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A new three-component domino synthesis of 1,4-dihydropyridines

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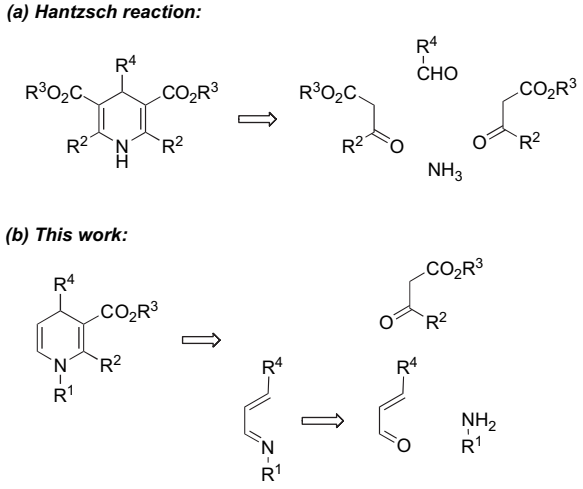
Abstract—Cerium ammonium nitrate (CAN) catalyzed the three-component domino reaction between aromatic amines, α,β-unsaturated aldehydes, and ethyl acetoacetate, providing an efficient new entry into 1,4-dihydropyridines. This new reaction requires very mild reaction conditions, has water as the only side product and is complementary to the classical Hantzsch synthesis in that it is well suited to the preparation of *N*-aryl-5,6-unsubstituted dihydropyridines. Experiments in the presence of a radical trap suggest that a one-electron oxidative mechanism can be excluded and that CAN acts as a Lewis acid.

1. Introduction

Multicomponent[1] and domino[2] reactions allow the creation of several bonds in a single operation and are attracting increasing attention as one of the most powerful emerging synthetic tools for the creation of molecular diversity and complexity.[3] They also have considerable advantages in terms of user and environmental friendliness because of the step reduction and atom economy associated to their use.

1,4-Dihydropyridines are among the most widely used drugs for the management of cardiovascular disease,[4] have a broad range of other pharmacological activities[5–9] and play a crucial role in CNS-targeted chemical delivery systems.[10] Also, in spite of initial, largely unfounded, misgivings about their stability, 1,4-dihydropyridines have also proven to be very important synthetic intermediates, finding application in the preparation of a large number of nitrogen alkaloids.[11] The synthesis of 1,4-dihydropyridines is often achieved by nucleophilic addition to pyridinium salts, available from the corresponding pyridine derivatives.[12] The best known procedure for the de novo preparation of 1,4-dihydropyridines is the classical Hantzsch synthesis, a multicomponent condensation involving, in its original version (Scheme 1a), two molecules of a β-ketoester, one molecule of an aldehyde, and one molecule of ammonia. In spite of their widespread use, neither the Hantzsch method nor related reactions[13] can be considered as general dihydropyridine syntheses as they do not allow the preparation of some important types of derivatives, including *N*-aryl-1,4-dihydropyridines[14] and C_5–C_6-unsubstituted 1,4-dihydropyridines. The development of efficient routes to these compounds is important to allow the systematic study of their biological activities and also from a synthetic point of view, since the presence of a C_5–C_6-unsubstituted bond enables the use of dihydropyridines as enamine-like reagents, allowing the preparation of a variety of complex heterocyclic frameworks.[15]



Scheme 1.

With these precedents in mind, we set as our goal the development of a new multicomponent procedure for the synthesis of dihydropyridines that is designed to overcome the above mentioned limitations and hence to be complementary

