Magnesium Perchlorate as Efficient Lewis Acid: A Simple and Convenient Route to 1,4-Dihydropyridines

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Abstract: A new protocol for the synthesis of various 1,2,3,4-tetrasubstituted 1,4-dihydropyridines from enamino or carbonylic derivatives promoted by $Mg(ClO_4)_2$ is presented.

Key words: magnesium perchlorate, 1,4-dihydropyridines, domino reaction, Michael addition, cyclization

1,4-Dihydropyridine (1,4-DHP) derivatives continue to be subject of notable interest and studies as analogues of NADH coenzymes that could be involve in hydrogen-transfer reactions.[2] In addition, the DHP heterocyclic ring is part of the fundamental skeleton of important classes of drugs.[2,3] 1,4-DHP derivatives, in fact, find application as calcium antagonists, as vasodilators, bronchodilators, antitumor agents and in the treatment of cardiovascular diseases.

The first 1,4-DHP systems were obtained more than one century ago by Hantzsch via a one-pot condensation of an aldehyde, ammonia and a ketoester.[4] Various modification of the original procedure have been set up during the years in order to improve the yields and the reaction conditions.[5] However, this strategy can not be considered general for the synthesis of all types of 1,4-dihydropyridines leading to completely substituted 1,4-DHP units.

On the contrary, to the best of our knowledge, only few methods are available for the synthesis of unsymmetrical tetrasubstituted derivatives.[6,7] Most of these procedures are based on a Michael addition on an α,β-unsaturated system promoted by a Lewis acid catalyst [LiI,[6a] $Sc(OTf)_3$,[6b] CAN[6c]].

During our studies on the ability of metal perchlorates to work as Lewis acids, we proved that metal perchlorates can behave as powerful Lewis acids, and their activity is comparable, and in some cases superior,[8] to that of metal triflates, which, however, are much more expensive. Moreover, the high activity is typical not only of heavy metal perchlorates, but also of perchlorate salts of alkaline and alkaline earth metals.[9] This is a very important peculiarity that makes the synthetic methodologies more eco-friendly. Finally, it has been demonstrated that, despite the common opinion, Li, Mg, Zn and Ni perchlorates are not dangerous chemicals if not employed under highly acidic conditions and not exposed to high temperatures (>300–500 °C).[10]

We report here that a new synthesis of 1,2,3,4-tetrasubstituted 1,4-dihydropyridines like **3** promoted by metal perchlorates is possible.

A few years ago, we set up a convenient procedure to obtain β-enaminoesters and β-enaminoketones by condensation of β-ketoesters and β-diketones with amines in the presence of $Zn(ClO_4)_2 \cdot 6H_2O$ and $MgSO_4$ as catalyst.[11] Owing to the nucleophilic character of β-enaminoesters and β-enaminoketones, a Michael addition to α,β-unsaturated carbonylic compounds could occur in the presence of a perchlorate salt, whose ability to activate β-bidentate substrates is actually well known.[12] If this is the case, a domino procedure could also be set up.

In order to evaluate the practicability of the reaction, preliminary experiments were carried out by reacting the starting enamino derivatives **1a** and **1b** with a slight excess (1.2 equiv) of (*E*)-4-methyl-2-pentenal (**2a**) in CH_2Cl_2, in the presence of different catalytic systems. After 24 hours at room temperature, the mixture was filtered on celite, the solvent was evaporated and the conversion was determined by NMR analysis of the crude product. The results are reported in Table 1.

Depending on the activity of the catalyst, together with the desired product **3**, variable amounts of the pyridinium salt **4** could be detected. $Zn(ClO_4)_2 \cdot 6H_2O$ proved to be very efficient since the reaction was complete after 24 hours. However, the reaction led to a mixture of the desired product **3aa** and a 25% yield of **4aa** (Table 1, entry 1). $LiClO_4$ seemed to be a good choice for the reaction of **1a**, giving **3aa** in 85% conversion without traces of the pyridinium salt (Table 1, entry 2), but it was not suitable for the less reactive β-enaminoketone **1b**, which was converted into **3ba** in only 33% yield (Table 1, entry 3). $Mg(ClO_4)_2$ proved to be the best choice among the selected perchlorates: enaminoester **1a** reacted almost completely giving **3aa** in 90% yield, and only a small amount of **4aa** (8%). Also enaminoketone **1b** gave the product **3ba** with 82% conversion, with no traces of **4ba** (Table 1, entries 4 and 5). Carrying out the reaction under an inert atmosphere did not change the reactivity and the proportion of the reaction products.

