DOI: 10.1002/chem.200900044

A Very Efficient Cerium(IV) Ammonium Nitrate Catalyzed, Four-Component Synthesis of Tetrahydropyridines and Its Application in the Concise Generation of Functionalized Homoquinolizine Frameworks

Vellaisamy Sridharan, Swarupananda Maiti, and J. Carlos Menéndez*[a]

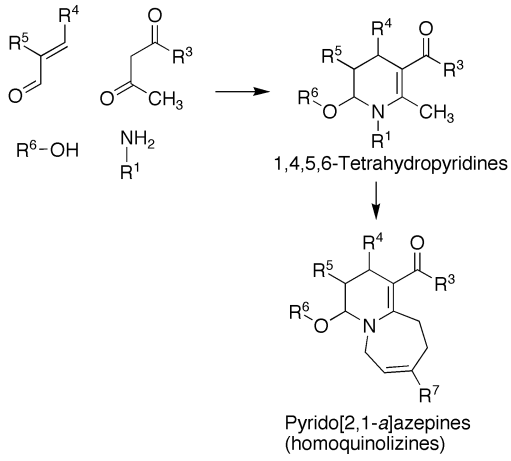
Abstract: The cerium(IV) ammonium nitrate (CAN) catalyzed, four-component reaction between primary aliphatic amines, β-ketoesters or β-ketothioesters, α,β-unsaturated aldehydes, and alcohols provided a very efficient and atom-economical access to substituted 6-alkoxy-2-methyl-1,4,5,6-tetrahydropyridines. These materials were then transformed into homoquinolizine derivatives in excellent yields by using a two-step sequence comprised of regioselective γ-deprotonation–allylation and ring-closing metathesis reactions. The possibility of displacing the alkoxy group by allylsilane nucleophiles, presumably through a vinylogous acyliminium intermediate species, was also demonstrated.

Keywords: heterocycles · iminium compounds · Lewis acids · metathesis · molecular diversity

Introduction

Pyridine and its partially or totally unsaturated derivatives, namely, the tetrahydropyridines, dihydropyridines, and piperidines, are ubiquitous structural motifs found in natural products and in compounds of interest for the pharmaceutical, agrochemical, and other chemical industries. Although many traditional procedures are available for the synthesis of these heterocyclic compounds, the development of efficient and versatile methods continues to be a relevant synthetic goal with the pyridines,[1] 1,4-dihydropyridines,[2] and piperidines[3] having received much attention in this regard. Most known methods for the synthesis of tetrahydropyridines are focused on the 1,2,3,6-tetrahydro system,[4] whereas the preparation of compounds containing other hydrogenation patterns, especially from acyclic precursors, remains relatively unexplored.[5]

We herein describe an efficient one-pot synthesis of highly substituted and functionalized tetrahydropyridine derivatives containing four adjacent hydrogenated atoms, together with their subsequent application in the generation of 6:7 fused heterocyclic frameworks derived from the pyrido[2,1-*a*]azepine system (Scheme 1). This ring system is a structural fragment of several families of bioactive alkaloids[6] and can be considered as a ring-expanded analogue of quinolizine. Derivatives of the quinolizine system are widespread in nature and constitute about 25–30% of all known alkaloids. They exhibit a wide range of pharmacological activities, which has led to intensive synthetic efforts in this field.[7] Although ring homology is one of the classical criteria for the design of analogues of bioactive compounds,



Scheme 1. Structures of the compounds described in this article.

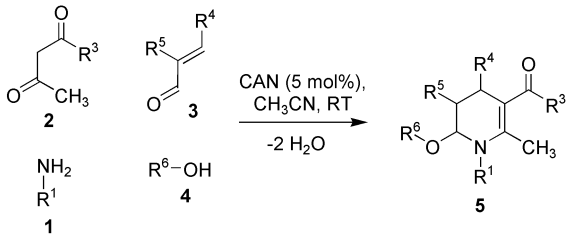
[a] Dr. V. Sridharan, Dr. S. Maiti, Prof. J. C. Menéndez
Departmento de Química Orgánica y
Farmacéutica Universidad Complutense
Facultad de Farmacia, Plaza de Ramón y Cajal, s.n. (Spain)
Fax: (+34) 91-3941822
E-mail: josecm@farm.ucm.es

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200900044.

it has not been applied to quinolizines because of the lack of suitable synthetic methods.

Results and Discussion

The sequential four-component reaction,[8,9] catalyzed by 5% cerium(IV) ammonium nitrate (CAN), between the primary aliphatic amines **1**, the β-ketoesters or β-ketothioesters **2**, the α,β-unsaturated aldehydes **3,** and the alcohols **4** in acetonitrile at room temperature afforded the tetrahydropyridines **5** in excellent yields (Scheme 2).[10] The reaction



Scheme 2. Four-component reaction between primary amines, β-keto(thio)esters, α,β-unsaturated aldehydes, and alcohols.

involves the generation of four bonds in a single operation (two C–N, one C–O, and one C–C), takes place under mild reaction conditions, and requires very simple and readily available starting materials. It also uses an inexpensive, air- and moisture-stable, nontoxic catalyst. Furthermore, it proceeds with high atom economy and has water as the only side product. As shown in Table 1, this reaction allowed the very efficient synthesis of 1,4,5,6-tetrahydropyridine systems with up to five substituents, two of which are functional groups. The ready availability of N-allyl-substituted tetrahydropyridine systems in high yields suggested the possibility of developing a very concise synthetic method towards biologically relevant bicyclic systems (Table 1, entry 3). These systems, containing a nitrogen atom at a ring-fusion position, were prepared by combining our four-component procedure

Abstract in Spanish: *La reacción en cuatro componentes entre aminas alifáticas primarias, β-cetoésteres o β-cetotioésteres, aldehídos α, β-insaturados y alcoholes, catalizada por CAN, permite un acceso muy eficiente a 6-alcoxi-2-metil-1,4,5,6-tetrahidropiridinas sustituidas. Estos compuestos se transformaron posteriormente en derivados del sistema de homoquinolizina, de nuevo con rendimientos excelentes, utilizando una secuencia de dos pasos consistente en un proceso de γ-desprotonación regioselectiva-alilación y una reacción de metátesis con cierre de anillo. También se demostró la posibilidad de llevar a cabo el desplazamiento nucleófilo del grupo alcoxi por alilsilanos, presumiblemente a través de una especie intermedia de tipo aciliminio vinílogo.*

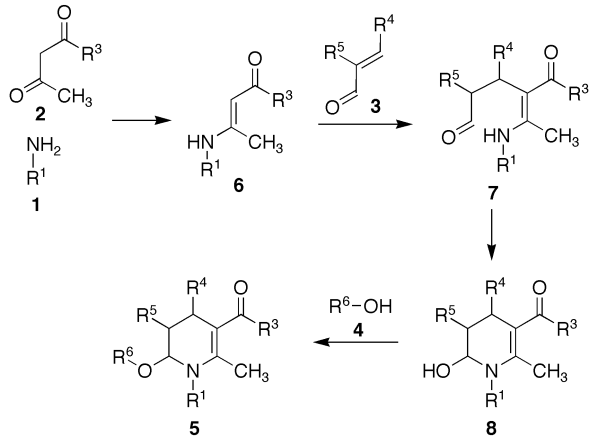
Table 1. CAN-catalyzed preparation of substituted 6-alkoxy-1,4,5,6-tetrahydropyridines.

Entry	Compound	R^1	R^3	R^4	R^5	R^6	Yield [%]
1	**5a**	*n*Bu	OEt	H	H	Et	93
2	**5b**[a]	*n*Bu	OEt	H	Me	Et	86
3	**5c**[b]	allyl	OMe	Me	H	Me	90
4	**5d**	*n*Hex	OEt	H	H	Et	91
5	**5e**[c]	2-Me-*n*Bu	OEt	H	H	Et	88
6	**5f**	*n*Bu	O*t*Bu	H	H	Et	87
7	**5g**	Bn	OEt	H	H	Et	80
8	**5h**	*n*Bu	OEt	H	H	Me	94
9	**5i**	*n*Bu	OEt	H	H	allyl	90
10	**5j**	allyl	OEt	H	H	Et	92
11	**5k**	allyl	OMe	H	H	Et	93
12	**5l**	allyl	OEt	H	H	Me	95
13	**5m**	allyl	OMe	H	H	Me	92
14	**5n**	allyl	S*t*Bu	H	H	Et	86
15	**5o**	allyl	S*t*Bu	H	H	Me	95

[a] As a 2:1 diastereomeric mixture. [b] As a 5:1 diastereomeric mixture. [c] As a 1:1 diastereomeric mixture.

for the synthesis of tetrahydropyridines with a ring-closing metathesis (RCM) reaction.

A mechanistic rationale of the tetrahydropyridine synthesis is summarized in Scheme 3. The initial CAN-catalyzed reaction[11] between the amines **1** and the β-keto(thio)esters



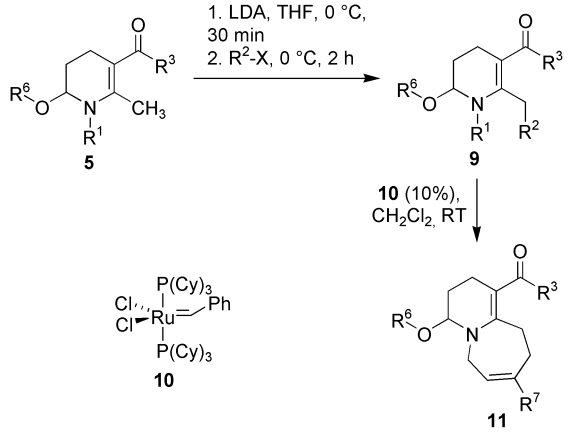
Scheme 3. Mechanistic rationale proposed for the four-component reaction leading to tetrahydropyridine compounds.

