Niobium Pentachloride-mediated Nucleophilic Additions to Cyclic *N*-Acyliminium Ions

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This paper is dedicated to professor Larry E. Overman on the occasion of his 60th birthday.

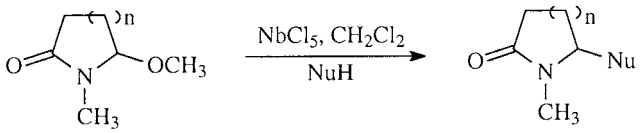
Abstract: Niobium chloride promoted the nucleophilic addition of allyltrimethylsilane, ethyl acetoacetate, indole and the silyl enol ether derived from acetone to cyclic *N*-acyliminium ions. The products were obtained in good yields.

Key words: *N*-acyliminium ions, niobium pentachloride, nucleophilic additions

The synthetic use of *N*-acyliminium ions is quite vast, involving the synthesis of peptides and pyrrolidines, Mannich reactions, among others.[1] These ions can be formed, for instance, from *N*,*O*-acetals by the intermediacy of Lewis acids such as $TiCl_4$, $BF_3{\cdot}OEt_2$, $InCl_3$ and TMSOTf.

The main goal of this work was to investigate the use of $NbCl_5$ in the generation of *N*-acyliminium ions. For this purpose, 5- and 6-membered rings *N*-acyliminium ion precursors were prepared and, in the presence of $NbCl_5$, various nucleophiles were added (Scheme 1).

Niobium pentachloride has received increased attention in recent years due to its good Lewis acidity. Indeed, it has been used in reactions such as Diels–Alder,[2] ring opening of epoxides,[3] additions of silyl enol ethers to aldehydes[4] and allylation of aldehydes[5] and imines,[5a,6] among others.



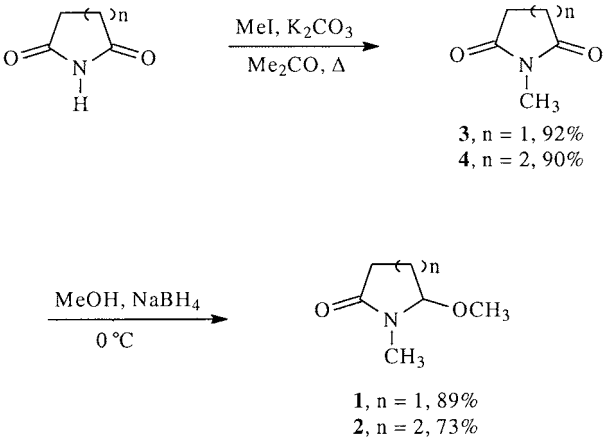
1, n = 1
2, n = 2

Scheme 1

Substrates **1** and **2** were prepared in two steps from succinimide and glutarimide, respectively (Scheme 2), according to known procedures.[7]

Next, these substrates were subjected to a suspension of $NbCl_5$ in CH_2Cl_2, followed by addition of the nucleophiles **5**–**8** shown in Figure 1.

It was found that a substoichiometric (0.6 equiv) amount of $NbCl_5$ was enough to generate the *N*-acyliminium ions, at 0 °C, in less than 20 minutes, as confirmed by consumption of substrates **1** and **2** (TLC). No reaction occurred when 0.1 equiv of $NbCl_5$ was used. The results of the nucleophilic additions are summarized in Table 1.



Scheme 2

Yields were better in all cases for substrate **1** probably due to the greater reactivity of 5-membered *N*-acyliminium ion substrates as compared to 6-membered substrates.[10] Products **9**–**12** were obtained in good yields (entries 1–4). Noteworthy is the good result obtained with indole (entry 4), which is not so commonly used as nucleophile in these reactions.[11]

Compounds **10** and **11** (labelled with ^{13}C in carbons 2 and 3) were used elsewhere as intermediates in the synthesis of (+/–)-hygrine, an alkaloid with medicinal properties.[12] Compound **11** was obtained as an inseparable mixture of isomers (1.7:1 as judged by ^1H NMR). The stereochemistry of the major isomer was not determined.

