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# CLAY MONTMORILLONITE-CATALYZED REGIOSELECTIVE ADDITION OF SILYL KETENE ACETALS TO PYRIDINE DERIVATIVES: SYNTHESIS OF N-SILYLDIHYDROPYRIDINES

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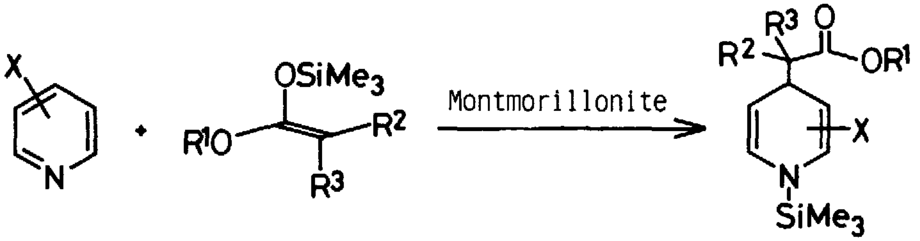
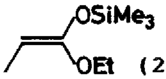
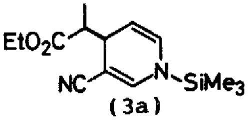
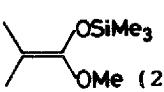
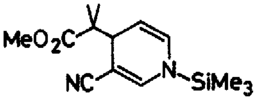
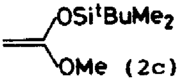
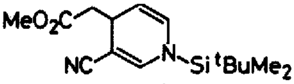
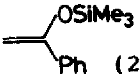
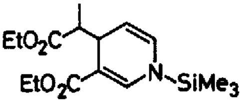
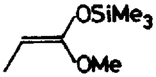
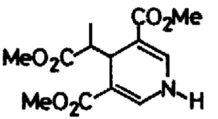
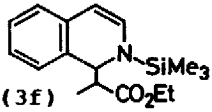
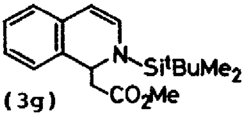
*Summary: Clay montmorillonite is an efficient catalyst for addition of silyl ketene acetals to pyridine derivatives with electron-withdrawing groups to afford N-silyldihydropyridines.*

We have been utilizing clay montmorillonite as a heterogeneous acid catalyst in carbon-carbon bond formation reactions such as aldol[1] and Michael[2] reactions of enol silanes. During investigating the Michael-type addition of silyl ketene acetals, we discovered that, in the presence of montmorillonite, silyl ketene acetals add to an electron-deficient pyridine nucleus. Here we wish to report that montmorillonite catalyzes the direct addition of silyl ketene acetals to pyridines bearing electron-withdrawing groups in a highly regioselective manner to afford N-silyldihydropyridines, comparing the clay catalyst with conventional, homogeneous promoters. Dihydropyridines have generally been synthesized via the addition of a nucleophile to reactive 1-acylpyridinium salts.[3]



In the presence of iron (III) or aluminium (III) ion-exchanged montmorillonite (abbreviated as Fe-Mont and Al-Mont, respectively),[4] silyl ketene acetal (**2a**) did not react with pyridine. However, pyridine derivatives bearing one electron-withdrawing group or more (**1a**, **1d**, **1e**, and **1f**) are subjected to regioselective addition reactions with silyl ketene acetals as shown in Table 1. Of the three cyano-substituted pyridines, only the meta form was reactive to **2a** to give 4-substituted N-silyl-1,4-dihydropyridine in 94% yield. The addition of **2a** at the 2- or 6-position of the pyridine nucleus was not observed. The work-up of the present method is so simple (only

Table 1. The reactions of pyridine derivatives with enol silanes.[a]

| Pyridine deriv. | Enol silane | Cat. | Time/h | Product[b] | Yield/% |
|---|---|---|---|---|---|
| m-Cyanopyridine (1a) |  (2a) | Fe-Mont | 0.2 |  (3a) | 94 |
| 1a | 2a | Al-Mont | 0.25 | 3a | 95 |
| o-Cyanopyridine (1b) | 2a | Al-Mont | 19 | -- | 0 |
| p-Cyanopyridine (1c) | 2a | Al-Mont | 19 | -- | 0 |
| 1a |  (2b) | Fe-Mont | 2.0 |  (3b) | 94 |
| 1a | 2b | Al-Mont | 3.3 | 3b | 94 |
| 1a |  (2c) | Fe-Mont | 6.0 |  (3c) | 89 |
| 1a | 2c | Al-Mont | 12 | 3c | 67 |
| 1a |  (2d) | Al-Mont | 17 | -- | 0 |
| Ethyl nicotinate (1d) | 2a | Al-Mont | 3.0 |  (3d) | 20[c] |
| 1d | 2a | Al-Mont | 1.5 | 3d | 84[d] |
| 3,5-Pyridine-dicarboxylic acid dimethyl ester (1e) |  (2e) | Al-Mont | 0.2 |  (3e) | 87[e] |
| Isoquinoline (1f) | 2a | Al-Mont | 3.0 |  (3f) | 80[c] |
| 1f | 2c | Al-Mont | 25 |  (3g) | 43 |

