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Synthesis of 4-functionalized aryl-3,5-diacyl-1,4-dihydropyridines

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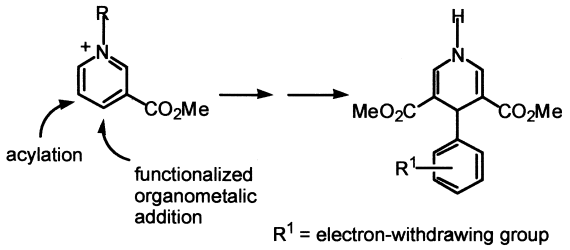
Abstract—The valuable *N*-unsubstituted 4-aryl-3,5-diacyl-1,4-dihydropyridines **12b–f**, bearing an electron-withdrawing substituent at the benzene ring, have been synthesized by the copper-mediated addition of functionalized arylmagnesium reagents **2b–f** to *N*-benzhydrylpyridinium salt **9**, followed by acylation with trichloroacetic anhydride and the subsequent haloform reaction and *N*-deprotection.

1. Introduction

The addition of organocopper reagents to the 4-position of *N*-acylpyridinium salts to give *N*-acyl-1,4-dihydropyridines is a well-known reaction, which usually constitutes the first step of a general synthesis of 4-substituted pyridines.[1,2] In contrast, the addition of organocopper reagents to the less electrophilic *N*-alkylpyridinium salts has received comparatively little attention.[3] Such additions are potentially useful because of the possibility of taking advantage of the nucleophilic character of the β-enaminic carbon in the resulting 4-substituted *N*-alkyl-1,4-dihydropyridines. A few years ago, we reported a general synthetic entry to 4-phenyl-3,5-diacyl-1,4-dihydropyridines,[4] which represent the basic structure of the most studied class of organic calcium channel modulators.[5] Our approach was based on the chemo- and regioselective addition of the organolithium-derived higher-order cyanocuprate $Ph_2Cu(CN)Li_2$ to the 4-position of several 3-acyl-*N*-alkylpyridinium salts,[6] followed by acylation of the unsubstituted enaminic side of the initially formed dihydropyridine adducts with trichloroacetic anhydride (TCAA). Since a phenyl group bearing an electron-withdrawing substituent is present in most of the therapeutically useful dihydropyridines, the extension of the above addition–acylation sequence to suitably functionalized organometallic derivatives attracted our interest (Scheme 1).

Functionalized organometallics are key intermediates for the synthesis of complex polyfunctional molecules.[7] Although organozinc reagents have been extensively used for this purpose,[7] their low reactivity precludes their reaction with *N*-alkylpyridinium salts.[6a,8] On the other hand, the use of organolithium precursors was also discarded because they display a high reactivity towards most functional groups.[9] Recently, Knochel et al. have shown that functionalized arylmagnesium reagents can be generated in mild conditions, compatible with the presence of several functional groups, by an iodine–magnesium exchange reaction.[10,11] We reasoned that organocopper complexes derived from these Grignard reagents, which have proven to efficiently participate in different types of transformations,[12] could undergo addition to the pyridinium ring giving regioselective access to valuable 4-aryl-1,4-dihydropyridines.



Scheme 1.

2. Results and discussion

We set out to explore the feasibility of this proposal using functionalized arylmagnesium halides **2b–e**, which bear different electron-withdrawing groups at the *ortho* (or *meta*) position, and the model *N*-methylpyridinium iodide **1** (Table 1). Arylmagnesium halides **2b–e** were prepared following the above protocol, by reaction of the respective aryl iodides with *i*-PrMgCl (for **2b** or **2c**) or *i*-PrMgBr (for **2d** and **2e**).[13] For each reagent the addition step was first carried out without any additive to give, after TCAA-acylation of the crude reaction mixtures, C-6 (entry 8) or C-2 (entries 12 and 15) adducts as the main or only products, except in the

Keywords: dihydropyridines; pyridinium salts; magnesium and compounds; copper and compounds.

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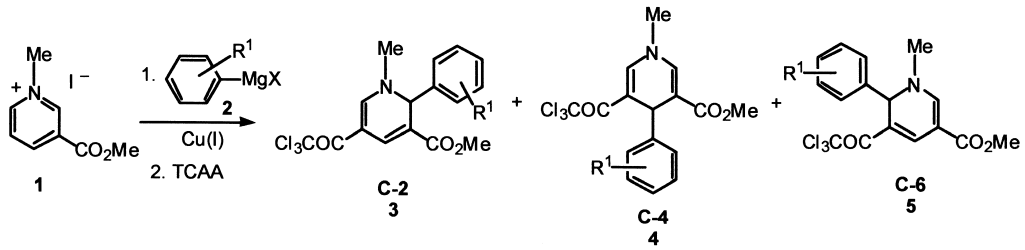
Table 1. Copper-mediated addition of arylmagnesium reagents **2** to pyridinium salt **1** followed by TCAA acylation



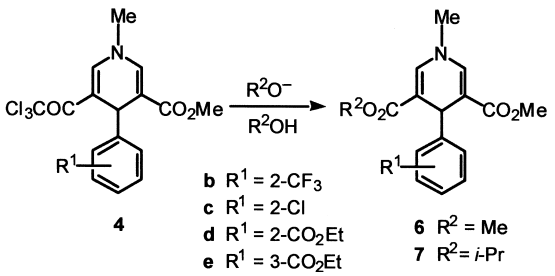
Entry	Arylmagnesium reagent	X	R^1	Cu(I) salt (equiv.)	C-2/C-4/C-6[a]	Overall yield (%)
1	**2a**	Cl	H	CuI (0.025)	0/1/0	90
2	**2a**	Cl	H	CuI (0.5)	0/5/1	95
3	**2a**	Cl	H	CuCN (0.5)	0/1/0	35
4	**2b**	Cl	2-CF_3	None	1/3/2	80
5	**2b**	Cl	2-CF_3	CuI (0.025)	0/2/1	70
6	**2b**	Cl	2-CF_3	CuI (0.5)	0/5/4	80
7	**2b**	Cl	2-CF_3	CuCN (0.5)	0/1/4	90
8	**2c**	Cl	2-Cl	None	1/0/8	80
9	**2c**	Cl	2-Cl	CuBr·SMe_2 (0.025)	1/5/8	80
10	**2c**	Cl	2-Cl	CuI (0.5)	0/1/1	90
11	**2c**	Cl	2-Cl	CuCN (0.5)	0/1/2	87
12	**2d**	Br	2-CO_2Et	None	1/0/0	54
13	**2d**	Br	2-CO_2Et	CuI (0.025)	1/2/1	30
14	**2d**	Br	2-CO_2Et	CuI (0.5)	0/1/0	35
15	**2e**	Br	3-CO_2Et	None	1/0/0	35
16	**2e**	Br	3-CO_2Et	CuI (0.025)	3/1/0	40
17	**2e**	Br	3-CO_2Et	CuI (0.5)	1/3/0	45

