DOI: 10.1002/adsc.200600343

Lewis Acid-Catalyzed Sequential Transformations: Straightforward Preparation of Functional Dihydropyridines

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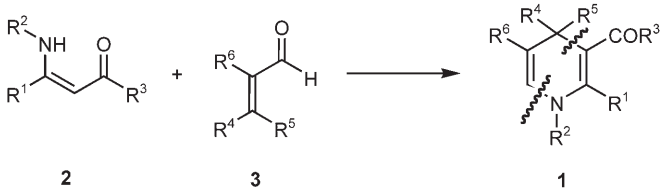
Received: July 11, 2006; Accepted: October 18, 2006

Abstract: Lewis acids catalyze the addition of β-enaminoacrylates or β-enaminones to α,β-unsaturated aldehydes leading to substituted dihydropyridines in high yields under mild reaction conditions.

Keywords: domino reactions; homogeneous catalysis; iron; Lewis acids; nitrogen heterocycles; scandium

4-Substituted Hantzsch-type 1,4-dihydropyridines are analogues of NADH coenzymes and represent an important class of drugs.[1] Current literature reveals that 1,4-dihydropyridines exhibit neuroprotectant and platelet anti-aggregratory activity, and show efficient biological properties as cerebral anti-ischemic agents in the treatment of Alzheimer's disease and as chemosensitizers in tumour therapy.[2–5] Dihydropyridines are usually subsequently oxidized to pyridines.[6] Many classical methods for the synthesis of symmetrical 1,4-dihydropyridines have been reported[7–11] based on conventional heating of a β-keto ester, an ammonium salt and an aldehyde in organic solvents, but most of these methods involve long reaction times, harsh reaction conditions and generally lead to low yields. Therefore, it is necessary to develop more efficient and versatile methods for the preparation of 1,4-dihydropyridines and the progress in this field has been recently achieved by the use of promoters such as microwaves,[6b,12] TMSCl,[5] ionic liquids,[13,14] polymers[15,16] and $Yb(OTf)_3$.[17] A synthesis of *N*-benzyl-1,4-dihydropyridines was also disclosed from 1-aza-1,3-butadiene *via* a Diels–Alder reaction.[18] However, to the best of our knowledge, few reports have been made so far about an efficient, versatile and mild procedure for the synthesis of unsymmetrical 1,4-dihydropyridines. β-Enamino ketones and esters are useful precursors in synthesis as they combine nucleophilicity of the enamine[19,20] and electrophilicity[20] of the enone moieties. They are subsequently potential intermediates in a domino-cascade 1,4-Michael addition/enamine formation to lead to *substituted and non-symmetrical 1,4-dihydropyridines* (Scheme 1).[21]



2 3 1

Scheme 1.

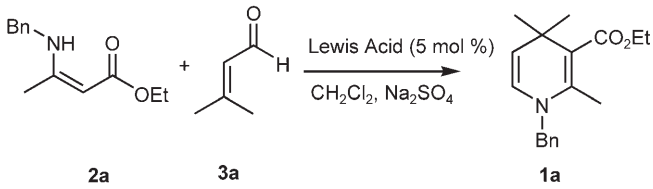
We report here our preliminary results on the preparation of this type of compound by a cascade reaction involving β-enaminocarbonyl derivatives and conjugated enals in the presence of a catalytic amount of a Lewis acid under mild conditions.

In our continuing work on Lewis acid-catalyzed synthesis of functionalized β-enamino esters and β-enaminones,[22] we anticipated that a Lewis acid could activate the unsaturated aldehyde, then favour the conjugated addition and the final amine condensation/isomerization (Scheme 1).