2 gives the β-enaminones **6**. The Michael addition[12] of these compounds to the enone system in the aldehydes **3** affords the intermediates **7**. The subsequent cyclization of the latter gives the 2-hydroxytetrahydropyridines **8**, which are finally transformed into the observed products **5** by nucleophilic displacement of the hydroxy group by the alcohol **4**. The main experimental observations that support this proposed mechanism can be summarized as follows: 1) reactions starting from the isolated enaminones **6** give identical products to those obtained when starting from compounds **1** and **2**, and 2) intermediates **8**, although unstable, can be isolated by carrying out the reaction in the absence of alcohols **4** and can then be transformed into the final products **5** by

treatment with **4** under the multicomponent reaction conditions.

In most synthetic applications that use the CAN catalyst, its activity is based on a radical mechanism, as expected from a powerful one-electron oxidant.[13] In an effort to determine whether the CAN catalyst exerts its role in our dihydropyridine synthesis through such an oxidative pathway, we performed the reaction between ethyl acetoacetate, butylamine, acrolein and ethanol (entry 1 in Table 1) in the presence of a large amount of a radical trap (1,1-diphenylethylene) and found no noticeable loss in yield. This indicates that a radical mechanism is not in operation under our conditions. In this regard, it has been noted that some literature precedent shows that the CAN catalyst may behave as a Lewis acid,[14] although this role has not been systematically studied. It is also relevant to note the use of catalytic amounts of the catalyst in our transformation, since most synthetic applications using CAN require stoichiometric quantities.[15]

At this stage, we reasoned that the functionalities present in compounds **5** should allow for their use as starting materials in novel routes to more complex nitrogen heterocycles. For instance, a RCM reaction between suitable substituents placed at N-1 and at the C_6 methyl group should provide ready access to bicyclic compounds. To install the latter substituent, we planned to take advantage of the acidity of the methyl protons (the acidity is due to their conjugation with the ester carbonyl) although we found no literature precedent of such a γ-deprotonation process in functionalized tetrahydropyridine systems.[16] The treatment of compounds **5** with lithium diisopropylamide (LDA) at 0°C followed by the addition of allyl iodide or propargyl bromide at the same temperature afforded the C_6-CH_3-substituted derivatives **9** in yields higher than 90% in all cases, without interference from the alkoxy group at C-2 (Scheme 4 and Table 2). Exposure of compounds **9** to the Grubbs first-generation catalyst (**10**) in dichloromethane at room temperature afforded the corresponding ring-closed metathesis products **11** (derivatives of the pyrido[2,1-*a*]azepine (homoquinolizine) system) in excellent yields. (Scheme 4 and Table 3). As expected, the ring-closing enyne metathesis (RCEYM) reactions of compounds **9h** and **9i** to give **11h** and **11i**, respectively, were quite slow but could be brought to completion by performing the reaction under an ethylene atmosphere.[17] Interestingly, the use of the generally more reactive Grubbs second-generation catalyst was inefficient in this case. The three-step sequence starting from the acyclic precursors led to homoquinolizines in overall yields of approximately 80%.



Scheme 4. Synthesis of hexahydropyrido[2,1-*a*]azepines through a γ-alkylation/RCM sequence.

Table 2. Yields for the γ-alkylation of the C_2-Me substituent in compounds **5**.

Entry	Reactant	Product	R^1	R^2	X	R^3	R^6	Yield [%]
1	**5a**	**9a**	*n*Bu	allyl	I	OEt	Et	95
2	**5j**	**9b**	allyl	allyl	I	OEt	Et	92
3	**5k**	**9c**	allyl	allyl	I	OMe	Et	95
4	**5l**	**9d**	allyl	allyl	I	OEt	Me	90
5	**5m**	**9e**	allyl	allyl	I	OMe	Me	95
6	**5n**	**9f**	allyl	allyl	I	S*t*Bu	Et	95
7	**5o**	**9g**	allyl	allyl	I	S*t*Bu	Me	92
8	**5k**	**9h**	allyl	propargyl	Br	OMe	Et	93
9	**5j**	**9i**	allyl	propargyl	Br	OEt	Me	94

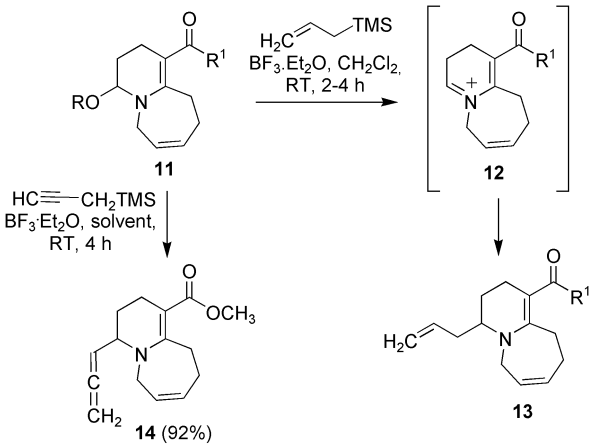
Table 3. Conditions and yields for the RCM reactions leading to homoquinolizines **11**.

Entry	Product[a]	R^3	R^6	R^7	*t* [h]	Yield [%]
1	**11b**	OEt	Et	H	4	95
2	**11c**	OMe	Et	H	4	95
3	**11d**	OEt	Me	H	3	95
4	**11e**	OMe	Me	H	4	92
5	**11f**	S*t*Bu	Et	H	4	92
6	**11g**	S*t*Bu	Me	H	2	90
7	**11h**[b]	OMe	Et	vinyl	16	90
8	**11i**[b]	OEt	Me	vinyl	22	90

[a] For greater clarity, the letters used to designate compounds **9** have been retained here, and hence compound **11a** does not exist. [b] The enyne RCM reactions were carried out in an ethylene atmosphere.

One very interesting feature of compounds **11** is the presence of an alkoxy group adjacent to nitrogen, which suggests the possibility of carrying out additional transformations based on the generation of a 4,5-dihydropyridinium intermediate **12** that can be viewed as a vinylogous acyliminium cation.[18,19] Although species related to **12** have been postulated as intermediates in the reduction of 1,4-dihydropyridines in acidic media, to the best of our knowledge they have not been used for carbon–carbon bond formation reactions, which are relevant because many natural quinolizidine and pyrido[2,1-*a*]azepine alkaloids are substituted at the position adjacent to nitrogen.[20] To test this possibility, we briefly examined the Lewis acid catalyzed reaction between the representative compounds **11** and various nucleophiles, finding that treatment of compounds **11c**, **11e**, and **11f** with allyltrimethylsilane in the presence of boron trifluoride efficiently afforded the corresponding allyl derivatives **13** in good to excellent yields, presumably through species **12** as

intermediates (Scheme 5 and Table 4). It is interesting to note that in these reactions the ethoxy group was found to be a better leaving group than methoxy (Table 4, entries 1 and 2) and, in addition, the Grubbs catalyst did not interfere with the allylation procedure, allowing the RCM allylation process to be carried out in a sequential protocol (Table 4, entry 3). In a related transformation, the use of propargyltrimethylsilane as the nucleophile allowed the preparation of compound **14** in excellent yield, which is of interest in view of the many synthetic applications of allenes.[21]



Scheme 5. C–C bond forming reactions at the position adjacent to nitrogen in compounds **11** through the intermediate vinylogous acyliminium cation **12**.

Table 4. Yields obtained in the nucleophilic allylation of compounds **11** to give **13**.

Entry	Reactant	Product	R	R^1	*t* [h]	Yield [%]
1	**11c**	**13a**	Et	OMe	2	95
2	**11e**	**13a**	Me	OMe	4	90
3	**11h**	**13b**	Et	S*t*Bu	3	70[a]

[a] Overall yield for the RCM–allylation sequence.

Conclusion

We have developed a new, experimentally convenient, user- and environmentally friendly procedure for the synthesis of 6-alkoxy-1,4,5,6-tetrahydropyridines in nearly quantitative yields. The synthetic procedure is based on a CAN-catalyzed, four-component reaction from very simple, acyclic building blocks. We have also demonstrated the use of the generated compounds as starting materials in the very efficient, two-step synthesis of homoquinolizine systems using a hitherto unknown γ-deprotonation–alkylation sequence on a tetrahydronicotinic ester. Finally, we have illustrated the formation of C–C bonds at the position adjacent to nitrogen of the homoquinolizine derivatives through the Lewis acid induced generation of a vinylogous acyliminium intermediate. The method could be easily applied to the generation of compound libraries.

Experimental Section

General: All reagents (Aldrich, Fluka, SDS, Probus) and solvents (SDS) were of commercial quality and were used as received. Reactions were monitored by thin layer chromatography (TLC), on aluminum plates coated with silica gel with fluorescent indicator (SDS CCM221254). Separations by flash chromatography were performed on alumina (Merck Al_2O_3 90). Melting points were measured on a Reichert 723 hot stage microscope, and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer Paragon 1000 FTIR spectrophotometer with all compounds examined as thin films on NaCl disks. NMR spectra were obtained on a Bruker Avance 250 spectrometer operating at 250 MHz for ^{1}H and 63 MHz for ^{13}C (CAI de Resonancia Magnética Nuclear, Universidad Complutense). Elemental analyses were determined by the CAI de Microanálisis Elemental, Universidad Complutense, by using a Leco 932 CHNS combustion microanalyzer.