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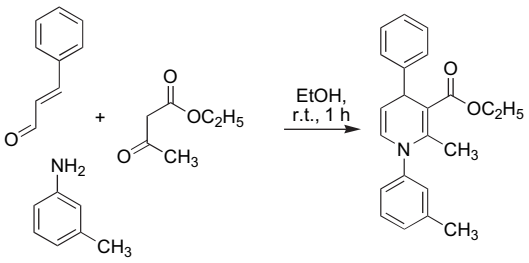
to the Hantzsch reaction. Our strategy (Scheme 1b) is based on a domino imine formation–Michael addition–condensation sequence, and is different from a recently introduced one that involves Michael-initiated multicomponent reactions starting from β-dicarbonyl compounds.[16] In spite of the existence of an early paper claiming the development of a two-component dihydropyridine synthesis by reaction between neat α,β-unsaturated imines and β-dicarbonyl compounds in the presence of sodium ethoxide at 150 °C,[17] the evidence provided for the proposed structures is insufficient (only mp, IR data, and analyses) and there is a considerable discrepancy between the description of the reaction products (crystalline solids, some with high melting points) and the fact that some compounds **4** recently obtained by alternative means have been reported to be non-crystallizable semisolids.[18] Indeed, in our hands the base-catalyzed reaction failed to give dihydropyridine systems, as shown by the NMR spectra of the crude reaction products. Reliable literature precedent exists, however, for the key step in our proposed reaction, namely a Michael reaction followed by cyclization between a β-dicarbonyl compound and a α,β-unsaturated imine in the presence of lithium iodide to give 1,4-dihydropyridines. However, besides being a two-component protocol, this method has serious limitations because it requires long reaction times (3 days), it is limited to the preparation of *N*-benzyl derivatives and it often gives low yields because of the formation of a transimination side product.[19] Hetero Diels–Alder reactions of 1-azadienes can also generate dihydropyridines,[20] including some *N*-aryl- and C_5–C_6-unsubstituted systems,[18] but these are two-component procedures that require unusual starting materials (e.g., allenic esters), toxic solvents, and drastic reaction conditions (e.g., 55–85 h reflux in benzene).[18] In this context, we present here the practical realization of the synthetic method proposed in Scheme 1b.

2. Results and discussion

We carried out an initial study in search for the optimal catalyst and solvent for the proposed transformation using as a model the reaction involving cinnamaldehyde, *m*-toluidine, and ethyl acetoacetate, and the most significant data obtained are summarized in Scheme 2 and Table 1. We first assayed indium trichloride,[21] triphenylphosphonium perchlorate,[22] and potassium hydrogen sulfate as catalysts,[23] which have been successfully employed in related condensation reactions, but the yields obtained were only moderate, even with high catalyst loadings. The best results were obtained with cerium ammonium nitrate (CAN) in ethanol, which gave the desired dihydropyridine derivative in 71% isolated yield after 1 h at room temperature and requiring only 5% of the catalyst. Although Ce(IV) derivatives are normally employed as one-electron oxidants, the use of the commercially available, inexpensive, and easily handled CAN in carbon–carbon and carbon–heteroatom bond forming reactions has recently attracted much attention,[24] although these studies are still in their early stages. As stated in a recent review on the subject,[24c] the main current goal in this area is the development of reactions that allow the use of catalytic amounts of CAN.[25] In this light, the result in entry 4 of Table 1 becomes particularly interesting.



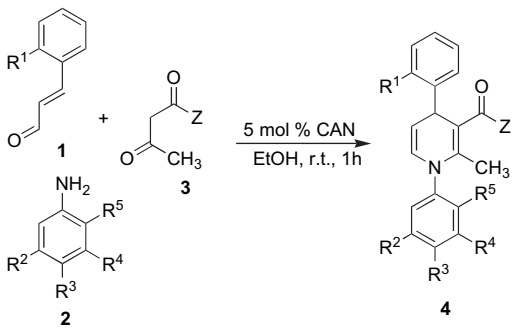
Scheme 2.

Table 1. Catalyst scan for the reaction between *m*-toluidine, cinnamaldehyde, and ethyl acetoacetate

Entry	Catalyst	Mol %	Yield (%)
1	$InCl_3$	20	45[a]
2	$PPh_3 \cdot HClO_4$	20	50[a]
3	$KHSO_4$	40	45[a]
4	CAN	5	71[b]

[a] Yields estimated from the ^1H NMR spectra of the crude reaction mixtures.
[b] Isolated yield.

The conditions developed for the model case were then applied to a range of substrates. As shown in Scheme 3 and Table 2, the reaction proceeds normally in good yields, and tolerates several types of electron-releasing and electron-withdrawing groups at all positions of the nitrogen aryl substituent, including alkyl (entries 2, 5, 6, 9, and 12), alkoxy (entry 10), bromo (entry 8), chloro (entries 4 and 7), and fluoro (entry 3). The aryl substituent at the α,β-unsaturated aldehyde component can also bear substituents, as shown by the result in entry 11, although in the chosen example the *ortho*-substitution leads to a lowered yield. When *tert*-butyl esters were employed, a longer time (2 h) was required and the yields were slightly lower than with their ethyl counterparts (entries 13–15). The reaction could also be extended to include the use of *tert*-butyl β-ketothioesters as the dicarbonyl component, in yields similar to those found for *tert*-butyl esters (entries 16–19). This possibility is interesting because it potentially allows exploiting the high reactivity of the thioester group toward alcohols and amines in the presence of thiophilic metals.[26] On the other hand, aliphatic amines (e.g., benzylamine) gave complex reaction mixtures containing only small amounts of the desired products, and attempts to use α,β-unsaturated aldehydes other than cinnamaldehyde derivatives were also unsuccessful.