A blank reaction carried out at room temperature in dichloromethane overnight from ethyl *N*-benzylaminobut-2-enoate (**2a**) and 3-methylbut-2-enal (**3a**), without any Lewis acid, did not lead to the desired dihydropyridine and only the starting substrates were isolated. Zinc(II) acetate, which was shown to be active in the synthesis of compound **2a** from ethyl 3-oxobutanoate and benzylamine,[22] was first tested as Lewis acid but no catalytic activity was found. By contrast, cerium(III) chloride promoted the formation of **1a** at room temperature in a moderate 15% yield. The structure of **1a** was assigned on the basis of ^1H NMR, ^{13}C NMR, and mass spectra. NMR analysis (^1H, ^{13}C, HMBC and HMQC) revealed that the product formed during this catalysis is the 4,4-dimethyldihydropyridine. By comparison with the thermal reaction involving a cyclic enamino ester and an α,β-unsa-

turated aldehyde, it is worthy of note that this reaction leads to the *other regioisomer* and thus complements the former process.[23] Encouraged by this initial result, we investigated the activity of other Lewis acids. Iron(III) chloride and scandium(III) triflate appeared to be good candidates to promote the formation of the dihydropyridine **1a** (Table 1). The reaction

Table 1. Lewis acid-catalyzed cascade cyclization.[a]



2a **3a** **1a**

Lewis Acid	Temperature	Yield [%]
$Zn(OAc)_2 \cdot 6H_2O$	reflux	N.R.
$CeCl_3 \cdot 7H_2O$	r.t.	15
$FeCl_3 \cdot 6H_2O$	reflux	53
$Sc(OTf)_3$	r.t.	54

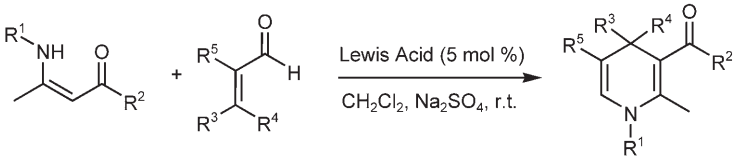
[a] *Reaction conditions:* 0.75 mmol of aldehyde, 0.5 mmol of β-enamino ester **1**, 0.025 mmol of Lewis acid (5 mol%) in 5 mL of CH_2Cl_2, 150 mg of Na_2SO_4 (1.5 mmol).

of 0.5 mmol of ethyl 3-*N*-benzylaminobut-2-enoate (**2a**) with 0.75 mmol of 3-methylbut-2-enal (**3a**) in the presence of 0.025 mmol (5 mol%) of Lewis acid and 1.5 mmol of sodium sulfate in dichloromethane led to the desired dihydropyridine in good yields under mild conditions. Even at room temperature, with scandium triflate as catalyst, the dihydropyridine was isolated in a satisfying yield (54%, Table 1). It is worthy of note that sodium sulfate was used to ensure an efficient elimination of water. Molecular sieves were also used in this process, however the yields were slightly lower.

Having established the high potential of this catalytic reaction, we extended it to various β-enamino esters and β-enaminones with α,β-unsaturated carbonyl compounds (Table 2). Thus *N*-benzyl- (**2a**) and *N*-phenyl-β-aminoacrylates (**2b**) reacted with cinnamaldehyde for 16 h to give the dihydropyridines **1b** and **1c** in high yields (entries 1–4, Table 2) at room temperature in the presence of 5 mol% of Lewis acid. The 1,4-dihydropyridines **1b–d** were obtained in very high yields from cinnamaldehyde and β-enamino esters (75–93%) and β-enaminones (90–99%) (Table 2). More substituted enals, such as citral and 2,3-dimethylbut-2-enal, were also reactive and the corresponding dihydropyridines (**1e**, **f**) were isolated in 40% and 87% yield, respectively (entries 7 and 8, Table 2). Both iron(III) chloride and scandium(III) triflate reacted smoothly and revealed good efficiencies.

After demonstrating that Lewis acids are effective catalysts for this ring formation reaction and, because we had previously described that such Lewis acids could also promote the synthesis of β-enamino esters and β-enamino ketones from the corresponding dicarbonyl compounds,[22] we envisioned to develop a one-pot process. Then, *via* a sequential reaction,[24] we could directly provide a one-pot access to the substituted dihydropyridines from β-keto esters or β-diketones, an amine and a conjugated aldehyde.