General procedure for the four-component tetrahydropyridine synthesis: Preparation of compounds 5: The CAN catalyst (5 mol%) was added to a stirred solution of amine **1** (3.9 mmol, 1.3 equiv) and β-keto ester **2** (3 mmol, 1 equiv) in acetonitrile (5 mL) and the stirring continued for 30 min at room temperature. The suitable α,β-unsaturated aldehyde **3** (3.3 mmol, 1.1 equiv) and the alcohol **4** (6 mmol, 2 equiv) were then added and stirring was continued for further 1 h. After completion of the reaction, the mixture was diluted with CH_2Cl_2 (60 mL), washed with water and then brine, and dried (anhydrous Na_2SO_4) before the solvent was evaporated under reduced pressure. Pure compounds **5** were obtained by rapid column chromatography on activated neutral alumina, eluting with a petroleum ether–ethyl acetate mixture (95:5, v/v).

*Ethyl 1-butyl-6-ethoxy-2-methyl-1,4,5,6-tetrahydropyridine-3-carboxylate (**5a**)*: Colorless viscous liquid; yield: 0.751 g, 93%; ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 0.95$ (t, $J = 7.2$ Hz, 3H), 1.21–1.38 (m, 8H), 1.39–1.59 (m, 3H), 1.99–2.08 (m, 1H), 2.30–2.54 (m, 2H), 2.47 (s, 3H), 3.11–3.24 (m, 1H), 3.42–3.58 (m, 3H), 4.12 (q, $J = 7.2$ Hz, 2H), 4.46 ppm (brs, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): $\delta = 14.3$, 15.0, 15.9, 16.7, 18.5, 20.5, 25.6, 32.5, 50.4, 59.2, 62.5, 86.7, 96.7, 152.3, 169.5 ppm; IR (neat): $\tilde{\nu} = 2959.3$, 2869.5, 1680.5, 1577.6, 1273.1, 1118.8, 1065.9 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{27}NO_3$: C 66.88, H 10.10, N 5.20; found: C 66.50, H 10.00, N 5.14.

*Ethyl 1-butyl-6-ethoxy-2,5-dimethyl-1,4,5,6-tetrahydropyridine-3-carboxylate (**5b**)*: Colorless viscous liquid (two diastereoisomers **A** and **B** in a 2:1 ratio); yield: 0.730 g, 86%; ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 0.82$ (d, $J = 7.0$ Hz, 2H; **A**), 0.92–0.99 (m, 3H; **A** & **B**), 1.07 (d, $J = 6.7$ Hz, 1H; **B**), 1.20–1.40 (m, 8H; **A** & **B**), 1.41–1.72 (m, 3H; **A** & **B**), 2.03–2.60 (m, 2H; **A** & **B**), 2.44 (s, 3H; **A** & **B**), 3.01–3.23 (m, 1H; **A** & **B**), 3.40–3.71 (m, 3H; **A** & **B**), 4.04–4.22 ppm (m, 3H; **A** & **B**); ^{13}C NMR ($CDCl_3$, 62.9 MHz): $\delta = 14.3$, 15.0, 15.1, 15.8, 16.0, 16.4, 16.6, 17.7, 20.4, 20.5, 25.3, 27.3, 27.4, 32.5, 32.6, 33.1, 50.3, 51.4, 59.2, 62.7, 64.7, 91.0, 91.6, 93.6, 97.4, 151.4, 151.6, 169.6, 170.0 ppm; IR (neat): $\tilde{\nu} = 2960.4$, 2873.4, 1681.5, 1577.7, 1252.1, 1142.4, 1058.3 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{29}NO_3$: C 67.81, H 10.31, N 4.94; found: C 67.53, H 10.21, N 4.88.

*Methyl 1-allyl-6-methoxy-2,4-dimethyl-1,4,5,6-tetrahydro-pyridine-3-carboxylate (**5c**)*: Colorless viscous liquid (two diastereoisomers **A** and **B** in a 5:1 ratio); yield: 0.645 g, 90%; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.06$ (d, $J = 8.1$ Hz, 3H; **B**), 1.19 (d, $J = 7.1$ Hz, 3H; **A**), 1.61–1.68 (m, 1H; **A** & **B**), 1.96–2.02 (m, 1H; **B**), 2.09–2.20 (m, 1H; **A**), 2.35 (s, 3H; **B**), 2.41 (s, 3H; **A**), 2.87–2.96 (m, 1H; **A** & **B**), 3.33 (s, 3H; **A** & **B**), 3.69 (s, 3H; **A** & **B**), 3.86–3.98 (m, 1H; **A** & **B**), 4.04–4.18 (m, 1H; **A** & **B**), 4.37 (brs, 1H; **A** & **B**), 5.08–5.27 (m, 2H; **A** & **B**), 5.78–5.87 ppm (m, 1H; **A** & **B**); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 16.8$ (**A**), 17.0 (**B**), 21.0 (**A**), 23.9 (**B**), 25.6 (**B**), 26.1 (**A**), 29.7 (**A**), 34.0 (**B**), 49.8 (**B**), 50.9 (**A**), 51.7 (**A**), 53.8 (**B**), 55.1 (**A**), 55.7 (**B**), 85.8 (**B**), 88.7 (**A**), 101.9 (**A**), 104.6 (**B**), 115.9 (**A**), 116.8 (**B**), 134.7 (**B**), 134.9 (**A**), 151.1 (**B**), 151.5 (**A**), 169.6 (**B**), 169.9 ppm (**A**); IR (neat): $\tilde{\nu} = 2946.6$, 1682.4, 1574.2, 1430.7, 1349.2,

1180.9, 1128.3, 1067.5 cm^{-1}; elemental analysis calcd (%) for $C_{13}H_{21}NO_3$: C 65.25, H 8.84, N 5.85; found: C 65.58, H 8.66, N 6.04.

*Ethyl 6-ethoxy-1-hexyl-2-methyl-1,4,5,6-tetrahydropyridine-3-carboxylate (**5d**)*: Colorless viscous liquid; yield: 0.811 g, 91%; ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 0.90$ (t, $J = 6.7$ Hz, 3H), 1.20–1.40 (m, 12H), 1.42–1.55 (m, 3H), 1.98–2.08 (m, 1H), 2.24–2.53 (m, 2H), 2.43 (s, 3H), 3.10–3.22 (m, 1H), 3.40–3.57 (m, 3H), 4.11 (q, $J = 7.1$ Hz, 2H), 4.46 ppm (brs, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): $\delta = 14.4$, 15.0, 15.9, 16.6, 18.5, 22.9, 25.6, 26.9, 30.4, 31.9, 50.7, 59.2, 62.5, 86.7, 96.7, 152.2, 169.5 ppm; IR (neat): $\tilde{\nu} = 2957.3$, 2858.1, 1681.9, 1574.3, 1272.7, 1119.2, 1067.4 cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{31}NO_3$: C 68.65, H 10.51, N 4.71; found: C 68.41, H 10.43, N 4.65.

*Ethyl 6-ethoxy-2-methyl-1-(2-methylbutyl)-1,4,5,6-tetrahydropyridine-3-carboxylate (**5e**)*: Colorless viscous liquid (two diastereoisomers **A** and **B** in a 1:1 ratio); yield: 0.747 g, 88%; ^1H NMR ($CDCl_3$, 250 MHz): $\delta =$ 0.85–0.95 (m, 6H; **A** & **B**), 0.99–1.17 (m, 1H; **A** & **B**), 1.20–1.29 (m, 6H; **A** & **B**), 1.34–1.70 (m, 3H; **A** & **B**), 2.00–2.08 (m, 1H; **A** & **B**), 2.29–2.53 (m, 2H; **A** & **B**), 2.42 (s, 3H; **A** & **B**), 2.85 (dd, $J = 14.9$, 8.9 Hz, 1H; **A**), 3.02 (dd, $J = 14.9$, 7.6 Hz, 1H; **B**), 3.36–3.61 (m, 3H; **A** & **B**), 4.05–4.16 (m, 2H; **A** & **B**), 4.45–4.47 ppm (m, 1H; **A** & **B**); ^{13}C NMR ($CDCl_3$, 62.9 MHz): $\delta = 11.8$, 11.9, 15.0, 15.9, 17.0, 17.1, 17.7, 18.7, 25.2, 25.3, 27.3, 27.6, 36.1, 36.6, 56.2, 56.9, 59.2, 62.6, 86.4, 87.3, 96.7, 152.6, 152.7, 169.6 ppm; IR (neat): $\tilde{\nu} = 2964.1$, 2878.8, 1681.8, 1574.2, 1381.2, 1270.3, 1116.4, 1067.5 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{29}NO_3$: C 67.81, H 10.31, N 4.94; found: C 67.45, H 10.11, N 4.82.

tert-*Butyl 1-butyl-6-ethoxy-2-methyl-1,4,5,6-tetrahydropyridine-3-carboxylate (**5f**)*: Colorless viscous liquid; yield: 0.775 g, 87%; ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 0.94$ (t, $J = 7.2$ Hz, 3H), 1.24 (t, $J = 7.0$ Hz, 3H), 1.26–1.40 (m, 2H), 1.41–1.61 (m, 3H), 1.47 (s, 9H), 1.96–2.06 (m, 1H), 2.20–2.49 (m, 2H), 2.39 (s, 3H), 3.09–3.22 (m, 1H), 3.39–3.60 (m, 3H), 4.45 ppm (t, $J = 2.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): $\delta = 14.3$, 15.9, 16.7, 19.0, 20.5, 25.6, 28.9, 32.6, 50.4, 62.4, 78.4, 86.7, 98.6, 150.9, 169.3 ppm; IR (neat): $\tilde{\nu} = 2961.7$, 2870.5, 1681.1, 1579.9, 1364.2, 1281.7, 1119.6, 1068.0 cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{31}NO_3$: C 68.65, H 10.51, N 4.71; found: C 68.27, H 10.38, N 4.50.