[a] The regioisomeric ratio was determined by ^1H NMR analysis based on the chemical shifts of the dihydropyridine moiety.

ortho-(trifluoromethyl) series, in which the C-4 adduct was the major product (entry 4). As expected, the proportion of the desired C-4 adduct increased when the addition–acylation sequence was effected after transmetallation of **2b** and **2c** with appropriate Cu(I) salts. However, in clear contrast with the excellent C-4 regioselectivity observed when organocopper species derived from commercial PhMgCl (**2a**) were used as nucleophiles (entries 1–3), significant amounts of C-6 or C-2 adducts were obtained in some assays. The most satisfactory results were observed in the CuI-catalysed addition (from **2a** and **2b**, entries 1 and 5) and in the Gilman homocuprate[14] addition (from **2c–e**, entries 10, 14, and 17, respectively). It is worth mentioning that the organomagnesium-derived higher-order cyanocuprate[14] often resulted in lower yields (e.g. from **2a**, entry 3) or in a surprisingly increased C-6 regioselectivity (e.g. from **2b** or **2c**, entries 7 and 11).

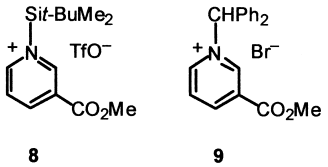
The above mixtures of acylated dihydropyridines were easily separated by column chromatography. As could be expected from our previous work,[4,6a] (trichloroacetyl)-1,4-dihydropyridines **4b–e** underwent a haloform-type reaction with sodium methoxide to give the corresponding methyl esters **6b–e** in high yields (80–95%). The use of alkoxides other than methoxide allows the preparation of 1,4-dihydropyridines bearing two different ester groups at the β-position. Thus, treatment of **4b** and **4c** with lithium isopropoxide in isopropanol led to dihydropyridines **7b** and **7c** in 70 and 78% yields (Scheme 2).

To increase the desired C-4 regioselectivity and subsequently reach *N*-unsubstituted 1,4-dihydropyridine derivatives, we next studied the use of pyridinium substrates whose 2- and 6-positions were sterically shielded due to the



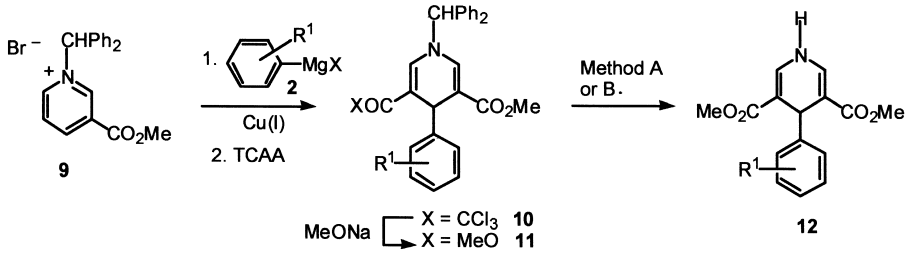
Scheme 2.

presence of a bulky, easily removable substituent at the nitrogen. We initially considered taking advantage of the regioselective addition of organomagnesium reagents to *N*-(*tert*-butyldimethylsilyl)pyridinium salts,[15] e.g. **8**, from which we had successfully synthesized *N*-unsubstituted 3,5-diacyl-4-phenyl-1,4-dihydropyridines.[4] However, the reaction of functionalized arylmagnesium reagents **2b** or **2c** with **8** resulted only in premature desilylation.



We focused then our attention on the use of *N*-benzhydrylpyridinium salt **9**.[16] Satisfactorily, when this substrate reacted with **2b–e** under the best conditions of the model series the desired C-4 adducts **10b–e** were isolated as the only products in acceptable yields (Table 2). The addition–acylation sequence was extended to **2f**,

Table 2. Synthesis of *N*-unsubstituted 3,5-diacyl-4-aryl-1,4-dihydropyridines



Entry	Arylmagnesium reagent	X	R^1	Cu(I) salt (equiv.)	**10** (yield, %)	**11** (yield, %)	Deprotection method[a]	**12** (yield, %)
1	**2b**	Cl	2-CF_3	None	**10b** (35)[b]			
				CuI (0.025)	**10b** (40)	**11b** (80)	A	**12b** (80)
2	**2c**	Cl	2-Cl	None	**10c** (40)[c]			
				CuI (0.5)	**10c** (45)	**11c** (80)	B	**12c** (98)
3	**2d**	Br	2-CO_2Et	CuI (0.5)	**10d** (55)	**11d** (87)	A	**12d** (76)
4	**2e**	Br	3-CO_2Et	CuI (0.5)	**10e** (60)	**11e** (81)	A	**12e** (73)
5	**2f**	Br	2-CH=CHCO_2Me	CuI (0.5)	**10f** (35)	**11f** (80)	A	**12f** (70)

[a] A: TFA, phenol; B: $AlCl_3$, C_6H_6.
[b] Trace amounts of the C-6 adduct.
[c] 10% of the C-6 adduct.

bearing an *ortho*-(methoxycarbonyl)vinyl substituent (entry 5). The high C-4 regioselectivity of the reactions of arylmagnesium reagents **2b** and **2c** carried out without any Cu(I) additive (entries 1 and 3) is worthy of mention.

As in the model series, (trichloroacetyl)-1,4-dihydropyridines **10b–f** smoothly reacted with sodium methoxide to give **11b–f** in 80–87%. At this point, the only remaining transformation required to complete the synthesis of *N*-unsubstituted 1,4-dihydropyridines **12b–f** was the removal of the *N*-benzhydryl group. This was accomplished by treatment of **11b** and **11d–f** with TFA–phenol (Method A). For **11c** (entry 2) the use of $AlCl_3$-benzene (Method B) was more satisfactory.

In conclusion, the results reported in this paper show that 3,5-diacyl-1,4-dihydropyridines, bearing a functionalized phenyl group at the 4-position, can be efficiently prepared by the chemo- and regioselective copper-mediated addition of functionalized arylmagnesium reagents to *N*-alkyl-3-acylpyridinium salts, followed by acylation.