Scheme 3.

In order to confirm that our reaction follows the pathway outlined in Scheme 1b, we carried out two additional

Table 2. Scope and yields of the CAN-catalyzed synthesis of 1,4-dihydropyridines

Entry	Compound	Z	R^1	R^2	R^3	R^4	R^5	Time (h)	Yield (%)
1	**4a**	OC_2H_5	H	H	H	H	H	1	74
2	**4b**	OC_2H_5	H	H	CH_3	H	H	1	70
3	**4c**	OC_2H_5	H	H	F	H	H	1	76
4	**4d**	OC_2H_5	H	H	Cl	H	H	1	74
5	**4e**	OC_2H_5	H	CH_3	H	H	H	1	71
6	**4f**	OC_2H_5	H	CH_3	CH_3	H	H	1	70
7	**4g**	OC_2H_5	H	Cl	H	H	H	1	72
8	**4h**	OC_2H_5	H	H	Br	H	H	1	74
9	**4i**	OC_2H_5	H	CH_3	H	CH_3	H	1	71
10	**4j**	OC_2H_5	H	OCH_3	H	H	H	1	65
11	**4k**	OC_2H_5	NO_2	H	H	H	H	1	50
12	**4l**[a]	OC_2H_5	H	H	CH_3	H	CH_3	1	72
13	**4m**	$O–C(CH_3)_3$	H	H	H	H	H	2	52
14	**4n**	$O–C(CH_3)_3$	H	H	CH_3	H	H	2	61
15	**4o**	$O–C(CH_3)_3$	H	H	Cl	H	H	2	65
16	**4p**	$S–C(CH_3)_3$	H	H	H	H	H	1	61
17	**4q**	$S–C(CH_3)_3$	H	H	F	H	H	1	62
18	**4r**	$S–C(CH_3)_3$	H	H	Cl	H	H	1	63
19	**4s**	$S–C(CH_3)_3$	H	H	CH_3	H	CH_3	1	61

[a] Isolated as an 1.1:1 rotamer mixture.

experiments. In the first of them, the purified imine derived from aniline and cinnamaldehyde was treated at room temperature for 1 h with ethyl acetoacetate in ethanol containing 5% CAN, and was found to give identical results to the three-component protocol. In a second experiment designed to discard an alternative Michael-initiated sequence similar to the one described by Rodriguez,[16] we have found that CAN does not catalyze the Michael reaction between ethyl acetoacetate and cinnamaldehyde in ethanol under our conditions, the crude reaction product being composed of unreacted starting materials and a small amount of cinnamaldehyde diethylacetal.

Most of the synthetic applications of CAN are based on radical mechanisms, as expected from a powerful one-electron oxidant. In an effort to clarify whether CAN exerts its role in our dihydropyridine synthesis through such an oxidative pathway, we have performed the reaction between cinnamaldehyde, aniline, and ethyl acetoacetate (entry 1 in Table 2) in the presence of a large amount of a radical trap, namely 1,1-diphenylethylene, and found no noticeable loss in yield, which indicates that a radical mechanism is not in operation under our conditions. In this regard, it is relevant to note that some literature results can be interpreted by assuming that CAN may behave as a Lewis acid, although this role has not been systematically studied. Some examples are our own results on the deviation of the [4+2] cycloaddition of 1-dimethylamino-1-azadienes and quinolinequinones toward the formation of furo[3,2-*f*]quinoline systems in the presence of CAN,[27] and its use as a catalyst for the ring-opening of aziridines by water[28] and Michael additions in indoles.[29] The clearest example can be found in a study about the use of CAN as a catalyst for acetal and ketal deprotection, where it has been proved by cyclic voltammetry that cerium remains in the Ce(IV) oxidation state, strongly suggesting that it acts as a Lewis acid.[30,31] Regarding the order of the steps of the three-component reaction, the imine formation step must occur first, as indicated in Scheme 1b, because treatment of isolated imines with β-dicarbonyl compounds under our conditions gave results identical to those of the three-component protocol.

3. Conclusion

In conclusion, we have developed a new strategy that provides an efficient entry into 1-aryl-5,6-disubstituted 1,4-dihydropyridines and is therefore complementary to existing procedures, particularly the Hantzsch synthesis. Our method involves mild reaction conditions, uses very simple and accessible starting materials and solvents, as well as an inexpensive and non-toxic catalyst. It also has the additional advantage of proceeding with high atom economy and having water as the only side product.