Table 2. Lewis acid-catalyzed synthesis of substituted dihydropyridines.[a]



2a: $R^1 = PhCH_2$, $R^2 = OC_2H_5$
2b: $R^1 = Ph$, $R^2 = OC_2H_5$
2c: $R^1 = PhCH_2$, $R^2 = CH_3$

1b – f

Entry	R^1	R^2	R^3	R^4	R^5	Lewis Acid	Compound	Yield [%]
1	$PhCH_2$	OEt	Ph	H	H	$FeCl_3 \cdot 6H_2O$	**1b**	90
2	$PhCH_2$	OEt	Ph	H	H	$Sc(OTf)_3$	**1b**	75
3	Ph	OEt	Ph	H	H	$FeCl_3 \cdot 6H_2O$	**1c**	93
4	Ph	OEt	Ph	H	H	$Sc(OTf)_3$	**1c**	80
5[b]	$PhCH_2$	CH_3	Ph	H	H	$FeCl_3 \cdot 6H_2O$	**1d**	99
6[b]	$PhCH_2$	CH_3	Ph	H	H	$Sc(OTf)_3$	**1d**	90
7	$PhCH_2$	OEt	$(CH_3)_2C{=}C(CH_2)_2$	CH_3	H	$FeCl_3 \cdot 6H_2O$	**1e**	40
8	$PhCH_2$	OEt	CH_3	H	CH_3	$Sc(OTf)_3$	**1f**	87

[a] *Reaction conditions:* 0.75 mmol of aldehyde, 0.5 mmol of β-enamino esters **2a**, **b**, 0.025 mmol of Lewis acid (5 mol%) in 5 mL of CH_2Cl_2, 150 mg (1.5 mmol) of Na_2SO_4, 16 h.
[b] 0.5 mmol of β-enamino ketone **2c** was used.

The β-keto esters or β-diketones (1 equiv.) were first treated with the amine (1.1 equivs.) in the presence of a catalytic amount of a Lewis acid (5 mol%) in dichloromethane. This first step was followed by TLC analysis and after completion, the α,β-unsaturated aldehyde (1.5 equivs.) was added. After 16 h, the reaction was quenched by filtration over Celite. The dihydropyridines **1b, g–l** were isolated after purification on silica gel in high yields, comparable to those obtained starting directly from isolated β-enamino esters. Whatever the substituent on the ester or the nature of the Lewis acid (iron or scandium), the reaction proceeded with very good efficiency (Table 3).

In conclusion, we have demonstrated that iron and scandium salts are efficient catalysts for the transformation of enamino esters and enaminones with conjugated enals to give functional dihydropyridine derivatives *via* a formal Michael addition/enamine formation cascade reaction. A tremendous advantage of these salts lies in the fact that they also catalyze the enamine formation from β-diketo compounds and primary amines, and thus make possible the sequential Lewis acid-catalyzed enamino derivatives/1,4-dihydropyridines synthesis. Further efforts will be devoted to the development of an asymmetric version for this cascade transformation.

Experimental Section

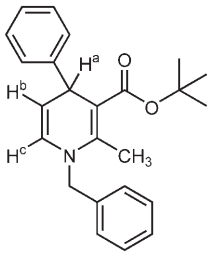
Preparation of 1,4-Dihydropyridines from Enamino Esters and Enals

To previously dried sodium sulfate (300 mg) were successively added under argon, ferric chloride or scandium triflate (5 mol%), dichloromethane (10 mL mmol^{-1}), the enamino ester (1 equiv.) and the unsaturated aldehyde (1.5 equivs.). The solution was stirred at room temperature until completion by TLC analysis. The solution was then filtered through Celite, and concentrated under vacuum. The crude oily mixture was purified on silica gel by flash chromatography (eluent: heptane/ethyl ether, 9/1).