*Ethyl 1-benzyl-6-ethoxy-2-methyl-1,4,5,6-tetrahydropyridine-3-carboxylate (**5g**)*: Colorless viscous liquid; yield: 0.727 g, 80%; ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 1.21$–1.31 (m, 6H), 1.52–1.66 (m, 1H), 2.03–2.12 (m, 1H), 2.33–2.47 (m, 1H), 2.42 (s, 3H), 2.57–2.66 (m, 1H), 3.38–3.62 (m, 2H), 4.14 (q, $J = 7.1$ Hz, 2H), 4.40–4.53 (m, 2H), 4.83 (d, $J = 17.6$ Hz, 1H), 7.18–7.41 ppm (m, 5H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): $\delta = 15.0$, 15.9, 16.9, 18.4, 25.3, 52.9, 59.4, 62.8, 86.6, 97.3, 126.5, 127.5, 129.2, 139.1, 152.5, 169.4 ppm; IR (neat): $\tilde{\nu} = 2975.4$, 2903.7, 1681.7, 1576.2, 1381.3, 1273.6, 1121.0, 1066.4 cm^{-1}; elemental analysis calcd (%) for $C_{18}H_{25}NO_3$: C 71.26, H 8.31, N 4.62; found: C 70.89, H 8.11, N 4.51.

*Ethyl 1-butyl-6-methoxy-2-methyl-1,4,5,6-tetrahydropyridine-3-carboxylate (**5h**)*: Colorless viscous liquid; yield: 0.719 g, 94%; ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 0.95$ (t, $J = 7.2$ Hz, 3H), 1.26 (t, $J = 7.1$ Hz, 3H), 1.26–1.38 (m, 2H), 1.39–1.58 (m, 3H), 2.01–2.10 (m, 1H), 2.19–2.36 (m, 1H), 2.48 (s, 3H), 2.48–2.58 (m, 1H), 3.10–3.22 (m, 1H), 3.34 (s, 3H), 3.47–3.59 (m, 1H), 4.12 (q, $J = 7.1$ Hz, 2H), 4.39 ppm (t, $J = 2.2$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): $\delta = 14.3$, 15.0, 16.7, 18.5, 20.5, 25.1, 32.6, 50.9, 54.7, 59.3, 88.1, 97.2, 152.0, 169.5 ppm; IR (neat): $\tilde{\nu} = 2958.3$, 2874.7, 1681.9, 1574.7, 1348.2, 1273.4, 1064.2 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{25}NO_3$: C 65.85, H 9.87, N 5.49; found: C 65.50, H 9.80, N, 5.32.

*Ethyl 6-allyloxy-1-butyl-2-methyl-1,4,5,6-tetrahydropyridine-3-carboxylate (**5i**)*: Colorless viscous liquid; yield: 0.759 g, 90%; ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 0.94$ (t, $J = 7.2$ Hz, 3H), 1.27 (t, $J = 7.1$ Hz, 3H), 1.27–1.35 (m, 2H), 1.40–1.55 (m, 3H), 2.01–2.08 (m, 1H), 2.32–2.49 (m, 2H), 2.44 (s, 3H), 3.08–3.21 (m, 1H), 3.44–3.57 (m, 1H), 4.02 (dd, $J = 5.7$, 1.2 Hz, 2H), 4.12 (q, $J = 7.1$ Hz, 2H), 4.52 (t, $J = 2.2$ Hz, 1H), 5.18–5.34 (m, 2H), 5.87–6.00 ppm (m, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): $\delta = 14.3$, 15.0, 16.7, 18.6, 20.5, 25.7, 32.6, 50.5, 59.3, 68.1, 86.1, 97.3, 117.4, 135.3, 152.1, 169.5 ppm; IR (neat): $\tilde{\nu} = 2958.8$, 2873.5, 1682.0, 1576.0, 1380.8, 1273.4, 1119.3, 1037.5 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{27}NO_3$: C 68.29, H 9.67, N 4.98; found: C 68.00, H 9.52, N 4.90.

*Ethyl 1-allyl-6-ethoxy-2-methyl-1,4,5,6-tetrahydropyridine-3-carboxylate (**5j**)*: Colorless viscous liquid; yield: 0.698 g, 92%; ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 1.21$–1.30 (m, 6H), 1.42–1.56 (m, 1H), 2.01–2.10 (m, 1H), 2.24–2.37 (m, 1H), 2.42 (s, 3H), 2.51–2.56 (m, 1H), 3.40–3.62 (m, 2H), 3.80–3.93 (m, 1H), 4.05–4.19 (m, 3H), 4.41 (brs, 1H), 5.09–5.21 (m, 2H), 5.76–5.91 ppm (m, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): $\delta = 15.0$, 15.9, 16.6, 18.3, 25.3, 51.9, 59.3, 62.7, 86.4, 96.9, 116.0, 135.0, 152.4, 169.4 ppm; IR (neat): $\tilde{\nu} = 2976.1$, 2900.7, 1681.6, 1578.0, 1273.9, 1121.9, 1066.4 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{23}NO_3$: C 66.37, H 9.15, N 5.53; found: C 66.01, H 8.99, N 5.50.

*Methyl 1-allyl-6-ethoxy-2-methyl-1,4,5,6-tetrahydropyridine-3-carboxylate (**5k**)*: Colorless viscous liquid; yield: 0.667 g, 93%; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 1.23$ (t, $J = 7.0$ Hz, 3H), 1.41–1.56 (m, 1H), 2.00–2.09 (m, 1H), 2.24–2.42 (m, 1H), 2.49 (s, 3H), 2.51–2.58 (m, 1H), 3.43–3.59 (m, 2H), 3.65 (s, 3H), 3.81–3.91 (m, 1H), 4.09–4.19 (m, 1H), 4.41(brs, 1H), 5.07–5.19 (m, 2H), 5.76–5.90 ppm (m, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 15.9$, 16.5, 18.3, 25.3, 50.8, 52.0, 62.7, 86.3, 96.5, 116.0, 134.9, 152.7, 169.6 ppm; IR (neat): $\tilde{\nu} = 2946.7$, 1682.3, 1580.1, 1430.6, 1277.4, 1176.4, 1119.9, 1067.9 cm^{-1}; elemental analysis calcd (%) for $C_{13}H_{21}NO_3$: C 65.25, H 8.84, N 5.85; found: C 65.51, H 8.70, N 6.05.

*Ethyl 1-allyl-6-methoxy-2-methyl-1,4,5,6-tetrahydropyridine-3-carboxylate (**5l**)*: Colorless viscous liquid; yield: 0.681 g, 95%; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 1.27$ (t, $J = 7.1$ Hz, 3H), 1.42–1.57 (m, 1H), 2.04–2.14 (m, 1H), 2.21–2.36 (m, 1H), 2.43 (s, 3H), 2.51–2.53 (m, 1H), 3.35 (s, 3H), 3.81–3.91 (m, 1H), 4.04–4.19 (m, 3H), 4.32–4.35 (m, 1H), 5.09–5.21 (m, 2H), 5.76–5.91 ppm (m, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 14.6$, 16.1, 18.1, 24.5, 52.3, 54.3, 58.7, 87.6, 96.8, 115.6, 135.6, 151.8, 168.6 ppm; IR (neat): $\tilde{\nu} = 2932.1$, 1682.7, 1574.0, 1430.2, 1347.2, 1273.7, 1115.8, 768.2 cm^{-1}; elemental analysis calcd (%) for $C_{13}H_{21}NO_3$: C 65.25, H 8.84, N 5.85; found: C 65.07, H 8.54, N 6.05.

*Methyl 1-allyl-6-methoxy-2-methyl-1,4,5,6-tetrahydropyridine-3-carboxylate (**5m**)*: Colorless viscous liquid; yield: 0.621 g, 92%; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 1.42$–1.56 (m, 1H), 2.04–2.13 (m, 1H), 2.21–2.33 (m, 1H), 2.42 (s, 3H), 2.49–2.56 (m, 1H), 3.33 (s, 3H), 3.66 (s, 3H), 3.81–3.91 (m, 1H), 4.12–4.22 (m, 1H), 4.33 (brs, 1H), 5.08–5.19 (m, 2H), 5.76–5.88 ppm (m, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 16.3$, 18.1, 24.6, 50.6, 52.4, 54.6, 87.7, 96.7, 115.9, 134.9, 152.4, 169.3 ppm; IR (neat): $\tilde{\nu} =$ 2946.0, 1682.7, 1579.8, 1430.0, 1347.4, 1277.4, 1170.2, 1117.9, 1067.5 cm^{-1}; elemental analysis calcd (%) for $C_{12}H_{19}NO_3$: C 63.98, H 8.50, N 6.22; found: C 64.04, H 8.37, N 6.50.