3. Experimental

3.1. General methods

All non-aqueous reactions were performed under an argon atmosphere. All solvents were dried by standard methods. Reaction courses and product mixture were routinely monitored by TLC on silica gel (pre-coated F_{254} Merck plates). Drying of organic extracts during the workup of reactions was performed over anhydrous Na_2SO_4. Evaporation of the solvents was accomplished under reduced pressure with a rotatory evaporator. Flash chromatography was carried out on SiO_2 (silica gel 60, SDS, 0.04–0.06 mm). Melting points were determined on samples crystallised or triturated with acetone–Et_2O, and are uncorrected. Unless otherwise indicated, ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution using TMS as an internal reference. Microanalyses and HRMS were performed by Centro de Investigación y Desarrollo (CSIC), Barcelona.

3.1.1. 1-Benzhydryl-3-(methoxycarbonyl)pyridinium bromide (9). A solution of methyl nicotinate (1.5 g, 11 mmol) and benzhydryl bromide (2.86 g, 11 mmol) in anhydrous acetone (15 mL) was stirred at rt for a week. Benzhydryl bromide (2.86 g, 11 mmol) was again added and the mixture was stirred for 4 more days. After removal of the solvent, the resulting residue was triturated with Et_2O to give **9** (3.3 g, 82%) as a white hygroscopic solid. ^1H NMR (200 MHz, DMSO-d_6) δ 3.94 (s, 3H, OMe), 7.29 (m, 4H, Ph), 7.49 (m, 6H, Ph), 7.84 (s, 1H, $CHPh_2$), 8.28 (dd, J=6.2, 8.2 Hz, 1H, 5-H), 9.05 (d, J=8.4 Hz, 1H, 4-H), 9.16 (d, J=8.4 Hz, 1H, 6-H), 9.51 (s, 1H, 2-H); ^{13}C NMR (50.3 MHz) δ 53.6 (CH_3), 76.2 (CH), 128.6 (CH), 129.3 (CH), 129.4 (CH), 130.5 (C), 135.5 (C), 145.4 (CH), 146.2 (CH), 147.1 (CH), 161.9 (C).

3.2. General procedure for the preparation of arylmagnesium halides 2b–f

A solution of the appropriate aryl iodide (2 mmol) in THF (3 mL) was slowly added to a cooled (−40°C) solution of *i*-PrMgCl (2 M in THF, 1.2 mL, 2.4 mmol, for **2b** and **2c**) or *i*-PrMgBr[13] (1 M in THF, 2.4 mL, 2.4 mmol, for **2d–f**) and the resulting mixture was stirred at −40°C for 1 h.

3.3. General procedure for the addition–acylation sequence

Pyridinium salt **1** or **9** (0.9 mmol) was added in portions to a solution of arylmagnesium halide **2** (2 mmol) at −40°C and the mixture was allowed to rise to rt for 3 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with AcOEt (3×10 mL). The organic extracts were dried and concentrated. The crude residue was dissolved in anhydrous THF (10 mL), treated with TCAA (2.7 mmol) at −40°C, and stirred at rt overnight. The

reaction mixture was poured into saturated aqueous Na_2CO_3 (10 mL) and extracted with AcOEt (3×10 mL). The solvent was removed and the crude dihydropyridine adducts were chromatographed.

3.4. General procedure for the copper-catalysed addition–acylation sequence

A solution of arylmagnesium halide **2** (2 mmol) at −40°C was treated with CuI or CuBr·SMe_2 (0.05 mmol) for 10 min and the mixture was allowed to react as above with pyridinium salts **1** or **9** (0.9 mmol) and TCAA (2.7 mmol). After extractive workup, the resulting residue was chromatographed.

3.5. General procedure for the copper-mediated addition–acylation sequence

A cooled solution (−40°C) of arylmagnesium halide **2** (4 mmol) was added to a suspension of CuI or CuCN (2 mmol) in THF (6 mL) at −78°C, and the mixture was allowed to warm slowly to rt (0°C for CuCN). The reaction mixture was cooled again to −40°C and treated as above with pyridinium salts **1** or **9** (0.9 mmol) and TCAA (2.7 mmol). After extractive workup, the resulting residue was chromatographed.

3.6. Analytical data of (trichloroacetyl)dihydropyridines 3–5 of Table 1

3.6.1. 2-(2-Chlorophenyl)-3-(methoxycarbonyl)-1-methyl-5-(trichloroacetyl)-1,2-dihydropyridine (3c). Elution with 92:8 hexanes–AcOEt; ^{1}H NMR (300 MHz) δ 3.16 (s, 3H, NMe), 3.66 (s, 3H, OMe), 6.15 (s, 1H, 2-H), 7.28 (m, 2H, Ph), 7.40 (dd, J=1.2, 7.8 Hz, 1H, Ph), 7.58 (dd, J=2, 7.4 Hz, 1H, Ph), 8.02 (s, 1H, 4-H), 8.15 (s, 1H, 6-H); ^{13}C NMR (75.4 MHz) δ 43.1 (NMe), 51.8 (OMe), 58.7 (C-2), 97.0 (C-3), 112.8 (C-5), 128.3 (CH, Ph), 129.4 (CH, Ph), 130.0 (CH, Ph), 130.3 (CH, Ph), 132.4 (C–Cl), 132.7 (C-4), 137.3 (C, Ph), 154.8 (C-6), 165.3, 176.1 (CO). Anal. calcd for $C_{16}H_{13}Cl_4NO_3$: C, 46.98; H, 3.20; N, 3.42. Found: C, 46.94; H, 3.15; N, 3.38.

3.6.2. 2-[2-(Ethoxycarbonyl)phenyl]-3-(methoxycarbonyl)-1-methyl-5-(trichloroacetyl)-1,2-dihydropyridine (3d). Elution with 9:1 hexanes–AcOEt; ^{1}H NMR (300 MHz) δ 1.46 (t, J=7.2 Hz, 3H, CH_3), 3.23 (s, 3H, NMe), 3.59 (s, 3H, OMe), 4.45 (q, J=6.9 Hz, 2H, OCH_2), 6.71 (s, 1H, 2-H), 7.37 (dt, J=1.5, 7.9 Hz, 1H, Ph), 7.53 (dt, J=1.5, 7.6 Hz, 1H, Ph), 7.73 (dd, J=1.2, 7.2 Hz, 1H, Ph), 7.80 (dd, J=1.5, 7.5 Hz, 1H, Ph), 8.01 (d, J=1.5 Hz, 1H, 4-H), 8.15 (d, J=1.5 Hz, 1H, 6-H); ^{13}C NMR (75.4 MHz) δ 14.2 (CH_3), 43.2 (NMe), 51.4 (OMe), 57.1 (C-2), 61.3 (OCH_2), 96.3 (C-3), 96.5 (CCl_3), 114.2 (C-5), 128.4 (CH, Ph), 128.9 (CH, Ph), 129.0 (CH, Ph), 129.8 (C, Ph), 131.6 (CH, Ph), 132.8 (C-4), 141.2 (C, Ph), 155.5 (C-6), 165.0, 167.2, 175.7 (CO). Anal. calcd for $C_{19}H_{18}Cl_3NO_5$: C, 51.09; H, 4.06; N, 3.14. Found: C, 51.15; H, 4.14; N, 2.98.