Notes of Table 1

a) In the presence of montmorillonite (0.5 g), the reaction of **1** (1 mmol) with **2** (2 mmol) was performed in $CH_2Cl_2$ at r.t.

b) All products were confirmed by $^1H$ and $^{13}C$ NMR, IR, and elemental analysis.

c) The reaction was performed at 0 °C.

d) The reaction was performed in $EtNO_2$ at 0 °C.

e) **3e** could be purified by recrystallization after hydrolysis of an N-silylated product. The N-silylated product could not be purified by distillation owing to its high boiling point.

filtering the montmorillonite off) that the adduct is isolable in the form of N-silyldihydropyridine without being hydrolyzed. **2b** and **2c** also add to **1a** at the 4-position.

The catalytic activity of the clay is dependent on the sort of exchageable cation in montmorillonite, and the following order was observed in the reaction of **1a** with **2c**: $Fe^{3+}$(89% yield) > $Co^{2+}$(68%) > $Cu^{2+}$(59%) $\sim$ $Zn^{2+}$(53%) > $Al^{3+}$(43%) $\sim$ $Ni^{2+}$(40%) $\sim$ $Sn^{4+}$(39%).[5]

In contrast to silyl ketene acetals, silyl enol ether (**2d**) gave no adducts.

Except for the reaction of ethyl nicotinate (**1d**), $CH_2Cl_2$ is a preferable solvent in the present system.

The reaction of isoquinoline (**1f**) with **2a** or **2c** afforded 1-substituted N-silyl-1,2-dihydroisoquinoline selectively, while quinoline produced no adducts.

Table 2 summarizes the comparison of catalytic activity between montmorillonite and some homogeneous promoters, showing that the montmorillonite catalyst has higher catalytic activities and the advantage of isolation of N-silylated 1,4-dihydropyridine in a pure form. We assume that pyridine derivatives are adsorbed on acid sites on montmorillonite and activated enough to be attacked by silyl ketene acetals.

A typical experimental procedure is as follows. Fe-Mont (0.5 g) was placed in a flask and dried at 120 °C/0.5 Torr for 3 h, and then suspended in $CH_2Cl_2$ (5 ml). **1a** (1 mmol) and **2a** (2 mmol) were added successively and stirred at r.t. for 0.2 h. The reaction mixture was passed through a pad of Celite and the filtrate was evaporated and distilled on Kugelrohr to yield **3a** in 94% yield.

N-Silyl-1,4-dihydropyridines (**3a**, **3b**, **3c**) were directly oxidized with ceric ammonium nitrate (2 eq, in $CH_3CN$, -45 °C) to give corresponding 4-substituted 3-cyanopyridines in 95, 26, and 65% yields, respectively.

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Table 2. Comparison of various promoters in the reaction of **1a** with **2a**.[a]

| Promoter | Solv. | Time/h | Yield of **3a**/% |
|---|---|---|---|
| Fe-Mont[b] | $CH_2Cl_2$ | 0.2 | 94 |
| Al-Mont[b] | $CH_2Cl_2$ | 0.25 | 95 |
| $Me_3SiOTf$[c] | $CH_2Cl_2$ | 0.3 | 73 |
| $Bu_4NF$[d] | THF | 2.0 | 68[e] |
| $ZnBr_2$[f] | $CH_2Cl_2$ | 0.35 | 34 |
| $BF_3 \cdot OEt_2$[f] | $CH_2Cl_2$ | 17 | 0 |
| None | $CH_2Cl_2$ | 3.5 | 0 |

a) The reaction of **1a** (1 mmol) with **2a** (2 mmol) was performed at r.t.

b) 0.5 g. c) 12 mol%. d) 10 mol%.

e) Total yield after oxidation to 4-substituted 3-cyanopyridine with ceric ammonium nitrate.[6]

f) 100 mol%.

## References and Notes

1. M. Kawai, M. Onaka, Y. Izumi, Bull. Chem. Soc. Jpn., **61**, 1237 (1988).
2. M. Kawai, M. Onaka, Y. Izumi, Bull. Chem. Soc. Jpn., **61**, 2157 (1988).
3. E. Piers, M. Soucy, Can. J. Chem., **52**, 3563 (1974); K. Akiba, Y. Iseki, M. Wada, Tetrahedron Lett., **23**, 429 (1982); D. L. Comins, A. H. Abdullah, J. Org. Chem., **47**, 4315 (1982); K. Akiba, Y. Nishihara, M. Wada, Tetrahedron Lett., **24**, 5269 (1983).
4. Fe-Mont and Al-Mont were prepared from sodium ion-exchanged montmorillonite and $Fe(NO_3)_3$ or $Al(NO_3)_3$. Ion exchange procedures, see Ref. 1.
5. In the presence of montmorillonite (0.5 g), the reaction **1a** (1 mmol) with **2c** (2 mmol) was performed in $CH_2Cl_2$ at r.t. for 6 h.
6. We could not isolate an N-silylated adduct.

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