S-tert-*Butyl 1-allyl-6-ethoxy-2-methyl-1,4,5,6-tetrahydropyridine-3-carbothioate (**5n**)*: Pale yellow viscous liquid; yield: 0.766 g, 86%; ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 1.23$ (t, $J = 7.0$ Hz, 3H), 1.47–1.60 (m, 1H), 1.50 (s, 9H), 2.04–2.13 (m, 1H), 2.38 (s, 3H), 2.40–2.47 (m, 1H), 2.55–2.63 (m, 1H), 3.39–3.62 (m, 2H), 3.81–3.92 (m, 1H), 4.08–4.19 (m, 1H), 4.38 (brs, 1H), 5.07–5.21 (m, 2H), 5.75–5.90 ppm (m, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): $\delta = 15.9$, 17.2, 18.9, 25.4, 30.7, 46.8, 51.9, 62.8, 85.9, 105.8, 116.3, 134.6, 150.8, 191.3 ppm; IR (neat): $\tilde{\nu} = 2961.5$, 2928.6, 1628.9, 1544.5, 1333.2, 1061.0 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{27}NO_2S$: C 64.60, H 9.15, N 4.71; found: C 64.42, H 9.00, N 4.60.

S-tert-*Butyl 1-allyl-6-methoxy-2-methyl-1,4,5,6-tetrahydropyridine-3-carbothioate (**5o**)*: Pale yellow viscous liquid; yield: 0.807 g, 95%; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 1.49$ (m, 9H), 1.56–1.60 (m, 1H), 2.07–2.16 (m, 1H), 2.26–2.33 (m, 1H), 2.38 (s, 3H), 2.55–2.63 (m, 1H), 3.33 (s, 3H), 3.82–3.92 (m, 1H), 4.04–4.42 (m, 1H), 4.31 (brs, 1H), 5.08–5.20 (m, 2H), 5.75–5.89 ppm (m, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 17.1$, 18.7, 24.7, 30.6, 46.6, 52.3, 54.8, 87.3, 105.9, 116.3, 134.5, 150.4, 191.3 ppm; IR (neat): $\tilde{\nu} = 2957.5$, 1628.8, 1538.4, 1345.9, 1254.8, 1068.5, 922.2, 767.2 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{25}NO_2S$: C 63.56, H 8.89, N 4.94, S 11.31; found: C 63.67, H 8.88, N 5.11, S 11.31.

General procedure for the γ-alkylation of compounds 5: Preparation of compounds 9: LDA (prepared from diisopropylamine (2 equiv) and *n*BuLi (1.6 M hexane solution, 2.05 equiv), 30 min, 0 °C) was added to a solution of the suitable 1,4,5,6-tetrahydropyridine derivative **5** (1 mmol) in dry THF (10 mL). The reaction mixture was stirred at −5 to 0 °C for 30 min before the addition of allyl iodide or propargyl bromide (1.1 equiv). The resulting solution was stirred at 0 °C for 2 h, and, after verifying the completion of the reaction by TLC, a few drops of cold water were added and the organic layer was concentrated to dryness. The residue was dissolved in CH_2Cl_2 and washed with brine. The organic

layer was dried over Na_2SO_4 and concentrated to dryness. The crude residue was subject to chromatography on neutral Al_2O_3 (activity II-III), eluting with a 98:2 petroleum ether–ethyl acetate mixture containing 0.25% Et_3N.

*Ethyl 1-butyl-2-(but-3-en-1-yl)-6-ethoxy-1,4,5,6-tetrahydropyridine-3-carboxylate (**9a**)*: Colorless viscous liquid; yield: 0.294 g, 95%; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 0.96$ (t, $J = 7.2$ Hz, 3H), 1.14–1.37 (m, 6H), 1.41–1.59 (m, 4H), 1.99–2.08 (m, 1H), 2.16–2.65 (m, 6H), 3.08–3.33 (m, 2H), 3.37–3.58 (m, 3H), 4.08–4.19 (m, 2H), 4.49 (brs, 1H), 4.99–5.14 (m, 2H), 5.87–6.04 ppm (m, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 14.3$, 15.0, 15.8, 18.8, 20.5, 26.1, 28.6, 32.8, 33.8, 50.7, 59.3, 62.4, 86.7, 97.5, 114.9, 138.5, 155.2, 168.9 ppm; IR (neat): $\tilde{\nu} = 2959.0$, 2930.4, 1681.8, 1573.4, 1273.5, 1144.9, 1121.2, 1052.1 cm^{-1}; elemental analysis calcd (%) for $C_{18}H_{31}NO_3$: C 69.86, H 10.10, N 4.53; found: C 69.65, H 9.89, N 4.32.

*Ethyl 1-allyl-2-(but-3-en-1-yl)-6-ethoxy-1,4,5,6-tetrahydropyridine-3-carboxylate (**9b**)*: Colorless viscous liquid; yield: 0.270 g, 92%; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.24$–1.33 (m, 6H), 1.42–1.57 (m, 1H), 1.99–2.09 (m, 1H), 2.16–2.61 (m, 5H), 3.19–3.42 (m, 1H), 3.47–3.58 (m, 2H), 3.70–3.90 (m, 1H), 4.08–4.19 (m, 3H), 4.44 (brs, 1H), 4.98–5.32 (m, 4H), 5.77–5.98 ppm (m, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 14.9$, 15.9, 18.6, 25.7, 28.6, 33.6, 52.1, 59.3, 62.6, 86.3, 97.2, 114.9, 116.5, 135.3, 138.3, 155.4, 168.7 ppm; IR (neat): $\tilde{\nu} = 2977.2$, 1681.9, 1574.0, 1446.7, 1272.1, 1168.3, 1122.5, 1067.4, 956.4, 913.9 cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{27}NO_3$: C 69.59, H 9.28, N 4.77; found: C 69.64, H 9.04, N 4.95.

*Methyl 1-allyl-2-(but-3-en-1-yl)-6-ethoxy-1,4,5,6-tetrahydropyridine-3-carboxylate (**9c**)*: Colorless viscous liquid; yield: 0.265 g, 95%; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.23$ (t, $J = 7.0$ Hz, 3H), 1.41–1.56 (m, 1H), 1.93–2.58 (m, 6H), 3.20–3.32 (m, 1H), 3.47–3.57 (m, 2H), 3.67 (s. 3H), 3.79–3.95 (m, 1H), 4.07–4.17 (m, 1H), 4.43 (brs, 1H), 4.97–5.23 (m, 4H), 5.76–6.01 ppm (m, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 15.8$, 18.5, 25.7, 28.7, 33.6, 50.9, 52.2, 62.6, 86.3, 96.9, 114.9, 116.5, 135.2, 138.3, 155.9, 169.0 ppm; IR (neat): $\tilde{\nu} = 2976.9$, 2946.2, 1687.0, 1573.8, 1275.4, 1174.3, 1132.1, 1067.8 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{25}NO_3$: C 68.79, H 9.02, N 5.01; found: C 68.54, H 8.81, N 4.87.

*Ethyl 1-allyl-2-(but-3-en-1-yl)-6-methoxy-1,4,5,6-tetrahydropyridine-3-carboxylate (**9d**)*: Colorless viscous liquid; yield: 0.251 g, 90%; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.21$ (t, $J = 7.1$ Hz, 3H), 1.47–1.55 (m, 1H), 1.95–2.67 (m, 7H), 3.33 (s, 3H), 3.78–3.87 (m, 1H), 4.07–4.22 (m, 3H), 4.34 (brs, 1H), 4.97–5.19 (m, 4H), 5.73–6.03 ppm (m, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 14.9$, 18.6, 25.1, 28.7, 33.7, 52.5, 54.8, 59.4, 87.9, 97.6, 114.9, 116.6, 135.2, 138.3, 155.1, 168.7 ppm; IR (neat): $\tilde{\nu} = 2978.3$, 2946.9, 1682.4, 1574.0, 1453.6, 1273.0, 1167.6, 1121.2, 1067.7, 914.6 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{25}NO_3$: C 68.79, H 9.02, N 5.01; found: C 68.75, H 8.77, N 4.85.

*Methyl 1-allyl-2-(but-3-en-1-yl)-6-methoxy-1,4,5,6-tetrahydropyridine-3-carboxylate (**9e**)*: Colorless viscous liquid; yield: 0.252 g, 95%; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.45$–1.57 (m, 1H), 2.03–2.60 (m, 7H), 3.35 (s, 3H), 3.68 (s, 3H), 3.80–3.89 (m, 1H), 4.12–4.21 (m, 1H), 4.36 (brs, 1H), 4.99–5.21 (m, 4H), 5.78–5.99 ppm (m, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 18.5$, 25.1, 28.7, 33.6, 51.0, 52.5, 54.8, 87.8, 97.2, 115.0, 116.6, 135.1, 138.3, 155.7, 169.1 ppm; IR (neat): $\tilde{\nu} = 2946.3$, 1684.2, 1573.9, 1432.5, 1274.5, 1167.9, 1120.5, 1067.9 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{23}NO_3$: C 67.90, H 8.74, N 5.28; found: C 68.15, H 9.07, N 5.52.

S-tert-*Butyl 1-allyl-2-(but-3-en-1-yl)-6-ethoxy-1,4,5,6-tetrahydropyridine-3-carbothioate (**9f**)*: Pale yellow viscous liquid; yield: 0.320 g, 95%; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.24$ (t, $J = 7.0$ Hz, 3H), 1.44–1.63 (m, 1H), 1.51 (s, 9H), 2.02–2.62 (m, 6H), 3.16–3.27 (m, 1H), 3.45–3.57 (m, 2H), 3.81–3.90 (m, 1H), 4.06–4.14 (m, 1H), 4.39 (brs, 1H), 4.98–5.20 (m, 4H), 5.76–5.95 ppm (m, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 15.9$, 18.9, 25.7, 28.7, 30.6, 33.4, 46.6, 51.9, 62.7, 85.9, 105.8, 115.0. 116.6, 134.9, 138.3, 153.2, 190.3 ppm; IR (neat): $\tilde{\nu} = 2961.9$, 2923.3, 1605.2, 1533.0, 1452.4, 1360.4, 1162.2, 1068.0, 918.2 cm^{-1}; elemental analysis calcd for $C_{19}H_{31}NO_3S$: C 67.61, H 9.26, N 4.15, S 9.50; found: C 67.90, H 9.32, N 4.38, S 9.42.