3.6.3. 2-[3-(Ethoxycarbonyl)phenyl]-3-(methoxycarbonyl)-1-methyl-5-(trichloroacetyl)-1,2-dihydropyridine (3e). Elution with 87:13 hexanes–AcOEt; mp 140°C; ^{1}H NMR (300 MHz) δ 1.38 (t, J=7.2 Hz, 3H, CH_3), 3.17 (s, 3H, NMe), 3.68 (s, 3H, OMe), 4.36 (q, J=7.2 Hz, 2H, OCH_2), 5.56 (s, 1H, 2-H), 7.45 (t, J=7.8 Hz, 1H, Ph), 7.62 (dt, J=1.5, 7.8 Hz, 1H, Ph), 8.02 (dt, J=1.5, 7.8 Hz, 1H, Ph), 8.07 (s, 1H, 4-H), 8.08 (d, J=1.5 Hz, 1H, Ph), 8.13 (s, 1H, 6-H); ^{13}C NMR (75.4 MHz) δ 14.3 (CH_3), 43.3 (NMe), 51.8 (OMe), 61.2 (OCH_2), 63.0 (C-2), 96.4 (CCl_3), 97.5 (C-3), 112.6 (C-5), 128.2 (CH, Ph), 129.1 (CH, Ph), 130.2 (CH, Ph), 131.2 (C, Ph), 131.7 (CH, Ph), 132.1 (C-4), 139.7 (C, Ph), 154.8 (C-6), 165.4, 165.9, 176.0 (CO). Anal. calcd for $C_{19}H_{18}Cl_3NO_5$: C, 51.09; H, 4.06; N, 3.14. Found: C, 50.91; H, 3.97; N, 3.04.

3.6.4. 3-(Methoxycarbonyl)-1-methyl-4-phenyl-5-(trichloroacetyl)-1,4-dihydropyridine (4a). Elution with 7:3 hexanes–AcOEt; ^{1}H NMR (300 MHz) δ 3.36 (s, 3H, NMe), 3.66 (s, 3H, OMe), 5.03 (s, 1H, 4-H), 7.10–7.35 (m, 6H, Ph, 2-H), 7.83 (s, 1H, 6-H); ^{13}C NMR (75.4 MHz) δ 37.0 (C-4), 42.4 (NMe), 51.6 (OMe), 96.5 (CCl_3), 106.7 (C-3), 111.5 (C-5), 126.7, 128.0, 128.2 (Ph), 136.3 (C-2), 143.7 (C-6), 145.0 (Ph), 166.5, 178.7 (CO); HRMS calcd for $C_{16}H_{14}NO_3Cl_3$ 373.0039, found 373.0047.

3.6.5. 3-(Methoxycarbonyl)-1-methyl-5-(trichloroacetyl)-4-[2-(trifluoromethyl)phenyl]-1,4-dihydropyridine (4b). Elution with 8:2 hexanes–AcOEt; mp 155–156°C; ^{1}H NMR (300 MHz) δ 3.36 (s, 3H, NMe), 3.61 (s, 3H, OMe), 5.61 (br q, J=2.1 Hz, 1H, 4-H), 7.19 (d, J=1.5 Hz, 1H, 2-H), 7.26 (m, 1H, Ph), 7.42 (m, 2H, Ph), 7.53 (d, J=8.1 Hz, 1H, Ph), 7.85 (d, J=1.2 Hz, 1H, 6-H); ^{13}C NMR (75.4 MHz) δ 33.5 (C-4), 42.3 (NMe), 51.3 (OMe), 95.7 (CCl_3), 107.6 (C-3), 111.9 (C-5), 126.7 (CH, Ph), 126.8 (CH, Ph), 127.7 (q, J=30.4 Hz, C–CF_3), 125.0 (q, J=269 Hz, CF_3), 130.9 (CH, Ph), 131.6 (CH, Ph), 136.7 (C-2), 143.9 (C-6), 144.1 (C, Ph), 166.3, 178.3 (CO). Anal. calcd for $C_{17}H_{13}Cl_3F_3NO_3$: C, 46.13; H, 2.96; N, 3.16. Found: C, 45.98; H, 3.01; N, 3.20.

3.6.6. 4-(2-Chlorophenyl)-3-(methoxycarbonyl)-1-methyl-5-(trichloroacetyl)-1,4-dihydropyridine (4c). Elution with 88:12 hexanes–AcOEt; mp 170°C; ^{1}H NMR (300 MHz) δ 3.39 (s, 3H, NMe), 3.64 (s, 3H, OMe), 5.38 (s, 1H, 4-H), 7.08 (td, J=1.8, 7.8, 8.1 Hz, 1H, Ph), 7.17 (s, 1H, 2-H), 7.17 (td, J=1.2, 7.5, 8.1 Hz, 1H, Ph), 7.28 (dd, J=1.2, 7.8 Hz, 1H, Ph), 7.35 (dd, J=2, 7.5 Hz, 1H, Ph), 7.84 (d, J=1.2 Hz, 1H, 6-H); ^{13}C NMR (75.4 MHz) δ 35.9 (C-4), 42.5 (NMe), 51.5 (OMe), 95.8 (CCl_3), 106.3 (C-3), 110.6 (C-5), 126.6 (CH, Ph), 127.9 (CH, Ph), 129.8 (CH, Ph), 131.6 (CH, Ph), 133.5 (C–Cl), 136.9 (C-2), 142.2 (C, Ph), 144.3 (C-6), 166.4, 178.4 (CO). Anal. calcd for $C_{16}H_{13}Cl_4NO_3$: C, 46.98; H, 3.20; N, 3.42. Found: C, 46.90; H, 3.20; N, 3.38.