4. Experimental

4.1. General

All reagents were of commercial quality (Aldrich, Fluka, SDS, Probus) and were used as received. Solvents (from SDS) were dried and purified using standard techniques. Reactions were monitored by thin layer chromatography, on aluminum plates coated with silica gel with fluorescent indicator (SDS CCM221254). Separations by flash chromatography were performed on silica gel (SDS 60 ACC, 230–40 mesh). Melting points were measured with 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 films on a NaCl disk. NMR spectra were obtained on a Bruker Avance instrument (250 MHz for ^{1}H NMR, 62.9 MHz for ^{13}C NMR), maintained by the Servicio de RMN, Universidad Complutense, with $CDCl_3$ as solvent. Combustion elemental analyses were determined by the Servicio de Microanálisis Elemental, Universidad Complutense, using a Leco 932 CHNS microanalyzer.

4.2. General procedure for the CAN-catalyzed synthesis of ethyl 1,4-dihydro-2-methyl-1,4-diarylpyridine-3-carboxylates (4)

To a solution of the suitable cinnamaldehyde **1** (2 mmol) and arylamine **2** (2 mmol) in 30 mL of absolute ethanol were

added ethyl acetoacetate **3** (2 mmol) and ceric ammonium nitrate, CAN (5 mol %). The mixture was stirred at room temperature under argon atmosphere for 60 min. After completion of the reaction, the solvent was evaporated under reduced pressure and extracted with ethyl ether (2×20 mL). The ethereal solution was washed twice with saturated sodium bicarbonate solution (30 mL), dried with anhydrous sodium sulfate, evaporated, and the resultant crude product was purified by flash silica column chromatography using petroleum ether–ethyl acetate as eluant (96:4). Yields are given in Table 2, and characterization data follow. With the exceptions of **4i** and **4p–s**, all compounds **4** were semi-solid and could not be crystallized. Compounds **4a–d** were previously known,[18] and our ^{13}C NMR data are substantially identical to those found in the literature.

4.2.1. Ethyl 2-methyl-1,4-diphenyl-1,4-dihydropyridine-3-carboxylate (4a).[18] IR (NaCl) ν: 1690.9, 1568.0, 1221.0 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.19 (t, 3H, J=7.1 Hz); 2.21 (s, 3H); 4.08 (q, 2H, J=7.1 Hz); 4.75 (d, 1H, J=5.5 Hz); 5.07 (dd, 1H, J=5.5 and 7.6 Hz); 6.23 (d, 1H, J=7.6 Hz); 7.24–7.47 (m, 10H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 14.7, 19.2, 40.6, 59.9, 102.1, 107.9, 126.6, 127.8, 127.9, 128.0, 128.8, 129.9, 130.0, 144.1, 148.4, 148.9, 169.2. Anal. Calcd for $C_{21}H_{21}NO_2$, M=319.4: C, 78.97; H, 6.63; N, 4.39. Found: C, 78.85; H, 6.39; N, 4.50.

4.2.2. Ethyl 2-methyl-4-phenyl-1-(4-methylphenyl)-1,4-dihydropyridine-3-carboxylate (4b).[18] IR (NaCl) ν: 1691.1, 1567.8, 1222.2 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.19 (t, 3H, J=7.1 Hz); 2.21 (s, 3H); 2.43 (s, 3H); 4.08 (q, 2H, J=7.1 Hz); 4.75 (d, 1H, J=5.4 Hz); 5.05 (dd, 1H, J=5.4 and 7.6 Hz); 6.19 (d, 1H, J=7.6 Hz); 7.14 (d, 2H, J=8.2 Hz); 7.25–7.44 (m, 7H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 14.6, 19.1, 23.1, 40.7, 59.8, 101.7, 107.7, 126.6, 127.8, 128.0, 128.7, 130.0, 130.6, 137.7, 141.5, 148.7, 149.1, 169.3. Anal. Calcd for $C_{22}H_{23}NO_2$, M=333.4: C, 79.25; H, 6.95; N, 4.20. Found: C, 79.16; H, 6.85; N, 4.46.

4.2.3. Ethyl 1-(4-fluorophenyl)-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (4c).[18] IR (NaCl) ν: 1693.2, 1568.8, 1215.6 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.19 (t, 3H, J=7.1 Hz); 2.20 (s, 3H); 4.09 (q, 2H, J=7.1 Hz); 4.75 (d, 1H, J=5.4 Hz); 5.06 (dd, 1H, J=5.4, 7.6 Hz); 6.14 (d, 1H, J=7.6 Hz); 7.11–7.20 (m, 5H); 7.24–7.33 (m, 4H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 14.7, 19.0, 40.6, 59.9, 102.3, 108.0, 116.9 (d, J=22.6 Hz), 126.6, 128.0, 128.8, 129.8 (d, J=8.2 Hz), 129.9, 140.1 (d, J=3.8 Hz), 148.2, 148.8, 161.9 (d, J=247.2 Hz), 169.1. Anal. Calcd for $C_{21}H_{20}FNO_2$, M=337.4: C, 74.76; H, 5.97; N, 4.15. Found: C, 74.51; H, 5.91; N, 4.18.