S-tert-*Butyl 1-allyl-2-(but-3-en-1-yl)-6-methoxy-1,4,5,6-tetrahydropyridine-3-carbothioate (**9g**)*: Pale yellow viscous liquid; yield: 0.297 g, 92%; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.49$ (s. 9H), 1.54–1.58 (m, 1H), 2.04–2.23 (m, 2H), 2.30–2.50 (m, 3H), 2.54–2.62 (m, 1H), 3.22–3.29 (m, 1H), 3.32 (s, 3H), 3.79–3.89 (m, 1H), 4.08–4.17 (m, 1H), 4.31–4.32 (m, 1H), 4.98–5.20 (m, 4H), 5.74–6.01 ppm (m, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 19.0$, 25.1, 28.7, 30.6, 33.5, 46.8, 52.2, 54.8, 87.3, 106.2, 115.1, 116.8, 134.9, 138.3, 152.9, 190.7 ppm; IR (neat): $\tilde{\nu} = 2959.2$, 2923.9, 1630.7, 1538.1, 1453.1, 1348.7, 1068.6, 921.4 cm^{-1}; elemental analysis calcd (%) for $C_{18}H_{29}NO_3S$: C 66.83, H 9.04, N 4.33, S 9.91; found: C 66.54, H 9.00, N 4.35, S 9.78.

*Methyl 1-allyl-2-(but-3-yn-1-yl)-6-ethoxy-1,4,5,6-tetrahydropyridine-3-carboxylate (**9h**)*: Colorless viscous liquid; yield: 0.258 g, 93%; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.23$ (t, $J = 7.0$ Hz, 3H), 1.43–1.56 (m, 1H), 2.02–2.07 (m, 2H), 2.25–2.64 (m, 4H), 2.70–2.81 (m, 1H), 3.33–3.45 (m, 1H), 3.52 (q, $J = 7.0$ Hz, 2H), 3.69 (s, 3H), 3.77–3.95 (m, 1H), 4.19–4.27 (m, 1H), 4.44 (brs, 1H), 5.12–5.22 (m, 2H), 5.79–5.93 ppm (m, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 15.8$, 18.4, 18.6, 25.6, 28.5, 51.1, 52.5, 62.7, 69.2, 84.2, 86.5, 97.5, 116.6, 135.1, 154.4, 168.8 ppm; IR (neat): $\tilde{\nu} =$ 3294.8, 2947.6, 1682.6, 1573.9, 1432.6, 1278.2, 1163.7, 1115.2, 1067.2 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{23}NO_3$: C 69.29, H 8.36, N 5.05; found: C 69.57, H 8.09, N 5.14.

*Ethyl 1-allyl-2-(but-3-yn-1-yl)-6-methoxy-1,4,5,6-tetrahydropyridine-3-carboxylate (**9i**)*: Colorless viscous liquid; yield: 0.260 g, 94%; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.28$ (t, $J = 7.1$ Hz, 3H), 1.40–1.55 (m, 1H), 1.99–2.10 (m, 2H), 2.19–2.44 (m, 2H), 2.50–2.74 (m, 3H), 3.34 (s, 3H), 3.38–3.47 (m, 1H), 3.82–3.92 (m, 1H), 4.11 (q, $J = 7.1$ Hz, 2H), 4.21–4.29 (m, 1H), 4.35 (brs, 1H), 5.10–5.21 (m, 2H), 5.76–5.91 ppm (m, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 13.5$, 17.0, 17.3, 23.7, 27.1, 51.5, 53.4, 58.1, 67.9, 82.7, 86.6, 96.9, 115.2, 133.6, 152.2, 167.0 ppm; IR (neat): $\tilde{\nu} =$ 3294.5, 2980.0, 2932.8, 1681.2, 1574.0, 1452.5, 1275.2, 1163.6, 1067.5, 770.9 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{23}NO_3$: C 69.29, H 8.36, N 5.05; found: C 69.29, H 8.42, N 5.05.

General procedure for the RCM reaction of compounds 9: Preparation of pyridoazepines 11: The Grubbs first-generation catalyst **10** (10 mol%) was added to a solution of the suitable 1,4,5,6-tetrahydropyridine derivative **9** (1 mmol) in dry CH_2Cl_2 (10 mL) and the reaction mixture was stirred at room temperature for the times indicated in Table 3. After verifying completion of the reaction by TLC, the organic layer was concentrated to dryness and the crude residue was purified by chromatography on a neutral Al_2O_3 (activity II-III) column, eluting with a 96:4 petroleum ether–ethyl acetate mixture containing 0.25% Et_3N. For the preparation of compounds **11h** and **11i**, the enyne RCM reactions were carried out under an ethylene atmosphere.

*Ethyl 4-ethoxy-2,3,4,6,9,10-hexahydropyrido[1,2-a]azepine-1-carboxylate (**11b**)*: Colorless viscous liquid; yield: 0.252 g, 95%; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.24$ (t, $J = 7.0$ Hz, 3H), 1.27 (t, $J = 7.1$ Hz, 3H), 1.44–1.58 (m, 1H), 1.96–2.05 (m, 1H), 2.24–2.56 (m, 4H), 3.29–3.45 (m, 2H), 3.53 (q, $J = 7$ Hz, 2H), 4.01 (brs, 2H), 4.14 (q, $J = 7.1$ Hz, 2H), 4.46 (brs, 1H), 5.73–5.75 ppm (m, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 15.0$, 16.1, 18.4, 26.2, 26.4, 29.3, 49.5, 59.5, 62.8, 88.8, 95.9, 125.6, 133.2, 157.7, 169.8 ppm; IR (neat): $\tilde{\nu} = 2974.3$, 2898.1, 1677.4, 1577.3, 1267.2, 1158.3, 1105.5, 1066.0 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{23}NO_3$: C 67.90, H 8.74, N 5.28; found: C 68.17, H 8.78, N 5.28.

*Methyl 4-ethoxy-2,3,4,6,9,10-hexahydropyrido[1,2-a]azepine-1-carboxylate (**11c**)*: Colorless viscous liquid; yield: 0.238 g, 95%; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.23$ (t, $J = 6.8$ Hz, 3H), 1.50–1.55 (m, 1H), 1.99–2.04 (m, 1H), 2.29–2.52 (m, 4H), 3.36–3.46 (m, 2H), 3.53 (q, $J = 6.7$ Hz, 2H), 3.65 (s, 3H), 4.01 (brs, 2H), 4.46 (brs, 1H), 5.74 ppm (brs, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 15.9$, 18.3, 26.2, 26.3, 29.1, 49.6, 50.9, 62.8, 88.9, 95.3, 125.4, 132.9, 157.9, 169.6 ppm; IR (neat): $\tilde{\nu} = 2927.8$, 1679.1, 1574.3, 1269.0, 1158.0, 1108.2, 1066.5 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{21}NO_3$: C 66.91, H 8.42, N 5.57; found: C 67.17, H 8.31, N 5.73.

*Ethyl 4-methoxy-2,3,4,6,9,10-hexahydropyrido[1,2-a]azepine-1-carboxylate (**11d**)*: Colorless viscous liquid; yield: 0.238 g, 95%; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.26$ (t, $J = 7.1$ Hz, 3H), 1.43–1.57 (m, 1H), 1.96–2.55 (m, 6H), 3.36 (s, 3H), 3.41–3.57 (m, 1H), 3.86–3.99 (m, 1H), 4.06–4.19 (m, 3H), 4.37 (brs, 1H), 5.69–5.80 ppm (m, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 14.9$, 18.2, 25.6, 26.4, 29.1, 49.9, 55.0, 59.3, 90.5, 95.9, 125.5, 132.9, 157.3, 169.2 ppm; IR (neat): $\tilde{\nu} = 2976.0$, 2929.3, 1678.3, 1578.1, 1267.8, 1158.8, 1106.9, 1064.4 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{21}NO_3$: C 66.91, H 8.42, N 5.57; found: C 67.10, H 8.30, N 5.59.

*Methyl 4-methoxy-2,3,4,6,9,10-hexahydropyrido[1,2-a]azepine-1-carboxylate (**11e**)*: Colorless viscous liquid; yield: 0.218 g, 92%; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.44–1.68 (m, 1H), 1.91–2.68 (m, 6H), 3.35–3.53 (m, 1H), 3.37 (s, 3H), 3.66 (s, 3H), 3.91–3.99 (m, 1H), 4.09–4.16 (m, 1H), 4.39 (brs, 1H), 5.75–5.81 ppm (m, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 18.2, 25.6, 26.4, 29.1, 50.0, 50.9, 55.1, 90.5, 95.6, 125.4, 133.0, 157.7, 169.6 ppm; IR (neat): $\tilde{\nu}$ = 2944.6, 1681.6, 1574.4, 1433.1, 1270.9, 1159.8, 1109.4, 1063.9 cm^{-1}; elemental analysis calcd (%) for $C_{13}H_{19}NO_3$: C 65.80, H 8.07, N 5.90; found: C 66.06, H 8.32, N 5.77.