3.6.7. 4-[2-(Ethoxycarbonyl)phenyl]-3-(methoxycarbonyl)-1-methyl-5-(trichloroacetyl)-1,4-dihydropyridine (4d). Elution with 8:2 hexanes–AcOEt; mp 115–116°C; ^{1}H NMR (300 MHz) δ 1.46 (t, J=6.9 Hz, 3H, CH_3), 3.34 (s, 3H, NMe), 3.60 (s, 3H, OMe), 4.48 (m, 2H, OCH_2), 6.13 (s, 1H, 4-H), 7.15 (d, J=1.5 Hz, 1H, 2-H), 7.19 (m, 1H, Ph), 7.37 (m, 2H, Ph), 7.75 (d, J=8.1 Hz, 1H, Ph), 7.82 (d, J=1.5 Hz, 1H, 6-H); ^{13}C NMR (75.4 MHz) δ 14.4 (CH_3), 32.9 (C-4), 42.4 (NMe), 51.4 (OMe), 60.8 (OCH_2), 95.9 (CCl_3), 107.6 (C-3), 112.0 (C-5), 126.3 (CH, Ph), 129.6 (2CH, Ph), 130.6 (C, Ph), 131.5 (CH, Ph), 136.6 (C-2), 143.8 (C-6), 145.9 (C, Ph), 166.3, 167.7, 178.1 (CO). Anal.

calcd for $C_{19}H_{18}Cl_3NO_5$: C, 51.09; H, 4.06; N, 3.14. Found: C, 51.51; H, 4.25; N, 2.98.

3.6.8. 4-[3-(Ethoxycarbonyl)phenyl]-3-(methoxycarbonyl)-1-methyl-5-(trichloroacetyl)-1,4-dihydropyridine (4e). Elution with 87:13 hexanes–AcOEt; ^{1}H NMR (200 MHz, from a 7:1 mixture of **4e** and **3e**) δ 1.37 (t, J=7.2 Hz, 3H, CH_3), 3.40 (s, 3H, NMe), 3.66 (s, 3H, OMe), 4.34 (q, J=7 Hz, 2H, OCH_2), 5.07 (s, 1H, 4-H), 7.19 (d, J=1.2 Hz, 1H, 2-H), 7.37 (t, J=7.5 Hz, 1H, Ph), 7.62 (m, 1H, Ph), 7.84 (m, 1H, Ph), 7.86 (d, J=1 Hz, 1H, 6-H), 7.98 (s, 1H, Ph).

3.6.9. 5-(Methoxycarbonyl)-1-methyl-3-(trichloroacetyl)-2-[(2-trifluoromethyl)phenyl]-1,2-dihydropyridine (5b). Elution with 9:1 hexanes–AcOEt; mp 158°C; ^{1}H NMR (300 MHz) δ 3.09 (s, 3H, NMe), 3.80 (s, 3H, OMe), 6.08 (s, 1H, 2-H), 7.44 (dd, J=7.5, 7.8 Hz, 1H, Ph), 7.56 (dd, J=7.5, 7.8 Hz, 1H, Ph), 7.67 (d, J=8.1 Hz, 1H, Ph), 7.71 (s, 1H, 4-H), 7.84 (d, J=8.1 Hz, 1H, Ph), 8.50 (s, 1H, 6-H); ^{13}C NMR (75.4 MHz) δ 43.3 (NMe), 51.3 (OMe), 58.0 (C-2), 95.4 (CCl_3), 96.0 (C-5), 110.4 (C-3), 124.2 (q, J=265 Hz, CF_3), 126.0 (CH, Ph), 127.0 (q, J=30 Hz, C–CF_3), 129.1 (CH, Ph), 130.1 (CH, Ph), 133.1 (CH, Ph), 139.2 (C-4), 152.0 (C-6), 165.3, 177.8 (CO). Anal. calcd for $C_{17}H_{13}Cl_3F_3NO_3$: C, 46.13; H, 2.96; N, 3.16. Found: C, 46.20; H, 2.97; N, 3.28.

3.6.10. 2-(2-Chlorophenyl)-5-(methoxycarbonyl)-1-methyl-3-(trichloroacetyl)-1,2-dihydropyridine (5c). Elution with 9:1 hexanes–AcOEt; mp 175°C; ^{1}H NMR (300 MHz) δ 3.14 (s, 3H, NMe), 3.79 (s, 3H, OMe), 6.19 (s, 1H, 2-H), 7.25 (m, 2H, Ph), 7.39 (dd, J=1.2, 7.8 Hz, 1H, Ph), 7.60 (dd, J=2, 7.4 Hz, 1H, Ph), 7.67 (s, 1H, 4-H), 8.50 (d, J=1.5 Hz, 1H, 6-H); ^{13}C NMR (75.4 MHz) δ 42.8 (NMe), 51.3 (OMe), 58.6 (C-2), 95.4 (CCl_3), 96.2 (C-5), 109.6 (C-3), 128.1 (CH, Ph), 129.3 (CH, Ph), 129.7 (CH, Ph), 130.1 (CH, Ph), 132.4 (C–Cl), 137.4 (C, Ph), 139.4 (C-4), 151.7 (C-6), 165.4, 177.9 (CO). Anal. calcd for $C_{16}H_{13}Cl_4NO_3$: C, 46.98; H, 3.20; N, 3.42. Found: C, 47.19; H, 3.18; N, 3.42.

3.6.11. 2-[(2-Ethoxycarbonyl)phenyl]-5-(methoxycarbonyl)-1-methyl-3-(trichloroacetyl)-1,2-dihydropyridine (5d). Elution with 92:8 hexanes–AcOEt; mp 122–123°C; ^{1}H NMR (300 MHz) δ 1.47 (t, J=7.2 Hz, 3H, CH_3), 3.19 (s, 3H, NMe), 3.80 (s, 3H, OMe), 4.49 (m, 2H, OCH_2), 6.77 (s, 1H, 2-H), 7.34 (dt, J=1.5, 7.6 Hz, 1H, Ph), 7.49 (dt, J=1.5, 7.4 Hz, 1H, Ph), 7.76 (s, 1H, 4-H), 7.80 (m, 2H, Ph), 8.38 (d, J=1.2 Hz, 1H, 6-H); ^{13}C NMR (75.4 MHz) δ 14.3 (CH_3), 43.0 (NMe), 51.4 (OMe), 57.2 (C-2), 61.5 (OCH_2), 95.6 (C-5, CCl_3), 111.2 (C-3), 128.5 (C, Ph), 129.0 (2CH, Ph), 129.9 (C, Ph), 132.8 (CH, Ph), 138.8 (C-4), 141.5 (C, Ph), 152.4 (C-6), 165.6, 167.4, 177.8 (CO). Anal. calcd for $C_{19}H_{18}Cl_3NO_5$: C, 51.09; H, 4.06; N, 3.14. Found: C, 51.20; H, 4.15; N, 2.92.