General Procedure for the One-Pot Sequential Transformation

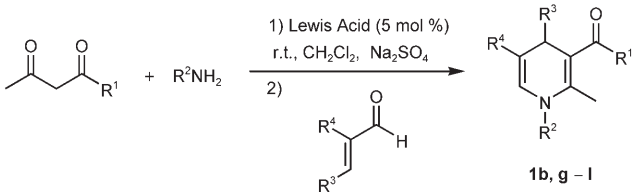
To previously dried sodium sulfate (300 mg) were successively added under argon, ferric chloride or scandium triflate (5 mol%), dichloromethane (10 mL mmol^{-1}), the dicarbonyl derivative (1 equiv.), and finally a primary amine (1.1 equivs.). The reaction mixture was stirred at room temperature until completion as detected by TLC analysis. Then, the unsaturated aldehyde (1 equiv.) was added and the solution stirred at room temperature or under reflux for 16 h. The solution was then filtered through Celite, and concentrated under vacuum. The crude oily mixture was purified on silica gel by flash chromatography (eluent: heptane/ethyl ether, 9/1).

Data for Product 1g: ^{1}H NMR (300.802 MHz, $CDCl_3$): $\delta = 1.30$ [s, C(CH_3)$_3$], 2.42 (s, CH_3), 4.58 (AB, $J = 17.1$ Hz,



1H, C*H*HPh), 4.66 (AB, $J = 17.1$ Hz, 1H, CH*H*Ph), 4.68 (d, $J = 5.0$ Hz, H^a, CHPh), 4.96 (dd, $J = 7.7$, 5.0 Hz, H^b), 5.94 (d, $J = 7.7$ Hz, H^c), 7.27–7.40 (m, 10H, CH_{Ar}); ^{13}C NMR (75.455 MHz, $CDCl_3$): $\delta = 15.8$ (CH_3), 28.1 [C(CH_3)$_3$], 41.1

Table 3. Lewis acid-catalyzed one-pot cascade reaction.[a]



Lewis Acid	R^1	R^2	R^3	R^4	Temperature	Compound	Yield [%]
$FeCl_3 \cdot 6H_2O$	EtO	Bn	Ph	H	r.t.	**1b**	98
$FeCl_3 \cdot 6H_2O$	*t*-BuO	Bn	Ph	H	reflux	**1g**	96
$FeCl_3 \cdot 6H_2O$	BnO	Bn	Ph	H	reflux	**1h**	98
$Sc(OTf)_3$	EtO	Bn	Ph	H	r.t.	**1b**	75
$Sc(OTf)_3$	EtO	*n*-Bu	Ph	H	r.t.	**1i**	80
$Sc(OTf)_3$	EtO	*n*-Bu	Me	Me	r.t.	**1j**	63
$Sc(OTf)_3$	Me	*n*-Bu	Ph	H	r.t.	**1k**	80
$Sc(OTf)_3$	Me	*n*-Bu	Me	Me	r.t.	**1l**	86

[a] *Reaction conditions:* 1) 0.55 mmol of amine, 0.5 mmol of keto ester or β-diketone, 0.025 mmol of Lewis acid (5 mol%) in 5 mL of CH_2Cl_2, 150 mg (1.5 mmol) of Na_2SO_4; 2) 0.5 mmol of unsaturated aldehyde.

(*CH*Ph), 53.6 (N*C*H_2Ph), 78.9 [Cq, *C*(CH_3)$_3$], 102.0 (C=*C*-CO_2-*t*Bu), 107.8 (*C*H[b]), 125.9 (CH_{Ar}), 126.2 (2 CH_{Ar}), 127.4 (CH_{Ar}), 127.5 (2 CH_{Ar}), 128.2 (2 CH_{Ar}), 128.9 (1 CH_{Ar}+ *C*H[c]), 129.3 (CH_{Ar}), 138.4 (Cq_{Ar}, NCH_2*C*), 147.7 [N-*C*(=C)-CH_3], 149.2 (Cq_{Ar}), 168.6 (CO).

Acknowledgements

The authors are grateful to the European Union COST Program Action D24/0005/02 and IDECAT NoE 011730–2 for support.

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