S-tert-*Butyl 4-ethoxy-2,3,4,6,9,10-hexahydropyrido[1,2-a]azepine-1-carbothioate (**11f**)*: Colorless viscous liquid; yield: 0.284 g, 92%; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.08 (t, J = 6.5 Hz, 3H), 1.26 (s, 9H), 1.58–2.33 (m, 7H), 3.15 (brs, 1H), 3.37 (q, J = 6.6 Hz, 2H), 3.85 (brs, 2H), 4.28 (brs, 1H), 5.57 ppm (s, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.9, 18.8, 26.2, 26.6, 28.7, 30.6, 46.5, 49.4, 62.8, 88.2, 104.7, 125.2, 132.8, 155.3, 190.8 ppm; IR (neat): $\tilde{\nu}$ = 2925.8, 2855.5, 1681.1, 1362.9, 1172.8, 1026.0, 909.9, 847.6, 732.3 cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{27}NO_2S$: C 65.98, H 8.79, N 4.53, S 10.36; found: C 65.72, H 8.43, N 4.31, S 10.12.

S-tert-*Butyl 4-methoxy-2,3,4,6,9,10-hexahydropyrido[1,2-a]azepine-1-carbothioate (**11g**)*: Colorless viscous liquid; yield: 0.266 g, 90%; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.49 (s, 9H), 1.56–1.59 (m, 1H), 2.03–2.10 (m, 1H), 2.29–2.58 (m, 4H), 3.20–3.31 (m, 2H), 3.35 (s, 3H), 3.92–4.11 (m, 2H), 4.34 (brs, 1H), 5.74–5.75 ppm (m, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 18.9, 25.6, 26.8, 28.9, 30.6, 46.9, 49.8, 55.1, 89.9, 105.2, 125.1, 133.2, 155.2, 191.4 ppm; IR (neat): $\tilde{\nu}$ = 2957.4, 2923.9, 1626.5, 1545.7, 1452.2, 1143.9, 1065.8, 1025.2, 789.7 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{25}NO_2S$: C 65.05, H 8.53, N 4.74, S 10.85; found: C 64.88, H 8.25, N 4.50, S 10.48.

*Methyl 4-ethoxy-8-vinyl-2,3,4,6,9,10-hexahydropyrido[1,2-a]azepine-1-carboxylate (**11h**)*: Colorless viscous liquid; yield: 0.249 g, 90%; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.22 (t, J = 7 Hz, 3H), 1.42–1.54 (m, 1H), 1.88–2.64 (m, 6H), 3.30–3.37 (m, 1H), 3.47–3.62 (m, 2H), 3.66 (s, 3H), 3.91–4.16 (m, 2H), 4.44 (brs, 1H), 4.98–5.18 (m, 2H), 5.70–5.86 (m, 1H), 6.25–6.35 ppm (m, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.9, 18.2, 25.6, 26.2, 27.7, 49.2, 50.9, 62.8, 88.6, 95.2, 113.0, 127.1, 140.5, 141.1, 157.6, 169.6 ppm; IR (neat): $\tilde{\nu}$ = 2932.4, 2853.5, 1681.2, 1574.1, 1432.6, 1274.0, 1154.5, 1111.6, 1067.7 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{23}NO_3$: C 69.29, H 8.36, N 5.05; found: C 69.03, H 8.12, N 4.87.

*Ethyl 4-methoxy-8-vinyl-2,3,4,6,9,10-hexahydropyrido[1,2-a]azepine-1-carboxylate (**11i**)*: Colorless viscous liquid; yield: 0.241 g, 90%; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.28 (t, J = 7.1 Hz, 3H), 1.44–1.57 (m, 1H), 2.00–2.57 (m, 6H), 3.35 (s, 3H), 3.38–3.54 (m, 1H), 4.09–4.19 (m, 4H), 4.34–4.46 (m, 1H), 5.00–5.21 (m, 2H), 5.73–5.85 (m, 1H), 6.27–6.38 ppm (m, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.0, 18.2, 25.7 (2 signals), 27.7, 49.7, 55.0, 59.4, 90.3, 95.8, 113.1, 127.2, 140.5, 141.1, 157.0, 169.2 ppm; IR (neat): $\tilde{\nu}$ = 2978.0, 2933.4, 1681.5, 1580.8, 1271.4, 1156.0, 1112.6, 1070.0, 769.9 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{23}NO_3$: C 69.29, H 8.36, N 5.05; found: C 69.13, H 8.17, N 4.91.

General procedure for the cross-coupling reaction of compounds 11: Preparation of pyridoazepines 13 and 14: BF_3·Et_2O (2 equiv) was added to a solution of the suitable pyridoazepine derivative **11** (1 mmol) in dry dichloromethane (10 mL), followed by allyltrimethylsilane for compounds **13** (1 equiv) or propargyltrimethylsilane for compounds **14**. The reaction mixture was stirred at −5 °C for 10 min and then at room temperature for 2–4 h. After verifying completion of the reaction by TLC, the reaction mixture was washed with water, dried over Na_2SO_4, and concentrated to dryness. The crude residue was purified on neutral Al_2O_3 column, eluting with a 97:3 petroleum ether–ethyl acetate mixture containing 0.25% Et_3N.

*Methyl 4-allyl-2,3,4,6,9,10-hexahydropyrido[1,2-a]azepine-1-carboxylate (**13a**)*: Colorless viscous liquid; yield: 0.235 g, 95%; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.54–1.72 (m, 1H), 1.81–1.90 (m, 1H); 2.10–2.56 (m, 7H), 3.16–3.27 (m, 1H), 3.52–3.74 (m, 2H), 3.66 (s, 3H), 4.14–4.27 (m, 1H), 5.01–5.15 (m, 2H), 5.66–5.79 (m, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 19.8, 24.9, 27.1, 29.4, 37.5, 50.7, 51.3, 61.6, 91.7, 118.5, 126.1, 133.5, 135.6, 160.0, 170.4; IR (neat): $\tilde{\nu}$ = 2926.2, 1728.6, 1674.1, 1564.6, 1433.7, 1262.9, 1156.1, 1099.5 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{21}NO_2$: C 72.84, H 8.56, N 5.66; found: C 72.53, H 8.60, N 5.34.

S-tert-*Butyl-4-allyl-2,3,4,6,9,10-hexahydropyrido[1,2-a]azepine-1-carbothioate (**13b**)*: Colorless viscous liquid; yield: 0.214 g, 70%; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.52 (brs, 10H), 1.86–1.93 (m, 1H), 2.16–2.65 (m, 7H), 3.19–3.29 (m, 1H), 3.64–3.89 (m, 2H), 4.14–4.27 (m, 1H), 5.08–5.22 (m, 2H), 5.65–5.82 ppm (m, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 18.1, 23.1, 25.9, 27.1, 29.5, 35.9, 45.2, 48.5, 59.4, 99.6, 117.2, 124.1, 131.7, 133.4, 156.2, 188.6 ppm; IR (neat): $\tilde{\nu}$ = 2925.0, 1616.0, 1532.2, 1455.6, 1360.8, 1144.2, 1023.8 cm^{-1}; elemental analysis calcd (%) for $C_{18}H_{27}NOS$: C 70.77, H 8.91, N 4.59, S 10.50; found: C 70.39, H 8.54, N 4.39, S 10.31.

*Methyl 4-(prop-1,2-dienyl)-2,3,4,6,9,10-hexahydropyrido[1,2-a]azepine-1-carboxylate (**14**)*: Colorless viscous liquid; yield: 0.225 g, 92%; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.26–1.35 (m, 1H), 1.83–1.89 (m, 2H), 2.27–2.59 (m, 4H), 3.38–3.46 (m, 1H), 3.67 (s, 3H), 3.71–3.88 (m, 2H), 4.05–4.16 (m, 1H), 4.79–4.92 (m, 2H), 5.12 (q, J = 6.6 Hz, 1H), 5.72–5.73 ppm (m, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 18.1, 25.0, 25.9, 27.6, 47.9, 49.4, 58.8, 75.8, 90.3, 90.8, 123.9, 131.5, 158.3, 168.3, 206.86 ppm; IR (neat): $\tilde{\nu}$ = 2947.8, 1955.0, 1683.7, 1558.4, 1435.8, 1266.3, 1156.0, 1097.2 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{19}NO_2$: C 73.44, H 7.81, N 5.71; found: C 73.15, H 7.64, N 5.47.

Acknowledgements

Financial support from MEC (grant CTQ2006-10930/BQU) and CAM-UCM (Grupos de Investigación UCM, grant 920234) is gratefully acknowledged.

[1] For comprehensive reviews of pyridine synthesis, see: a) G. D. Henry, *Tetrahedron* **2004**, *60*, 6043–6061; b) D. Spitzner in *Science of Synthesis* (Ed.: D. Black), Thieme, Stuttgart, **2005**, pp. 11–284; for selected more recent methods, see: c) D. Craig, G. D. Henry, *Tetrahedron Lett.* **2005**, *46*, 2559–2562; d) M. C. Bagley, C. Glover, E. A: Merritt, *Synlett* **2007**, 2459–2482, and references therein; e) A.-L. Blayo, S. Le Meur, D. Grée, R. Grée, *Adv. Synth. Catal.* **2008**, *350*, 471–476; f) F. Liéby-Muller, C. Allais, T. Constantieux, J. Rodriguez, *Chem. Commun.* **2008**, 4207–4209, and references therein.