3.7. Analytical data of (trichloroacetyl)dihydropyridines 10 of Table 2

3.7.1. 1-Benzhydryl-3-(methoxycarbonyl)-5-(trichloroacetyl)-4-[2-(trifluoromethyl)phenyl]-1,4-dihydropyridine (10b). Elution with 93:7 hexanes–AcOEt; mp 80°C; ^{1}H NMR (300 MHz) δ 3.57 (s, 3H, OMe), 5.63 (q, J=2 Hz, 1H, 4-H), 6.10 (s, 1H, $CHPh_2$), 7.20–7.45 (m, 15H, 2-H, Ph), 7.88 (s, 1H, 6-H); ^{13}C NMR (75.4 MHz) δ 34.3 (C-4), 51.4 (OMe), 71.3 ($CHPh_2$), 95.6 (CCl_3), 107.3 (C-3), 112.4 (C-5), 126.9, 127.0, 128.2, 128.5, 128.8, 128.9, 129.2, 129.3, 130.7, 131.5 (CH, Ph), 136.5 (C-2), 137.0 (C, Ph), 137.2 (C, Ph), 142.5 (C-6), 144.0 (C, Ph), 166.5, 178.5 (CO). Anal. calcd for $C_{29}H_{21}Cl_3F_3NO_3$: C, 58.56; H, 3.56; N, 2.35. Found: C, 59.00; H, 3.93; N, 2.54.

3.7.2. 1-Benzhydryl-4-(2-chlorophenyl)-3-(methoxycarbonyl)-5-(trichloroacetyl)-1,4-dihydropyridine (10c). Elution with 95:5 hexanes–AcOEt; ^{1}H NMR (300 MHz) δ 3.57 (s, 3H, OMe), 5.43 (s, 1H, 4-H), 6.04 (s, 1H, $CHPh_2$), 7.05 (m, 1H, Ph), 7.15 (m, 1H, Ph), 7.20–7.45 (m, 13H, 2-H, Ph), 7.89 (s, 1H, 6-H); ^{13}C NMR (75.4 MHz) δ 36.6 (C-4), 51.4 (OMe), 71.3 ($CHPh_2$), 95.7 (CCl_3), 105.8 (C-3), 110.9 (C-5), 126.5, 127.8, 128.1, 128.6, 128.7, 128.9, 129.2, 131.5 (CH, Ph), 133.6 (C–Cl), 136.6 (C-2), 137.1 (C, Ph), 137.2 (C, Ph), 142.0 (C, Ph), 142.9 (C-6), 166.3, 178.6 (CO); HRMS calcd for $C_{28}H_{21}NO_3Cl_4$ 559.0275, found 559.0265.

3.7.3. 1-Benzhydryl-4-[2-(ethoxycarbonyl)phenyl]-3-(methoxycarbonyl)-5-(trichloroacetyl)-1,4-dihydropyridine (10d). Elution with 88:12 hexanes–AcOEt; mp 140°C; ^{1}H NMR (300 MHz) δ 1.45 (t, J=7.2 Hz, 3H, CH_3), 3.54 (s, 3H, OMe), 4.45 (m, 2H, OCH_2), 6.01 (s, 1H, $CHPh_2$), 6.20 (s, 1H, 4-H), 7.20–7.50 (m, 14H, 2-H, Ph), 7.75 (d, J=8 Hz, 1H, Ph), 7.86 (d, J=1.2 Hz, 1H, 6-H); ^{13}C NMR (75.4 MHz) δ 14.3 (CH_2), 33.4 (C-4), 51.4 (OMe), 60.8 (OCH_2), 71.1 ($CHPh_2$), 95.8 (CCl_3), 107.1 (C-3), 112.4 (C-5), 126.2, 128.2, 128.4, 128.7, 128.8, 129.1, 129.4, 129.7 (CH, Ph), 130.6 (C, Ph), 131.4 (CH, Ph), 136.3 (C-2), 137.1 (C, Ph), 137.4 (C, Ph), 142.4 (C-6), 145.8 (C, Ph), 166.3, 167.7, 178.3 (CO). Anal. calcd for $C_{31}H_{26}Cl_3NO_5$: C, 62.17; H, 4.38; N, 2.34. Found: C, 62.09; H, 4.51; N, 2.23.

3.7.4. 1-Benzhydryl-4-[3-(ethoxycarbonyl)phenyl]-3-(methoxycarbonyl)-5-(trichloroacetyl)-1,4-dihydropyridine (10e). Elution with 3:7 hexanes–CH_2Cl_2; mp 130°C; ^{1}H NMR (300 MHz) δ 1.39 (t, J=7.5 Hz, 3H, CH_3), 3.62 (s, 3H, OMe), 4.38 (dq, J=1.5, 7.2 Hz, 2H, OCH_2), 5.10 (s, 1H, 4-H), 6.06 (s, 1H, $CHPh_2$), 7.25–7.45 (m, 12H, 2-H, Ph), 7.60 (d, J=7.8 Hz, 1H, Ph), 7.86 (d, J=7.6 Hz, 1H, Ph), 7.90 (s, 1H, 6-H), 8.07 (s, 1H, Ph); ^{13}C NMR (75.4 MHz) δ 14.4 (CH_2), 37.7 (C-4), 51.6 (OMe), 60.8 (OCH_2), 71.3 ($CHPh_2$), 95.6 (CCl_3), 105.9 (C-3), 111.6 (C-5), 128.0, 128.4, 128.8, 128.9, 129.3 (CH, Ph), 130.6 (C, Ph), 132.9 (CH, Ph), 136.3 (C-2), 137.0 (C, Ph), 137.5 (C, Ph), 142.7 (C-6), 145.4 (C, Ph), 166.3, 166.5, 178.8 (CO). Anal. calcd for $C_{31}H_{26}Cl_3NO_5$: C, 62.17; H, 4.38; N, 2.34. Found: C, 61.98; H, 4.51; N, 2.45.