4.2.4. Ethyl 1-(4-chlorophenyl)-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (4d).[18] IR (NaCl) ν: 1692.6, 1567.7, 1222.1 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.18 (t, 3H, J=7.1 Hz); 2.19 (s, 3H); 4.07 (q, 2H, J=7.1 Hz); 4.73 (d, 1H, J=5.4 Hz); 5.07 (dd, 1H, J=5.4, 7.6 Hz); 6.16 (d, 1H, J=7.6 Hz); 7.16–7.44 (m, 9H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 14.6, 19.1, 40.6, 59.9, 102.9, 108.2, 126.7, 127.9, 128.8, 129.2, 129.5, 130.2, 133.4, 142.6, 147.7, 148.6, 169.1. Anal. Calcd for $C_{21}H_{20}ClNO_2$, M=353.8: C, 71.28; H, 5.70; N, 3.96. Found: C, 70.97; H, 5.79; N, 3.91.

4.2.5. Ethyl 2-methyl-4-phenyl-1-(3-methylphenyl)-1,4-dihydropyridine-3-carboxylate (4e). IR (NaCl) ν: 1693.0, 1568.0, 1226.4 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.20 (t, 3H, J=7.1 Hz); 2.24 (s, 3H); 2.44 (s, 3H); 4.10 (q, 2H, J=7.1 Hz); 4.77 (d, 1H, J=5.5 Hz); 5.06 (dd, 1H, J=5.5, 7.6 Hz); 6.22 (d, 1H, J=7.6 Hz); 7.05–7.08 (m, 2H); 7.17–7.46 (m, 7H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 14.7, 19.2, 21.8, 40.7, 59.8, 101.9, 107.8, 125.0, 126.6, 128.0, 128.5, 128.6, 128.8, 129.8, 129.9, 140.1, 144.0, 148.6, 149.0, 169.3. Anal. Calcd for $C_{22}H_{23}NO_2$, M=333.4: C, 79.25; H, 6.95; N, 4.20. Found: C, 79.03; H, 6.84; N, 4.23.

4.2.6. Ethyl 2-methyl-1-(3,4-dimethylphenyl)-4-phenyl-1,4-dihydropyridine-3-carboxylate (4f). IR (NaCl) ν: 1693.5, 1567.9, 1228.6 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.19 (t, 3H, J=7.1 Hz); 2.21 (s, 3H); 2.33 (s, 6H); 4.08 (q, 2H, J=7.1 Hz); 4.74 (d, 1H, J=5.5 Hz); 5.04 (dd, 1H, J=5.5, 7.6 Hz); 6.18 (d, 1H, J=7.6 Hz); 6.95–7.02 (m, 2H); 7.19–7.31 (m, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 14.7, 19.1, 19.8, 20.3, 40.7, 59.8, 101.5, 107.6, 125.2, 126.5, 128.0, 128.7, 129.0, 130.1, 131.0, 136.4, 138.5, 141.8, 148.9, 149.2, 169.3. Anal. Calcd for $C_{23}H_{25}NO_2$, M=347.5: C, 79.51; H, 7.25; N, 4.03. Found: C, 79.06; H, 6.92; N, 4.23.

4.2.7. Ethyl 1-(3-chlorophenyl)-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (4g). IR (NaCl) ν: 1694.0, 1590.9, 1222.0 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.18 (t, 3H, J=7.1 Hz); 2.20 (s, 3H); 4.07 (q, 2H, J=7.1 Hz); 4.73 (d, 1H, J=5.5 Hz); 5.07 (dd, 1H, J=5.5, 7.6 Hz); 6.19 (d, 1H, J=7.6 Hz); 7.12–7.40 (m, 9H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 14.6, 19.2, 40.6, 60.0, 103.3, 108.4, 126.2, 126.7, 127.9, 128.0, 128.1, 128.8, 129.4, 130.9, 135.4, 145.2, 147.5, 148.5, 169.1. Anal. Calcd for $C_{21}H_{20}ClNO_2$, M=353.8: C, 71.28; H, 5.70; N, 3.96. Found: C, 70.99; H, 5.48; N, 3.72.