In order to improve the yields in the case of 6-membered ring substrate **2**, we thought that the use of a polar solvent along with an increase in the amount of $NbCl_5$ would be beneficial. Indeed, this turned out to be correct. When acetonitrile was used (entry 8) along with 1.0 equivalent of $NbCl_5$ (entry 9), the yields of product **13** were better as compared to entry 5.

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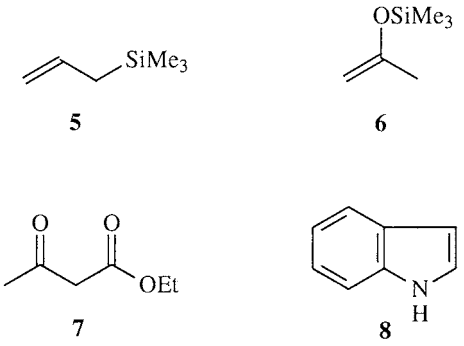

5 6 7 8

Figure 1 Nucleophiles used in this study

The yields obtained in this study for both substrates are comparable to those obtained with common Lewis acids such as $BF_3{\cdot}OEt_2$ and TMSOTf. However it should be pointed out that $NbCl_5$ is used in a substoichiometric amount and there is no need for cryogenic temperatures.

In summary, $NbCl_5$ has proved to be an efficient Lewis acid in the formation of *N*-acyliminium ions broadening even more the scope of this versatile reagent in organic synthesis. Studies on the stereoselectivity of this reaction using chiral *N*-acyliminium ion precursors are currently in progress and will be published in due course.

Acknowledgment

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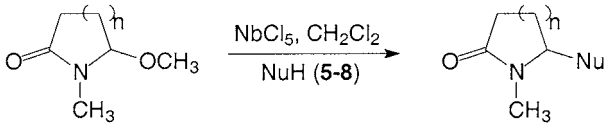
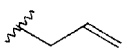
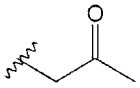
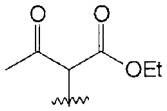
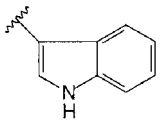
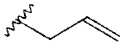
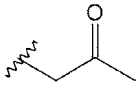
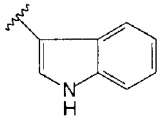
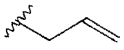
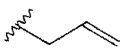
Table 1 Experimental Conditions and Results of the $NbCl_5$-mediated Additions to *N*-Acyliminium Ions[8]



1, n = 1
2, n = 2

9-15

Entry	Substrate	NuH[a]	Product[9]	Nu	Solvent	$NbCl_5$ (equiv)	Yield[b] (%)
1	**1**	**5**	**9**		CH_2Cl_2	0.6	84
2	**1**	**6**	**10**		CH_2Cl_2	0.6	66
3	**1**	**7**	**11**		CH_2Cl_2	0.6	64[c]
4	**1**	**8**	**12**		CH_2Cl_2	0.6	70
5	**2**	**5**	**13**		CH_2Cl_2	0.6	30
6	**2**	**6**	**14**		CH_2Cl_2	0.6	46
7	**2**	**8**	**15**		CH_2Cl_2	0.6	50
8	**2**	**5**	**13**		CH_3CN	0.6	44
9	**2**	**5**	**13**		CH_3CN	1.0	73

[a] 2 Equiv of the nucleophiles were employed.
[b] Isolated yields of the chromatographically pure products.
[c] Product obtained as a 1.7:1 mixture of isomers by ^1H NMR.