3.7.5. 1-Benzhydryl-3-(methoxycarbonyl)-4-[2-[2-(methoxycarbonyl)vinyl]phenyl]-5-(trichloroacetyl)-1,4-dihydropyridine (10f). Elution with 8:2 hexanes–AcOEt; ^{1}H NMR (300 MHz) δ 3.54 (s, 3H, OMe), 3.82 (s, 3H, OMe), 5.36 (s, 1H, 4-H), 6.06 (s, 1H, $CHPh_2$), 6.39 (d, J=15.6 Hz, 1H, CH=*CH*–CO_2), 7.10–7.50 (m, 15H, 2-H, Ph), 7.90 (s, 1H, 6-H), 8.71 (d, J=15.6 Hz, 1H, *CH*=CH–CO_2); ^{13}C NMR (50.3 MHz) δ 34.2 (C-4), 51.4 (OMe), 51.7 (OMe), 71.3 ($CHPh_2$), 95.6 (CCl_3), 107.1 (C-3), 112.3 (C-5), 119.5 (CH=*C*H–CO_2), 126.1, 127.0, 128.2, 128.6, 128.8, 129.0,

129.3, 129.4, 130.0 (CH, Ph), 133.1 (C, Ph), 136.1 (C-2), 137.1 (C–Ph), 137.3 (C, Ph), 142.4 (C-6), 144.0 (*C*H=CH–CO_2), 145.1 (C, Ph), 166.4, 167.5, 178.7 (CO).

3.8. General procedure for the preparation of (methoxycarbonyl)-1,4-dihydropyridines 6 and 11

A solution of (trichloroacetyl)-1,4-dihydropyridine **4** or **10** (0.50 mmol) in MeOH–THF (1:1, 30 mL) was added dropwise to a solution of MeONa (1.5 mmol) in MeOH (30 mL), and the mixture was stirred at rt for 1 min. The solvent was removed, and the resulting residue was partitioned between Et_2O (20 mL) and H_2O (20 mL), and extracted with Et_2O (2×20 mL). After removal of the solvent, the crude products were chromatographed.

3.8.1. 3,5-Bis(methoxycarbonyl)-1-methyl-4-[2-(trifluoromethyl)phenyl]-1,4-dihydropyridine (6b). Elution with 1:1 hexanes–AcOEt; yield 95%; mp 178°C; ^{1}H NMR (300 MHz) δ 3.26 (s, 3H, NMe), 3.57 (s, 6H, OMe), 5.49 (q, J=1.5 Hz, 1H, 4-H), 7.21 (s, 2H, 2-H, 6-H), 7.25 (m, 1H, Ph), 7.45 (m, 2H, Ph), 7.52 (d, J=8.1 Hz, 1H, Ph); ^{13}C NMR (75.4 MHz) δ 32.7 (q, J=4.5 Hz, C-4), 41.4 (NMe), 51.0 (OMe), 109.1 (C-3,5), 125.0 (q, J=274.9 Hz, CF_3), 126.4 (CH, Ph), 131.5 (CH, Ph), 131.6 (CH, Ph), 138.6 (C-2,6), 145.9 (C, Ph), 167.0 (CO). Anal. calcd for $C_{17}H_{16}F_3NO_4 \cdot 1/2H_2O$: C, 56.04; H, 4.70; N, 3.84. Found: C, 56.13; H, 4.38; N, 3.82.

3.8.2. 4-(2-Chlorophenyl)-3,5-bis(methoxycarbonyl)-1-methyl-1,4-dihydropyridine (6c). Elution with 8:2 hexanes–AcOEt; yield 80%; ^{1}H NMR (300 MHz) δ 3.26 (s, 3H, NMe), 3.61 (s, 6H, OMe), 5.34 (s, 1H, 4-H), 7.05 (m, 1H, Ph), 7.15 (m, 1H, Ph), 7.18 (s, 2H, 2-H, 6-H), 7.35 (m, 2H, Ph); ^{13}C NMR (75.4 MHz) δ 34.5 (C-4), 41.5 (NMe), 51.2 (OMe), 108.1 (C-3,5), 126.8 (CH, Ph), 127.5 (CH, Ph), 129.2 (CH, Ph), 131.4 (CH, Ph), 132.8 (C–Cl), 138.7 (C-2,6), 144.4 (C, Ph), 167.1 (CO); HRMS calcd for $C_{16}H_{16}NO_4Cl$ 321.0767, found 321.0760.

3.8.3. 4-[2-(Ethoxycarbonyl)phenyl]-3,5-bis(methoxycarbonyl)-1-methyl-1,4-dihydropyridine (6d). Elution with 6:4 hexanes–AcOEt; yield 80%; mp 158–159°C; ^{1}H NMR (300 MHz) δ 1.44 (t, J=7.2 Hz, 3H, CH_3), 3.24 (s, 3H, NMe), 3.57 (s, 6H, OMe), 4.44 (q, J=7.2 Hz, 2H, OCH_2), 5.98 (s, 1H, 4-H), 7.18 (m, 1H, Ph), 7.18 (s, 2H, 2-H, 6-H), 7.39 (m, 2H, Ph), 7.70 (d, J=7.5 Hz, 1H, Ph); ^{13}C NMR (75.4 MHz) δ 14.4 (CH_3), 32.3 (C-4), 41.5 (NMe), 51.2 (OMe), 60.7 (OCH_2), 109.0 (C-3,5), 126.0 (CH, Ph), 129.4 (CH, Ph), 130.1 (C, Ph), 130.2 (CH, Ph), 131.5 (CH, Ph), 138.6 (C-2,6), 147.2 (C, Ph), 167.1, 168.0 (CO). Anal. calcd for $C_{19}H_{21}NO_6 \cdot 1/3H_2O$: C, 62.47; H, 5.98; N, 3.83. Found: C, 62.38; H, 5.97; N, 3.68.

3.8.4. 4-[3-(Ethoxycarbonyl)phenyl]-3,5-bis(methoxycarbonyl)-1-methyl-1,4-dihydropyridine (6e). Elution with 6:4 hexanes–AcOEt; yield 80%; ^{1}H NMR (300 MHz, from a 7:1 mixture of **6e** and the corresponding C-2 isomer) δ 1.26 (t, J=7.5 Hz, 3H, CH_3–CH_2), 3.28 (s, 3H, NMe), 3.62 (s, 6H, OMe), 4.12 (q, J=7.5 Hz, 2H, OCH_2), 5.30 (s, 1H, 4-H), 7.20 (s, 2H, 2-H, 6-H), 7.35 (t, J=7.8 Hz, 1H, Ph), 7.56 (d, J=7.8 Hz, 1H, Ph), 7.86 (d, J=7.5 Hz, 1H, Ph), 7.97 (s, 1H, Ph).