[2] For a review of the chemistry of dihydropyridines, see: a) R. Lavilla, *J. Chem. Soc. Faraday Trans. 1* **2002**, 1141–1156; b) for a review of several types of multicomponent reactions leading to dihydropyridines, including the traditional Hantzsch synthesis and related reactions, see reference [9]; for selected more recent synthetic approaches to 1,4-dihydropyridines, see: c) V. Sridharan, P. T. Perumal, C. Avendaño, J. C. Menéndez, *Tetrahedron* **2007**, *63*, 4407–4413, and references therein; d) G. Bartoli, K. Babiuch, M. Bosco, A. Carlone, P. Galzerano, P. Melchiorre, L. Sambri, *Synlett* **2007**, 2897–2901; e) L. Singh, M. P. Singh Ishar, M. Elango, V. Subramanian, V. Gupta, V. P. Kanwal, *J. Org. Chem.* **2008**, *73*, 2224–2233; f) M. Li, Z. Zuo, L. Wen, S. Wang, *J. Comb. Chem.* **2008**, *10*, 436–441.

[3] For some recent reviews of piperidine synthesis, see: a) S. Laschat, T. Dickner, *Synthesis* **2000**, 1781–1813; b) R. W. Bates, S.-E. Kanicha, *Tetrahedron* **2002**, *58*, 5957–5978; c) P. M. Weintraub, J. S. Sabol, J. M. Kane, D. R. Borcherding, *Tetrahedron* **2003**, *59*, 2953–2989; d) F.-X. Felpin, J. Lebreton, *Eur. J. Org. Chem.* **2003**, 3693–3712; e) M. G. P. Buffat, *Tetrahedron* **2004**, *60*, 1701–1729; f) C. Escolano, M. Amat, J. Bosch, *Chem. Eur. J.* **2006**, *12*, 8198–8207; g) C. De Risi, G. Fanton, G. P. Pollini, C. Trapella, F. Valente, V. Zanirato, *Tetrahedron: Asymmetry* **2008**, *19*, 131–264; h) S. Källström, R. Leino, *Bioorg. Med. Chem.* **2008**, *16*, 601–635.

[4] For representative examples, see: a) A. D. Abell, J. Gardiner, A. J. Phillips, W. T. Robinson, *Tetrahedron Lett.* **1998**, *39*, 9563–9566; b) Y. Ishidaa, K. Hattoria, H. Yamamotoa, A. Iwashitab, K. Miharab, N. Matsuoka, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4221–4225; c) D. Jansone, M. Fleisher, G. Andreeva, L. Leite, E. Lukevics, *Chem. Heterocycl. Compd.* **2005**, *41*, 1537–1538; for a review of the synthesis and applications of 2,6-dialkyl-1,2,5,6-tetrahydropyridines, see: d) F.-X. Felpin, J. Lebreton, *Curr. Org. Synth.* **2004**, *1*, 83–109.

[5] For a recent example, see: S. V. Karthikeyan, S. Perumal, K. K. Balasubramanian, *Tetrahedron Lett.* **2007**, *48*, 6133–6136.
[6] Y.-Z. Wang, C.-P. Tang, P.-H. Dien, Y. Ye, *J. Nat. Prod.* **2007**, *70*, 1356–1359.
[7] For recent reviews of the chemistry and applications of quinolizines and quinolizidines, see: a) C. Avendaño, J. C. Menéndez in *Comprehensive Heterocyclic Chemistry III* (Eds.: A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, R. J. K. Taylor), Elsevier, Amsterdam, **2008**, Chapter 12.1; b) J. P. Michael, *Nat. Prod. Rep.* **2008**, *25*, 139–165; c) J. P. Michael, *Nat. Prod. Rep.* **2007**, *24*, 191–222.
[8] For selected reviews and monographs on multicomponent reactions, see: a) A. Dömling, I. Ugi, *Angew. Chem.* **2000**, *112*, 3300–3344; *Angew. Chem. Int. Ed.* **2000**, *39*, 3168–3210; b) H. Bienaymé, C. Hulme, G. Oddon, P. Schmitt, *Chem. Eur. J.* **2000**, *6*, 3321–3329; c) A. Ugi, *Pure Appl. Chem.* **2001**, *73*, 187–191; d) A. Ugi, *Molecules* **2003**, *8*, 53–66; e) R. V. A. Orru, M. de Greef, *Synthesis* **2003**, 1471–1499; f) J. Zhu, *Eur. J. Org. Chem.* **2003**, 1133–1144; g) D. J. Ramón, M. Yus, *Angew. Chem.* **2005**, *117*, 1628–1661; *Angew. Chem. Int. Ed.* **2005**, *44*, 1602–1634; h) *Multicomponent Reactions* (Eds.: J. Zhu, H. Bienaymé), Wiley-VCH, Weinheim, **2005**; i) A. Dömling, *Chem. Rev.* **2006**, *106*, 17–89; j) G. Guillena, D. J. Ramón, M. Yus, *Tetrahedron: Asymmetry* **2007**, *18*, 693–700; k) N. Isambert, R. Lavilla, *Chem. Eur. J.* **2008**, *14*, 8444–8454.
[9] For a review of the use of β-dicarbonyl compounds in multicomponent reactions, see: C. Simon, T. Constantieux, J. Rodriguez, *Eur. J. Org. Chem.* **2004**, 4957–4980.
[10] While this manuscript was in preparation, a related three-component reaction between β-dicarbonyl compounds, α,β-unsaturated aldehydes, and β-aminoalcohols in toluene and in the presence of molecular sieves was described. This reaction afforded oxazino-[3,2*b*]pyridine derivatives, although only in an average of 47% yield, see: R. Noël, M.-C. Fargeau-Bellassoued, C. Vanucci-Bacqué, G. Lhommet, *Synthesis* **2008**, 1948–1954. A two-component version of this reaction can be found in reference [12].
[11] For the precedent of the fast generation of enaminones from amines and β-ketoesters under CAN catalysis, see: V. Sridharan, C. Avendaño, J. C. Menéndez, *Synlett* **2007**, 881–884.
[12] For the precedent for the Michael additions of β-enaminones, see, for instance: a) P. M. T. De Kok, L. A. M. Bastiaansen, P. M. Van Lier, J. A. J. M. Vekemans, H. M. Buck, *J. Org. Chem.* **1989**, *54*, 1313–1320; b) E. Caballero, P. Puebla, M. Medarde, A. San Feliciano, *Tetrahedron* **1993**, *49*, 10079–10088.
[13] For some reviews of CAN-promoted synthetic transformations, see: a) V. Nair, J. Matthew, J. Prabhakaran, *Chem. Soc. Rev.* **1997**, *26*, 127–132; b) J. R. Hwu, K.-Y. King, *Curr. Sci.* **2001**, *81*, 1043–1053; c) V. Nair, S. B. Panicker, L. G. Nair, T. G. George, A. Augustine, *Synlett* **2003**, 0156–0165; d) V. Nair, L. Balagopal, R. Rajan, J. Mathew, *Acc. Chem. Res.* **2004**, *37*, 21–30; e) V. Nair, A. Deepthi, *Chem. Rev.* **2007**, *107*, 1862–1891.
[14] I. E. Markó, A. Ates, A. Gautier, B. Leroy, J.-M. Plancher, Y. Quesnel, J.-C. Vanherck, *Angew. Chem.* **1999**, *111*, 3411–3413; *Angew. Chem. Int. Ed.* **1999**, *38*, 3207–3209.
[15] Some CAN-catalyzed reactions have been described recently; for representative examples, see: a) V. Sridharan, J. C. Menéndez, *Org. Lett.* **2008**, *10*, 4303–4306; b) V. Sridharan, C. Avendaño, J. C. Menéndez, *Synthesis* **2008**, 1039–1044; c) V. Sridharan, V. C. Avendaño, J. C. Menéndez, *Tetrahedron* **2007**, *63*, 4407–4413; d) V. Nair, K. Mohanan, T. D. Suja, E. Suresh, *Tetrahedron Lett.* **2006**, *47*, 705–709; e) X.-F. Zeng, S.-J. Ji, S. Y. Wang, *Tetrahedron* **2005**, *61*, 10235–10241; f) see also reference [11].
[16] For the generation of dianions of β-isopropylamino-α,β-enones with 2,2,6,6-tetramethylpiperidinolithium, see: G. Bartoli, M. Bosco, C. Cimarelli, R. Dalpozzo, G. Palmieri, *Synlett* **1991**, 229–230.
[17] For a recent example of the acceleration of RCEYM reactions in the presence of ethylene, see: A. Núñez, A. M. Cuadro, J. Álvarez-Builla, J. J. Vaquero, *Chem. Commun.* **2006**, 2690–2692.
[18] For selected reviews on the use of acyliminium cations as synthetic intermediates, see: a) W. N. Speckamp, H. Hiemstra, *Tetrahedron* **1985**, *41*, 4367–4416; b) W. N. Speckamp, M. J. Moolenaar, *Tetrahedron* **2000**, *56*, 3817–3856; c) B. E. Maryanoff, H.-C. Zhang, J. H. Cohen, I. J. Turchi, C. A. Maryanoff, *Chem. Rev.* **2004**, *104*, 1431–1628; d) J. Royer, M. Bonin, L. Micouin, *Chem. Rev.* **2004**, *104*, 2311–2352.
[19] For a theoretical study that shows that 4,5-dihydropyridinium species are stabilized by an electron-withdrawing group at C-3, see: E. Pop, M. E. Brewster, M.-J. Huang, N. Bodor, *J. Mol. Struct.* **1995**, *344–373*, 49–55.
[20] See, for instance: J. P. Michael, C. Accone, C. B. de Koning, C. W. van der Westhuyzen, *Beilstein J. Org. Chem.* **2008**, *4*, 5.
[21] For a recent monograph on the synthesis and applications of allenes, see: *Modern Allene Chemistry* (Eds.: N. Krause, A. S. K. Hashmi), Wiley-VCH, **2004**.

Received: January 7, 2009
Published online: March 13, 2009