4.2.8. Ethyl 1-(4-bromophenyl)-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (4h). IR (NaCl) ν: 1691.0, 1565.4, 1221.3 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.18 (t, 3H, J=7.1 Hz); 2.20 (s, 3H); 4.08 (q, 2H, J=7.1 Hz); 4.74 (d, 1H, J=5.5 Hz); 5.07 (dd, 1H, J=5.5, 7.6 Hz); 6.17 (d, 1H, J=7.6 Hz); 7.12 (d, 2H, J=8.1 Hz); 7.23–7.38 (m, 5H); 7.58 (d, 2H, J=8.1 Hz). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 14.7, 19.2, 40.6, 60.1, 103.0, 108.3, 121.3, 126.7, 128.0, 128.8, 129.5, 129.6, 135.2, 143.1, 147.6, 148.6, 169.0. Anal. Calcd for $C_{21}H_{20}BrNO_2$, M=398.3: C, 63.33; H, 5.06; N, 3.52. Found: C, 63.04; H, 5.15; N, 3.42.

4.2.9. Ethyl 2-methyl-1-(3,5-dimethylphenyl)-4-phenyl-1,4-dihydropyridine-3-carboxylate (4i). Mp 96–97 °C. IR (NaCl) ν: 1691.9, 1567.9, 1236.6 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.21 (t, 3H, J=7.1 Hz); 2.24 (s, 3H); 2.41 (s, 6H); 4.10 (q, 2H, J=7.1 Hz); 4.77 (d, 1H, J=5.5 Hz); 5.06 (dd, 1H, J=5.5 and 7.6 Hz); 6.21 (d, 1H, J=7.6 Hz); 6.89 (s, 2H); 7.02 (s, 1H); 7.25–7.47 (m, 5H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 14.7, 19.2, 21.7 (2 signals), 40.7, 59.8, 101.7, 107.6, 125.6, 126.5, 128.0, 128.7, 129.4, 130.0, 139.8, 144.0, 148.7, 149.1, 169.3. Anal. Calcd for $C_{23}H_{25}NO_2$, M=347.5: C, 79.51; H, 7.25; N, 4.03. Found: C, 79.29; H, 6.96; N, 3.98.

4.2.10. Ethyl 2-methyl-1-(3-methoxyphenyl)-4-phenyl-1,4-dihydropyridine-3-carboxylate (4j). IR (NaCl) ν:

1690.5, 1569.0, 1213.7, 1199.9 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 1.18 (t, 3H, J=7.1 Hz); 2.22 (s, 3H); 3.86 (s, 3H); 4.07 (q, 2H, J=7.1 Hz); 4.73 (d, 1H, J=5.5 Hz); 5.05 (dd, 1H, J=5.5 and 7.6 Hz); 6.22 (d, 1H, J=7.6 Hz); 6.77–6.83 (m, 3H); 6.91–7.42 (m, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 14.7, 19.1, 40.6, 55.9, 59.6, 102.2, 107.8, 113.2, 113.7, 120.2, 126.6, 128.0, 128.8, 129.8, 130.6, 145.2, 148.3, 148.9, 160.9, 169.2. Anal. Calcd for $C_{22}H_{23}NO_3$, M=349.4: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.37; H, 6.51; N, 4.33.

4.2.11. Ethyl 2-methyl-4-(2-nitrophenyl)-1-phenyl-1,4-dihydropyridine-3-carboxylate (4k). IR (NaCl) ν: 1693.9, 1567.9, 1523.6, 1354.5, 1221.3 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 0.95 (t, 3H, J=7.1 Hz); 2.24 (s, 3H); 3.90 (q, 2H, J=7.1 Hz); 5.21–5.25 (m, 2H); 6.14–6.16 (m, 1H); 7.22–7.50 (m, 6H); 7.62 (t, 1H, td, J=8.1 and 1.5 Hz); 7.75 (dd, 2H, J=8.1 and 1.5 Hz). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 14.3, 19.0, 36.6, 59.9, 100.6, 106.6, 123.6, 127.1, 128.0, 128.1, 130.1, 130.4, 131.6, 133.6, 143.7, 143.8, 148.2, 150.3, 168.3. Anal. Calcd for $C_{21}H_{20}N_2O_4$, M=364.4: C, 69.22; H, 5.53; N, 7.69. Found: C, 68.93; H, 5.33; N, 7.42.

