetate (**6**, mixture of *cis* and *trans* isomers)

6 trans. IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3072, 3029, 2935, 1738, 1692, 1677, 1448, 1240, 1033, 703; $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 2.02 (s, 3H), 2.53 (dd, J 18.0, 1.5 Hz, 1H), 3.10 (ddd, J 18.0, 6.9, 0.8 Hz, 1H), 3.15 (dd, J 17.5, 6.4 Hz, 1H), 3.27 (dd, J 17.5, 4.9 Hz, 1H), 4.00 (ddd, J 6.3, 4.9, 1.2 Hz, 1H), 4.18 (d, J 15.2 Hz, 1H), 4.75 (d, J 15.2 Hz, 1H), 5.12 (dt, J_d 6.73 Hz, J_t 1.5 Hz, 1H), 7.10-7.80 (m, 10H). $^{13}\text{C-NMR}$ (75MHz, CDCl_3): δ 20.9, 36.9, 39.3, 44.8, 61.0, 72.1, 127.6, 127.9, 128.6, 128.7, 133.5, 136.1, 136.2, 170.5, 172.4, 196.4.

6 cis. IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3072, 3029, 2935, 1738, 1692, 1677, 1448, 1240, 1033, 703; $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 2.02 (s, 3H), 2.41 (dd, J 18.0, 2.1 Hz, 1H), 2.83-2.91 (m, 1H), 2.97 (dd, J 7.0, 1.1 Hz, 1H), 3.03 (dd, J 7.0, 0.8 Hz, 1H), 4.16-4.22 (m, 1H), 4.17 (d, J 15.5 Hz, 1H), 4.92 (d, J 15.5 Hz, 1H), 5.0 (ddd, J 7.0, 2.06, 0.96 Hz, 1H), 7.10-7.80 (m, 10H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 20.9, 35.9, 39.3, 43.4, 61.0, 73.8, 127.6, 127.9, 128.6, 128.7, 133.6, 136.1, 136.2, 170.5, 172.2, 196.4.

(2*R*,3*S*)-1-Benzyl-2-(1-*H*-indol-3-yl)-5-oxopyrrolidin-3-yl acetate (**7a**, mixture of *cis* and *trans* isomers)

7a trans. IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3227, 2927, 1745, 1689, 1442, 1366, 1340, 1233, 1030, 744, 703. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 2.03 (s, 3H), 2.56 (dd, J 17.6 and 1.8 Hz, 1H), 3.05 (ddd, J 17.6, 6.3 and 1.0 Hz, 1H), 3.73 (d, J 16.0 Hz, 1H), 4.76 (d, J 1.4 Hz, 1H), 5.19-5.23 (m, 1H), 5.25 (d, J 16.0 Hz, 1H), 7.01 (d, J 2.3 Hz, 1H), 7.10-7.35 (m, 7H), 7.40 (d, J 8.1 Hz, 1H), 7.65 (d, J 7.5 Hz, 1H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 20.9, 36.7, 44.1, 61.1, 73.5, 111.4, 111.7, 118.8, 120.1, 122.5, 125.0, 127.5, 127.8, 128.4, 136.0, 136.5, 170.4, 172.3.

7a cis. IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3227, 2927, 1745, 1689, 1442, 1366, 1340, 1233, 1030, 744, 703. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 2.03 (s, 3H), 2.78 (ddd, J 17.6, 4.3 and 0.9 Hz, 1H), 3.05 (dd, J 17.6 and 7.4 Hz, 1H), 3.55 (d, J 14.3 Hz, 1H), 5.03 (d, J 6.2 Hz), 5.17 (d, J 14.3 Hz, 1H), 5.56 (ddd, J 7.4, 6.2 and 4.3 Hz, 1H), 7.01 (d, J 2.3 Hz, 1H), 7.10-7.35 (m, 7H), 7.40 (d, J 8.1 Hz, 1H), 7.54 (d, J 8.0 Hz, 1H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 20.3, 37.2, 44.4, 59.0, 69.0, 108.3,

111.4, 111.7, 118.8, 120.1, 122.5, 125.0, 127.5, 127.8, 128.4, 136.0, 136.5, 170.2, 172.1.

(2*R*,3*S*)-1-Benzyl-2-(1-sulfonyl-indol-3-yl)-5-oxopyrrolidin-3-yl acetate (**7b trans**)

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3010, 2925, 1742, 1698, 1448, 1374, 1237, 1177, 1095, 1035, 977, 756, 727. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 2.01 (s, 3H), 2.54 (dd, J 17.7 and 1.9 Hz, 1H), 2.94 (ddd, J 17.7, 6.3 and 1.0 Hz, 1H), 3.64 (d, J 15.0 Hz, 1H), 4.61 (s br, 1H), 5.12 (dt, J 6.2 and 1.9 Hz, 1H), 5.25 (d, J 15.0 Hz, 1H), 7.01 (d, J 2.3 Hz, 1H), 7.10-7.35 (m, 7H), 7.40 (d, J 8.1 Hz, 1H), 7.65 (d, J 7.5 Hz, 1H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 20.8, 36.3, 44.4, 60.3, 72.4, 113.9, 118.3, 119.9, 123.9, 125.6, 126.8, 127.8, 128.6, 129.4, 134.1, 135.5, 135.8, 137.9, 170.3, 172.0. $[\alpha]_{\text{D}} = -21.7$ (c 0.15, CHCl_3).

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