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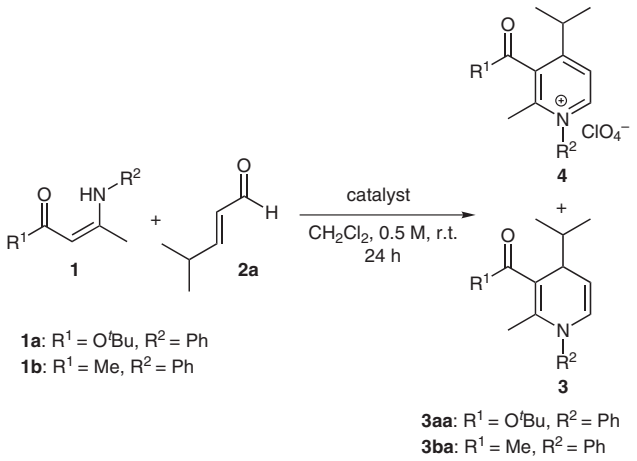
Table 1 Reaction of β-Enamino Derivatives **1** with (*E*)-4-Methylpentenal **2a** (1.2 equiv) under Various Reaction Conditions



Entry	Substrate	Catalyst (equiv)	Conversion (%) **3** (**4**)
1	**1a**	$Zn(ClO_4)_2 \cdot 6H_2O$ (0.1), $MgSO_4$ (0.2)	>74 (25)
2	**1a**	$LiClO_4$ (0.1), $MgSO_4$ (0.2)	85 (0)
3	**1b**	$LiClO_4$ (0.1), $MgSO_4$ (0.2)	33 (0)
4	**1a**	$Mg(ClO_4)_2$ (0.1), $MgSO_4$ (0.2)	90 (8)
5	**1b**	$Mg(ClO_4)_2$ (0.1), $MgSO_4$ (0.2)	74 (8)
6	**1a**	$Mg(ClO_4)_2$ (0.1)	85 (0)
7	**1b**	$Mg(ClO_4)_2$ (0.1)	50 (0)

The addition of a catalytic amount of $MgSO_4$ as dehydration agent was necessary; in fact, on carrying out the reaction in the absence of $MgSO_4$, a decrease in the conversion was observed (Table 1, entries 6 and 7).

The protocol was applied to various β-enaminoesters and β-enaminoketones with various aldehydes. The results are reported in Table 2. The reaction works well, both with β-enaminoesters and β-enaminoketones, even if the former substrates are generally more reactive.

β-Enaminoesters **1a** and **1c–f** were totally reactive and were predominantly converted into the corresponding dihydropyridines **3**, and partially into the pyridinium salt **4**. They showed the same reactivity irrespective of the nature of the ester group (R^1 = OEt, O*t*-Bu) and of the N-substituent (R^2 = Ph, Bz, Bu) (Table 2, entries 1–13), whereas the nature of the aldehyde affected the rate of the reaction. In fact the reactions with cinnamaldehyde (R^3 = Ph, Table 2, entries 2, 5, 8 and 12) required longer reaction times; the presence of an electron-withdrawing group on the phenyl ring, such as a 2-NO_2 substituent, increased the rate (Table 2, entries 6 and 13).

On the other hand, β-enaminoketones **1b** and **1g** were less reactive, giving the corresponding dihydropyridines **3** with conversions ranging from 50% to >99%. Even in this case, with aromatic α,β-unsaturated aldehydes, longer reaction times were required (Table 2, entries 16 and 23). Carrying out the reaction with cinnamaldehyde at 40 °C could improve the conversion (Table 2, entry 17). The presence of an aromatic moiety on the ketone (R^1 = Ph) makes the β-enaminoketone completely unreactive (Table 2, entry 24).

The amount of the pyridinium salt **4** increased when both β-enaminoesters and β-enaminoketones were reacted with cinnamaldehyde. We were able to isolate and characterize the pyridinium salt **4** only in two cases: compound **4db**, which crystallized from the crude reaction mixture, and compound **4ea**, from the column chromatography.