4.2.12. Ethyl 2-methyl-4-(2,4-dimethylphenyl)-1-phenyl-1,4-dihydropyridine-3-carboxylate (4l). This compound was isolated as a 1.1:1 rotamer mixture (**4la** major rotamer, **4lb** minor rotamer). IR (NaCl) ν: 1684.8, 1559.7, 1210.4 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 1.10–1.18 (m, **4la** and **4lb**, $CO_2CH_2CH_3$); 2.10 and 2.12 (2s, **4la** and **4lb**, CH_3); 2.25 and 2.28 (2s, **4la** and **4lb**, CH_3); 2.38 and 2.39 (2s, **4la** and **4lb**, CH_3); 4.04 (q, J=7.1 Hz, **4la** and **4lb**); 4.72 (d, 1H, J=5.5 Hz, **4lb**); 4.79 (d, 1H, J=5.5 Hz, **4la**); 4.98–5.04 (m, **4la** and **4lb**); 5.90 (d, 1H, J=7.6 Hz, **4lb**); 5.96 (d, 1H, J=7.6 Hz, **4la**); 7.03–7.35 (m, **4la** and **4lb**). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 14.6, 17.9, 18.0, 18.1, 18.2, 21.5, 40.7, 40.8, 59.7, 100.0, 100.3, 107.7, 107.8, 126.4, 126.5, 128.0, 128.2, 128.4, 128.6, 128.7, 128.9, 129.2, 129.3, 129.6, 131.7, 132.1, 132.5, 136.5, 136.8, 138.4, 138.6, 140.0, 140.4, 149.2, 149.4, 149.5, 153.3, 169.3, 169.4. Anal. Calcd for $C_{23}H_{25}NO_2$, M=347.5: C, 79.51; H, 7.25; N, 4.03. Found: C, 79.23; H, 7.03; N, 3.78.

4.2.13. *tert*-Butyl 2-methyl-1,4-diphenyl-1,4-dihydropyridine-3-carboxylate (4m). IR (NaCl) ν: 1689.9, 1570.0, 1234.3 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 1.34 (s, 9H); 2.16 (s, 3H); 4.71 (d, 1H, J=5.1 Hz); 5.00 (dd, 1H, J=5.1, 7.7 Hz); 6.16 (d, 1H, J=7.7 Hz); 7.22–7.47 (m, 10H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 19.1, 28.6, 41.3, 79.6, 103.7, 107.6, 126.5, 127.6, 128.0, 128.7, 129.7, 129.9, 144.2, 147.2, 149.2, 168.8 (one aromatic carbon signal is merged with others). Anal. Calcd for $C_{23}H_{25}NO_2$, M=347.5: C, 79.51; H, 7.25; N, 4.03. Found: C, 79.28; H, 6.96; N, 3.94.

4.2.14. *tert*-Butyl 1,4-dihydro-2-methyl-1-(4-methylphenyl)-4-phenylpyridine-3-carboxylate (4n). IR (NaCl) ν: 1693.3, 1568.3, 1234.8 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 1.34 (s, 9H); 2.17 (s, 3H); 2.42 (s, 3H); 4.71 (d, 1H, J=5.2 Hz); 4.98 (dd, 1H, J=5.2, 7.7 Hz); 6.13 (d, 1H, J=7.7 Hz); 7.12 (d, 2H, J=8.3 Hz); 7.23–7.43 (m, 7H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 19.0, 21.5, 28.6, 41.3, 79.5, 103.3, 107.5, 126.4, 127.8, 128.0, 128.7, 129.8, 130.5, 137.5, 141.7, 147.6, 149.4, 168.8. Anal. Calcd for $C_{24}H_{27}NO_2$, M=361.5: C, 79.74; H, 7.53; N, 3.87. Found: C, 79.54; H, 7.52; N, 3.85.

4.2.15. *tert*-Butyl 1-(4-chlorophenyl)-1,4-dihydro-2-methyl-4-phenylpyridine-3-carboxylate (4o). IR (NaCl) ν: 1690.5, 1569.5, 1235.6 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 1.33 (s, 9H); 2.14 (s, 3H); 4.69 (d, 1H, J=5.1 Hz); 4.99 (dd, 1H, J=5.1, 7.7 Hz); 6.10 (d, 1H, J=7.7 Hz); 7.14–7.41 (m, 9H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 19.1, 28.6, 41.3, 79.7, 104.5, 108.0, 126.6, 127.9, 128.8, 129.2, 129.3, 130.1, 133.2, 142.8, 146.5, 148.9, 168.6. Anal. Calcd for $C_{23}H_{24}ClNO_2$, M=381.9: C, 72.34; H, 6.33; N, 3.67. Found: C, 72.05; H, 6.10; N, 3.45.