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(8) **Typical Experimental Procedure:** To a $NbCl_5$ (0.6 mmol) suspension in CH_2Cl_2 (3 mL) at 0 °C, under an argon atmosphere, was added substrate **1** or **2** (1.0 mmol), diluted in CH_2Cl_2 (2 mL). After 20 min, the nucleophile (2.0 mmol) was added. After 2 h, the reaction was quenched with sat. $NaHCO_3$ (4 mL), extracted with CH_2Cl_2 (2 × 10 mL), dried with Na_2SO_4 and concentrated at reduced pressure to furnish the crude products **9**–**15**, which were purified by silica gel chromatography (10% MeOH in EtOAc).

(9) Selected spectroscopic data for compounds **9**–**15**:
Compound **9**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.75–1.80 (m, 2 H, -CH_2-C**H$_2$**-CH), 2.10–2.20 (m, 2 H, -CH-C**H$_2$**-CH=CH_2), 2.75–2.79 [m, 2 H, -C(O)-C**H$_2$**-CH_2], 2.78 (s, 3 H, N-C**H$_3$**), 3.51–3.59 (m, 1 H, -C**H**-NCH_3), 5.08–5.16 (m, 2 H, -CH=C**H$_2$**), 5.60–5.80 (m, 1 H, -C**H**=CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.4 [-C(O)-CH_2-**C**H_2-CH], 28.0 (N-**C**H_3), 30.1 [-C(O)-**C**H_2-CH_2], 37.6 (CH-**C**H_2-CH=CH_2), 59.5 (N-**C**H-CH_2-), 119.1 (-CH=**C**H_2), 132.8 (-**C**H=CH_2), 175.5 (**C**=O).
Compound **10**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35–1.70 (m, 2 H, CH-C**H$_2$**-CH_2), 1.90–2.10 [m, 2 H, CH-C**H$_2$**-C(O)], 2.05 [s, 3 H, C(O)C**H$_3$**], 2.30–2.70 [m, 2 H, -C(O)-C**H$_2$**-CH_2], 2.60 (s, 3 H, N-C**H$_3$**), 3.50–3.80 (m, 1 H, -C**H**-NCH_3).
Compound **11**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (t, major isomer, -O-CH_2-C**H$_3$**, *J* = 7.0 Hz), 1.32 (t, minor isomer, -O-CH_2-C**H$_3$**, *J* = 8.0 Hz), 1.90–2.10 (m, 2 H, CH_2-C**H$_2$**-CH), 2.26 [s, minor isomer, -C(O)-C**H$_3$**] 2.28–2.36 [m, 2 H, -C(O)C**H$_2$**-CH_2], 2.29 [s, major isomer, -C(O)-C**H$_3$**], 2.79 (s, minor isomer, -NC**H$_3$**), 2.80 (s, major isomer, -NC**H$_3$**), 3.72 [d, minor isomer, -C(O)-C**H**-C(O), *J* = 2.5 Hz), 3.82 [d, major isomer, -C(O)-C**H**-C(O), *J* = 3.0 Hz], 4.18–4.28 (m, 2 H, -O-C**H$_2$**-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 [C(O)-OCH_2-**C**H_3], 22.7 [-C(O)-CH_2-**C**H_2-CH], 28.4 (N-**C**H_3), 29.4 [-C(O)-**C**H_2-CH_2], 29.9 [C(O)-**C**H_3], 58.9 [C(O)-**C**H-C(O)], 60.7 (-N**C**H), 62.3 (O-C**H$_2$**), 167.6 [-**C**(O)-O-CH_2], 175.3 [**C**(O)-NCH_3], 201.0 [-**C**(O)-CH_3].