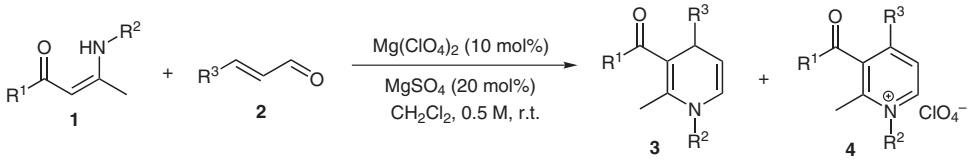
The synthesis of dihydropyridine **3** could be also be achieved through a domino reaction starting from β-ketoesters or β-diketones **5** by adding one equivalent of amine, in the presence of $Mg(ClO_4)_2$ (10%) and $MgSO_4$ (20%), and subsequently the aldehydes when the formation of the enamino derivative was complete, generally after 1–2 hours. The results obtained via the domino reaction are reported in Table 3. The yields and times are comparable with those obtained starting from β-enamino derivatives.[13]

Although the conversion yields calculated from the ^{1}H NMR spectra of the crude of the reactions were generally very high, we found various difficulties in the isolation of the pure products (see Table 3). Although we found in the literature that this kind of compound can be purified by a simple column chromatography on SiO_2, without any precaution, in our hand this technique did not work and the yields of the purified products **3** were generally much lower than the ^{1}H NMR conversions.[14]

After trying various conditions for the column chromatography (the solvent with or without the addition of Et_3N) and various stationary phases (SiO_2, Florosil, neutral Al_2O_3, basic Al_2O_3), we found that the best condition to obtain a good separation and the best yield for the dihydropyridine **3** was to carry out the column chromatography on SiO_2, using a petroleum ether–acetone solvent mixture with 5% Et_3N added during the conditioning process, and then the solvent mixture alone for the separation step. The column should be preferentially short (40 g of SiO_2 for 1 g of product) and the separation should be quickly carried out under a nitrogen atmosphere. To exclude the possibility that traces of magnesium perchlorate could be responsible for the low yields, the pure isolated product **3aa** was subjected to another column chromatography. The yield was low again, demonstrating that these products are very labile, and, probably, traces of oxygen are sufficient to oxidize them on the solid support. Moreover, even if the workup step was carried out by adding water and extracting the product with CH_2Cl_2, instead of a filtration on celite, the results are exactly the same.

In order to evaluate the possibility of increasing the scale of application of our methodology we carried out the sequential synthesis of dihydropyridine **3da** starting from 10 mmol of ethyl acetoacetate. The conversion yield of **3da** calculated from the ^{1}H NMR spectra was almost the same as that from the small-scale (0.3 mmol) run, but the

Table 2 Reaction of Enamino Derivatives **1** (1 equiv) with Various Enals **2** (1.2 equiv) in the Presence of $Mg(ClO_4)_2$ and $MgSO_4$ in CH_2Cl_2 at Room Temperature



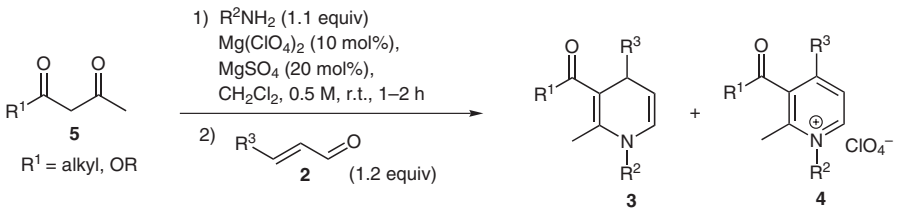
Entry	Starting **1**	R^1	R^2	R^3	Product	Time	Conversion (%)[a,b] of **3** (**4**)	Yield (%)[c] of **3**
1	**1a**	O*t*-Bu	Ph	*i*-Pr	**3aa**	24	95 (5)	75
2	**1a**			Ph	**3ab**	70	75 (10)	58
3	**1c**	O*t*-Bu	Bu	*i*-Pr	**3ca**	24	75 (24)	63
4	**1c**			Pr	**3cc**	24	82 (18)	67
5	**1c**			Ph	**3cb**	70	70 (30)	52
6	**1c**			2-$O_2NC_6H_4$	**3cd**	48	89 (11)	64
7	**1d**	OEt	Ph	*i*-Pr	**3da**	24	90 (0)	67
8	**1d**			Ph	**3db**	70	71 (19)	55
9	**1e**	OEt	Bn	*i*-Pr	**3ea**	24	96 (4)	64
10	**1f**	OEt	Bu	*i*-Pr	**3fa**	24	93 (7)	66
11	**1f**			Pr	**3fc**	24	93 (7)	59
12	**1f**			Ph	**3fb**	70	75 (12)	65
13	**1f**			2-$O_2NC_6H_4$	**3fd**	48	96 (4)	72
14	**1b**	Me	Ph	*i*-Pr	**3ba**	24	80 (2)	65
15	**1b**			Pr	**3bc**	24	64 (6)	47
16	**1b**			Ph	**3bb**	70	54 (10)	40
17	**1b**			Ph	**3bb**	70[d]	70 (nd)	55
18	**1b**			2-$O_2NC_6H_4$	**3bd**	48	90 (nd)	68
19	**1b**			4-$O_2NC_6H_4$	**3be**	70	95 (nd)	62
20	**1b**			CO_2Et	**3bf**	24	99 (nd)	60
21	**1g**	Me	Bn	*i*-Pr	**3ga**	24	74 (11)	52
22	**1g**			Pr	**3gc**	48	62 (nd)	44
23	**1g**			Ph	**3gb**	70	50 (nd)	32
24	**1h**	Ph	Ph	*i*-Pr	**3ha**	70	0	