4.2.16. *S-tert*-Butyl 2-methyl-1,4-diphenyl-1,4-dihydropyridine-3-carbothioate (4p). Mp 104–105 °C. IR (NaCl) ν: 1673.6, 1628.5, 1533.4, 1155.9 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 1.45 (s, 9H); 2.12 (s, 3H); 4.86 (d, 1H, J=5.8 Hz); 5.13 (dd, 1H, J=5.8, 7.5 Hz); 6.19 (d, 1H, J=7.5 Hz); 7.19–7.48 (m, 10H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 19.5, 30.5, 41.2, 47.7, 107.8, 110.8, 126.7, 127.7, 127.8, 127.9, 128.9, 129.8, 130.0, 143.8, 144.8, 147.7, 194.5. Anal. Calcd for $C_{23}H_{23}NOS$, M=363.5: C, 75.99; H, 6.93; N, 3.85. Found: C, 75.93; H, 7.07; N, 3.90.

4.2.17. *S-tert*-Butyl 2-methyl-4-phenyl-1-(4-fluorophenyl)-1,4-dihydropyridine-3-carbothioate (4q). Mp 138–139 °C. IR (NaCl) ν: 1672.9, 1628.5, 1508.4, 1153.7 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 1.43 (s, 9H); 2.08 (s, 3H); 4.83 (d, 1H, J=5.8 Hz); 5.10 (dd, 1H, J=5.8, 7.5 Hz); 6.10 (d, 1H, J=7.5 Hz); 7.12–7.38 (m, 9H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 19.2, 30.4, 41.2, 47.8, 107.2, 111.0, 116.9 (d, J=22.6 Hz), 126.8, 127.7, 128.9, 129.6, 129.7 (d, J=8.2 Hz), 139.8 (d, J=3.8 Hz), 144.3, 147.5, 161.9 (d, J=247.4 Hz), 194.7. Anal. Calcd for $C_{23}H_{24}FNOS$, M=381.5: C, 72.41; H, 6.34; N, 3.67. Found: C, 72.31; H, 6.41; N, 3.74.

4.2.18. *S-tert*-Butyl 1-(4-chlorophenyl)-2-methyl-4-phenyl-1,4-dihydropyridine-3-carbothioate (4r). Mp 119–120 °C. IR (NaCl) ν: 1670.3, 1635.9, 1540.2, 1155.5 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 1.42 (s, 9H); 2.07 (s, 3H); 4.82 (d, 1H, J=5.8 Hz); 5.11 (dd, 1H, J=5.8, 7.5 Hz); 6.13 (d, 1H, J=7.5 Hz); 7.12–7.42 (m, 9H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 19.3, 30.4, 41.2, 47.8, 108.0, 111.6, 126.8, 127.7, 128.9, 129.1, 129.5, 130.2, 133.5, 142.3, 143.7, 147.3, 194.7. Anal. Calcd for $C_{23}H_{24}ClNOS$, M=397.9: C, 69.42; H, 6.08; N, 3.52. Found: C, 69.55; H, 6.15; N, 3.60.

4.2.19. *S-tert*-Butyl 1-(2,4-dimethylphenyl)-2-methyl-4-phenyl-1,4-dihydropyridine-3-carbothioate (4s). This compound was isolated as a 1:0.75 rotamer mixture (**4la** major rotamer, **4lb** minor rotamer). Mp 132–133 °C. IR (NaCl) ν: 1672.6, 1627.6, 1525.8, 1152.4 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 1.42 and 1.43 (2s, **4sa** and **4sb**, $C(CH_3)_3$); 2.04 and 2.06 (2s, **4sa** and **4sb**, CH_3); 2.17 and 2.23 (2s, **4sa** and **4sb**, CH_3); 2.37 and 2.38 (2s, **4sa** and **4sb**, CH_3); 4.84 (d, 1H, J=5.9 Hz, **4sb**); 4.91 (d, 1H, J=5.9 Hz, **4sa**); 5.06–5.15 (m, **4sa** and **4sb**); 5.85 (d, 1H, J=7.5 Hz, **4sb**); 5.94 (d, 1H, J=7.5 Hz, **4sa**); 7.01–7.53 (m, **4sa** and **4sb**). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 17.9, 18.1, 18.4, 18.6, 21.5, 30.5, 41.0, 41.1, 47.6, 107.8, 107.9, 108.5, 108.9, 126.5, 126.6, 127.7, 128.1, 128.4, 128.5,

128.7, 128.8, 128.9, 129.1, 129.3, 132.1, 132.5, 136.3, 136.7, 138.5, 138.7, 139.7, 140.1, 146.0, 146.4, 148.0, 148.2, 194.2, 194.3. Anal. Calcd for $C_{25}H_{29}NOS$, M=391.6: C, 76.68; H, 7.46; N, 3.58. Found: C, 76.59; H, 7.47; N, 3.68.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.03.092.

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