Compound **12**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.13–2.69 [m, 4 H, C(O)-C**H$_2$**-CH_2- and C(O)-CH_2-C**H$_2$**-], 2.93 (s, 3 H, N-C**H$_3$**), 4.90 (t, 1 H, -C**H**-NCH_3, *J* = 6.9 Hz), 7.13 (ddd, 1 H, aromatic, *J* = 1.1, 7.0, 8.0 Hz), 7.22 (ddd, 1 H, aromatic, *J* = 1.2, 7.3, 8.4 Hz), 7.44 (d, 1 H, aromatic, *J* = 8.0 Hz), 7.54 (d, 1 H, aromatic, *J* = 7.8 Hz), 9.10 (br s, 1 H, N**H**). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.1 [-C(O)-CH_2-**C**H_2-CH], 28.1 (N-**C**H_3), 29.8 [-C(O)-**C**H_2-CH_2], 58.1 (-**C**H-NCH_3), 111.9 (**C**H, aromatic), 115.2 (**C$_0$**, aromatic), 118.8 (**C**H, aromatic), 120.0 (**C**H, aromatic), 122.5 (**C**H, aromatic), 122.8 (**C**H, aromatic), 125.4 (**C$_0$**, aromatic), 137.2 (HN-**C**-CH), 175.4 (N-**C**=O).
Compound **13**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.60–1.87 (m, 4 H, CH_2-C**H$_2$**-C**H$_2$**-CH), 2.14–2.50 [m, 4 H, -C(O)-C**H$_2$**-CH_2 and -C**H$_2$**-CH=CH_2], 2.91 (s, 3 H, N-C**H$_3$**), 3.30–3.36 (m, 1 H, C**H**-NCH_3), 5.04–5.13 (m, 2 H, -CH=C**H$_2$**), 5.56–5.77 (m, 1 H, -C**H**=CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 5.7 (CH_2-**C**H_2-CH_2), 14.5 (CH_2-**C**H_2-CH), 20.1 [-C(O)-**C**H_2-CH_2], 21.5 (N-**C**H_3), 25.3 (**C**H_2-CH=CH_2), 46.6 (N-**C**H-CH_2-), 106.4 (CH=**C**H_2), 122.0 (-**C**H=CH_2), 158.7 (**C**=O).
Compound **14**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.60–1.97 (m, 4 H, CH_2-C**H$_2$**-C**H$_2$**-CH), 2.17 [s, 3 H, C(O)-C**H$_3$**], 2.34–2.40 [m, 2 H, C(O)-C**H$_2$**-CH_2], 2.68–2.76 [m, 2 H, CH-C**H$_2$**-C(O)], 2.87 (s, 3 H, N-C**H$_3$**), 3.80–3.94 (m, 1 H, C**H**-NCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 5.6 (CH_2-**C**H_2-CH_2), 15.7 (CH_2-**C**H_2-CH), 17.8 [CH_3-C(O)-**C**H_2], 18.9 [**C**H_2-C(O)-NCH_3], 20.0 [C(O)-**C**H_3], 34.6 (N-**C**H_3), 42.5 (N-**C**H-CH_2), 158.5 (**C**=O), 193.9 [**C**(O)-CH_3].
Compound **15**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.63–1.94 (m, 2 H, C**H$_2$**-CH-NCH_3), 2.09–2.60 [m, 4 H, C(O)-C**H$_2$**-C**H$_2$**], 2.94 (s, 3 H, N-C**H$_3$**), 4.90 (t, 1 H, CH_2-C**H**-NCH_3, *J* = 5.1 Hz), 7.01 (d, 1 H, C**H**-NH, *J* = 2.5 Hz), 7.10–7.27 (m, 1 H, aromatic), 7.42 (d, 1 H, aromatic, *J* = 8.0 Hz), 7.55 (d, 1 H, aromatic, *J* = 7.6 Hz), 8.83 (br s, N-**H**). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.9 (CH_2-**C**H_2-CH_2), 30.4 (CH-**C**H_2-CH_2), 32.1 [C(O)-**C**H_2], 34.3 (N-**C**H_3), 56.9 (-**C**H-NCH_3), 111.8 (**C**H, aromatic), 116.2 (**C$_0$**, aromatic), 118.6 (**C**H, aromatic), 119.9 (**C**H, aromatic), 122.4 (**C**H, aromatic), 122.5 (CH, aromatic), 125.6 (**C$_0$**, aromatic), 137.0 (HN-**C**-CH), 171.3 (N-**C**=O).

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