[a] Conversion calculated from the ^1H NMR spectra.
[b] When the conversion was not complete, starting material **1** was also detected.
[c] Isolated yields.
[d] The reaction was carried out at 40 °C.

isolated yield increased (94%, Table 3, entry 4). Therefore we could observe that the separation step was better when a reasonable amount of the crude material was present. Yields reported in the Table 2 refer to those obtained from the reactions carried out on a 0.3–3.0 mmol scale of starting material.

In conclusion, we have demonstrated an another interesting application of $MgClO_4$ to act as a Lewis acid in promoting the synthesis of 1,2,3,4-tetrasubstituted 1,4-dihydropyridines **3**, by addition of enamino esters and ketones to enals. Considering the ability of perchlorates to catalyze the formation of the enamino derivatives from

Table 3 Sequential One-Pot Synthesis of 1,4-Dihydropyridines **3** from β-Keto Derivatives **5**, Amines and Enals **2**



Entry	R^1	R^2	R^3	Product	Time (h)	Isolated yield (%) of **3** (**4**[a])
1	O*t*-Bu	Bu	*i*-Pr	**3ca**	25	65 (11)
2			Ph	**3cb**	64	58 (23)
3	O*t*-Bu	Bn	CO_2Et	**3if**	26	71 (8)
4	OEt	Ph	*i*-Pr	**3da**	26	94[b] (4)
5	OEt	Bn	*i*-Pr	**3ea**	25	78 (10)
6	OEt	Bu	2-$O_2NC_6H_4$	**3fd**	30	70 (0)
7	Me	Ph	*i*-Pr	**3ba**	26	61
8	Me	Bn	Ph	**3gb**	70	45 (0)
9			Pr	**3gc**	26	51 (5)

[a] Calculated from ^{1}H NMR.
[b] Reaction carried out starting from 10 mmol of **4**.

carbonyl derivatives and amines, a more convenient sequential procedure to obtain **3** is also possible. Notably, the only by-product of the reaction is water.

Studies are in progress in our laboratories to apply this procedure to other carbonyl derivatives, such as β-keto-amides, and to obtain enantiomerically pure 1,4-dihydro-pyridine.

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(13) **General Procedure for the Synthesis of Dihydropyridine 3 from Enamino Derivatives 1**: In a two-necked flask equipped with a magnetic stirring bar, $Mg(ClO_4)_2$ (0.10 mmol), $MgSO_4$ (0.20 mmol), and the enamino derivative **1** (1.0 mmol) were suspended in anhyd CH_2Cl_2 (2 mL) and the aldehyde **2** (1.2 mmol) was added. The mixture was stirred at r.t. until completion of the reaction or for 70 h. The crude reaction mixture was filtered on celite and the solvent was removed by rotary evaporation. The dihydropyridine **3** was purified by flash chromatography on silica gel pretreated with the solvent mixture of PE–acetone (95:5) added with 5% Et_3N.

General Procedure for the Synthesis of Dihydropyridine 3 from Carbonyl Derivatives 5: In a two-necked flask equipped with a magnetic stirring bar, $Mg(ClO_4)_2$ (0.10 mmol), $MgSO_4$ (0.20 mmol), and the carbonyl derivative **5** (1.0 mmol) were suspended in anhyd CH_2Cl_2 (2 mL) and the amine (1.1 mmol) was added. When the reaction was completed (check with TLC), the aldehyde **2** (1.2 mmol) was added. The mixture was stirred at r.t until completion of the reaction or for 70 h. The crude reaction mixture was filtered on celite and the solvent was removed by rotary evaporation. The dihydropyridine **3** was purified by flash chromatography on silica gel pre-treated with the solvent mixture of PE–acetone (95:5) added with 5% Et_3N.

Spectroscopic data for selected compounds are as follows:

1-(4-Isopropyl-2-methyl-1-phenyl-1,4-dihydropyridin-3-yl)ethanone (3ba): ^{1}H NMR: δ = 0.91 (d, $J_{H,H}$ = 6.9 Hz, 6 H), 1.50–1.60 (m, 1 H), 2.00 (s, 3 H), 2.27 (s, 3 H), 3.41 (dd, $J_{H,H}$ = 4.4, 6.0 Hz, 1 H), 4.93 (dd, $J_{H,H}$ = 6.2, 7.5 Hz, 1 H), 6.30 (d, $J_{H,H}$ = 7.5 Hz, 1 H), 7.05–7.15 (m, 2 H), 7.25–7.30 (m, 1 H), 7.35–7.45 (m, 2 H). ^{13}C NMR: δ = 16.8 (Me), 18.6 (Me), 19.1 (Me), 29.0 (Me), 35.5 (CH), 40.6 (CH), 103.5 (CH), 111.1 (C), 126.96 (CH), 126.99 (CH), 129.3 (CH), 131.3 (CH), 143.6 (C), 146.4 (C), 200.9 (C). HRMS: *m*/*z* calcd for $C_{17}H_{21}NO$: 255.1623; found: 255.1623.

1-[2-Methyl-4-(2-nitrophenyl)-1-phenyl-1,4-dihydropyridin-3-yl]ethanone (3bd): ^{1}H NMR: δ = 1.99 (s, 3 H), 2.18 (s, 3 H), 5.26 (dd, $J_{H,H}$ = 5.5, 7.5 Hz, 1 H), 5.32 (d, $J_{H,H}$ = 5.5 Hz, 1 H), 6.10 (d, $J_{H,H}$ = 7.5 Hz, 1 H), 7.15–7.20 (m, 2 H), 7.35–7.40 (m, 2 H), 7.40–7.45 (m, 2 H), 7.60–7.65 (m, 2 H), 7.80–7.85 (m, 1 H). ^{13}C NMR: δ = 19.6 (Me), 29.8 (Me), 37.3 (CH), 106.4 (CH), 108.9 (C), 124.3 (CH), 127.4 (CH), 127.8 (CH), 128.1 (CH), 130.0 (CH), 130.3 (CH), 131.1 (CH), 134.0 (CH), 141.7 (C), 143.3 (C), 147.7 (C), 149.2 (C), 199.0 (C). HRMS: *m*/*z* calcd for $C_{20}H_{18}N_2O_3$: 334.1317; found: 334.1315.

***tert*-Butyl 1-Butyl-2-methyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (3cd)**: ^{1}H NMR: δ = 0.95 (t, $J_{H,H}$ = 7.3 Hz, 3 H), 1.10 (s, 9 H), 1.35–1.40 (m, 2 H), 1.55–1.60 (m, 2 H), 2.49 (s, 3 H), 3.20–3.30 (m, 1 H), 3.40–3.50 (m, 1 H), 5.04 (d, $J_{H,H}$ = 4.9 Hz, 1 H), 5.15 (dd, $J_{H,H}$ = 4.9, 7.7 Hz, 1 H), 5.82 (d, $J_{H,H}$ = 7.7 Hz, 1 H), 7.10–7.15 (m, 1 H), 7.55–7.60 (m, 2 H), 7.80–7.85 (m, 1 H). ^{13}C NMR: δ = 13.8 (Me), 15.3 (Me), 19.8 (CH_2), 27.8 (3 × Me), 32.4 (CH_2), 37.3 (CH), 50.1 (CH_2), 78.9 (C), 99.7 (C), 106.2 (CH), 123.4 (CH), 126.2 (CH), 129.3 (CH), 130.9 (CH), 133.2 (CH), 144.2 (C), 147.4 (C), 149.6 (C), 167.8 (C). HRMS: *m*/*z* calcd for $C_{21}H_{28}N_2O_4$: 372.2049; found: 372.2048.

Ethyl 1-Butyl-2-methyl-4-propyl-1,4-dihydropyridine-3-carboxylate (3fc): ^{1}H NMR: δ = 0.87 (t, $J_{H,H}$ = 6.8 Hz, 3 H), 0.93 (t, $J_{H,H}$ = 7.3 Hz, 3 H), 1.26 (t, $J_{H,H}$ = 7.1 Hz, 3 H), 1.20–1.40 (m, 6 H), 1.45–1.55 (m, 2 H), 2.36 (s, 3 H), 3.10–3.20 (m, 1 H), 3.30–3.40 (m, 1 H), 3.40–3.50 (m, 1 H), 4.05–4.20 (m, 2 H), 4.86 (dd, $J_{H,H}$ = 6.3, 7.4 Hz, 1 H), 5.84 (d, $J_{H,H}$ = 7.4 Hz, 1 H). ^{13}C NMR: δ = 14.0 (Me), 14.5 (Me), 14.6 (Me), 15.8 (Me), 18.2 (CH_2), 20.0 (CH_2), 32.6 (CH_2), 33.0 (CH), 41.6 (CH_2), 50.0 (CH_2), 59.2 (CH_2), 99.7 (C), 107.5 (CH), 130.0 (CH), 149.3 (C), 169.7 (C). HRMS: *m*/*z* calcd for $C_{16}H_{27}NO_2$: 265.2042; found: 265.2043.

1,4-Diphenyl-3-(ethoxycarbonyl)-2-methylpyridinium Perchlorate (4db): ^{1}H NMR (CD_2Cl_2): δ = 1.06 (t, $J_{H,H}$ = 7.2 Hz, 3 H), 2.60 (s, 3 H), 4.25 (q, $J_{H,H}$ = 7.2 Hz, 2 H), 7.60–7.70 (m, 7 H), 7.75–7.80 (m, 3 H), 8.11 (d, $J_{H,H}$ = 6.6 Hz, 1 H), 8.78 (d, $J_{H,H}$ = 6.6 Hz, 1 H). ^{13}C NMR (CD_2Cl_2): δ = 13.6 (Me), 19.9 (Me), 63.8 (CH_2), 125.7 (CH), 127.1 (CH), 128.5 (CH), 129.7 (CH), 131.3 (CH), 131.7 (CH), 132.3 (CH), 134.0 (C), 135.3 (C), 140.8 (C), 146.3 (CH), 153.6 (C), 158.3 (C), 164.6 (C). MS (ESI^+): *m*/*z* = 318. MS (ESI^-): *m*/*z* = 99.

1-Benzyl-3-(ethoxycarbonyl)-2-methyl-4-isopropylpyridinium Perchlorate (4ea): ^{1}H NMR: δ = 1.33 (t, $J_{H,H}$ = 7.1 Hz, 6 H), 1.40 (t, $J_{H,H}$ = 7.0 Hz, 3 H), 2.72 (s, 3 H), 3.00–3.10 (m, 1 H), 4.48 (q, $J_{H,H}$ = 7.1 Hz, 2 H), 5.83 (s, 2 H), 7.25–7.30 (m, 2 H), 7.35–7.45 (m, 3 H), 7.93 (d, $J_{H,H}$ = 7.0 Hz, 1 H), 8.92 (d, $J_{H,H}$ = 7.0 Hz, 1 H). ^{13}C NMR: δ = 13.8 (Me), 18.2 (Me), 22.3 (2 × Me), 47.3 (CH), 61.9 (CH_2), 63.4 (CH_2), 123.7 (CH), 127.9 (CH), 129.5 (CH), 129.6 (CH), 131.2 (C), 134.7 (C), 146.5 (CH), 151.8 (C), 164.2 (C), 165.4 (C). MS (ESI^+): *m*/*z* = 298. MS (ESI^-): *m*/*z* = 99.

(14) We compared our results with those from the previously reported procedure, employing $Sc(OTf)_3$ as Lewis acid (see ref. 6b) and we found conversion yields similar to those obtained with our method facing the same separation problems. These results mean that the perchlorate anion is not responsible in any way for the low recovered yields.