3.8.5. 1-Benzhydryl-3,5-bis(methoxycarbonyl)-4-[2-(trifluoromethyl)phenyl]-1,4-dihydropyridine (11b, Table 2). Elution with 7:3 hexanes–AcOEt; yield 80%; ^{1}H NMR (200 MHz) δ 3.53 (s, 6H, OMe), 5.56 (q, J=2.2, 1H, 4-H), 5.92 (s, 1H, $CHPh_2$), 7.20–7.45 (m, 16H, 2-H, 6-H, Ph); ^{13}C NMR (50.3 MHz) δ 33.5 (q, J=4.6 Hz, C-4), 51.2 (OMe), 70.1 ($CHPh_2$), 109.7 (C-3,5), 126.5 (CH, Ph), 126.6 (q, J=5 Hz, CH, Ph), 128.3, 128.6, 129.1, 129.2, 131.4, 131.6 (CH, Ph), 137.5 (C-2,6), 137.8 (C, Ph), 145.7 (C, Ph), 167.1 (CO). Anal. calcd for $C_{29}H_{24}F_3NO_4$: C, 68.63; H, 4.77; N, 2.76. Found: C, 68.44; H, 4.97; N, 2.72.

3.8.6. 1-Benzhydryl-4-(2-chlorophenyl)-3,5-bis(methoxycarbonyl)-1,4-dihydropyridine (11c, Table 2). Elution with 93:7 hexanes–AcOEt; yield 80%; mp 170°C; ^{1}H NMR (200 MHz) δ 3.54 (s, 6H, OMe), 5.40 (s, 1H, 4-H), 5.92 (s, 1H, $CHPh_2$), 7.0–7.20 (m, 2H, Ph), 7.23–7.45 (m, 14H, 2-H, 6-H, Ph); ^{13}C NMR (50.3 MHz) δ 35.3 (C-4), 51.3 (OMe), 70.9 ($CHPh_2$), 108.6 (C-3,5), 126.7, 127.5, 128.4, 128.5, 129.1, 129.2, 131.3 (CH, Ph), 133.0 (C–Cl), 137.5 (C-2,6), 137.9 (C, Ph), 144.2 (C, Ph), 167.0 (CO). Anal. calcd for $C_{28}H_{24}ClNO_4 \cdot 3/4H_2O$: C, 68.99; H, 5.11; N, 2.87. Found: C, 68.82; H, 5.08; N, 2.87.

3.8.7. 1-Benzhydryl-4-[2-(ethoxycarbonyl)phenyl]-3,5-bis(methoxycarbonyl)-1,4-dihydropyridine (11d, Table 2). Elution with 8:2 hexanes–AcOEt; yield 87%; ^{1}H NMR (200 MHz) δ 1.43 (t, J=7 Hz, 3H, CH_3), 3.51 (s, 6H, OMe), 4.43 (q, J=7 Hz, 2H, OCH_2), 5.90 (s, 1H, $CHPh_2$), 6.06 (s, 1H, 4-H), 7.15–7.45 (m, 15H, 2-H, 6-H, Ph), 7.70 (d, J=7.2 Hz, 1H, Ph); HRMS calcd for $C_{31}H_{29}NO_6$ 511.1994, found 511.1988.

3.8.8. 1-Benzhydryl-4-[3-(ethoxycarbonyl)phenyl]-3,5-bis(methoxycarbonyl)-1,4-dihydropyridine (11e, Table 2). Elution with 95:5 hexanes–AcOEt; yield 81%; ^{1}H NMR (300 MHz) δ 1.39 (t, J=7.2 Hz, 3H, CH_3), 3.56 (s, 6H, OMe), 4.37 (q, J=6.6 Hz, 2H, OCH_2), 4.99 (s, 1H, 4-H), 5.97 (s, 1H, $CHPh_2$), 7.25–7.45 (m, 13H, 2-H, 6-H, Ph), 7.54 (d, J=7.5 Hz, 1H, Ph), 7.84 (d, J=7.8 Hz, 1H, Ph), 8.04 (s, 1H, Ph); HRMS calcd for $C_{31}H_{29}NO_6$ 511.1994, found 511.1990.

3.8.9. 1-Benzhydryl-3,5-bis(methoxycarbonyl)-4-[2-[2-(methoxycarbonyl)vinyl]phenyl]-1,4-dihydropyridine (11f, Table 2). Elution with 85:15 hexanes–AcOEt; yield 80%; ^{1}H NMR (300 MHz) δ 3.50 (s, 6H, OMe), 3.82 (s, 3H, OMe), 5.29 (s, 1H, 4-H), 5.93 (s, 1H, $CHPh_2$), 6.36 (d, J=15.9 Hz, 1H, CH=C*H*–CO_2), 7.15–7.25 (m, 8H, Ph), 7.30 (s, 2H, 2-H, 6-H), 7.40 (m, 6H, Ph), 8.63 (d, J=15.9 Hz, 1H, C*H*=CH–CO_2); ^{13}C NMR (75.4 MHz) δ 33.5 (C-4), 51.2 (OMe), 51.6 (OMe), 70.9 ($CHPh_2$), 109.3 (C-3,5), 119.1 (CH=*C*H–CO_2), 125.7, 126.6, 128.3, 128.5, 129.0, 130.0, 130.1 (CH, Ph), 132.4 (C, Ph), 137.2 (C-2,6), 137.8 (C, Ph), 146.5 (C, Ph), 167.0, 167.5 (CO); HRMS calcd for $C_{32}H_{29}NO_6$ 523.1994, found 523.1984.

3.9. General procedure for the preparation of (isopropoxycarbonyl)-1,4-dihydropyridines 7b and 7c

A solution of (trichloroacetyl)dihydropyridine **4b** or **4c** (0.50 mmol) in THF–*i*-PrOH (1:1, 30 mL) was added to a cooled (0°C) solution of *i*-PrOLi (1.5 mmol) in THF

(15 mL), and the mixture was stirred at rt for 2.5 h. Workup as above gave **7b** or **7c**.

3.9.1. 3-(Isopropoxycarbonyl)-5-(methoxycarbonyl)-1-methyl-4-[2-(trifluoromethyl)phenyl]-1,4-dihydropyridine (7b). Elution with 8:2 hexanes–AcOEt; yield 70%; ^{1}H NMR (300 MHz) δ 0.96 (d, J=6 Hz, 3H, MeCH), 1.18 (d, J=6 Hz, 3H, MeCH), 3.26 (s, 3H, NMe), 3.59 (s, 3H, OMe), 4.95 (h, J=6 Hz, 1H, OCH), 5.50 (br s, 1H, 4-H), 7.20, 7.23 (2 s, 2H, 2-H, 6-H), 7.24 (m, 1H, Ph), 7.45 (m, 2H, Ph), 7.52 (d, J=8 Hz, 1H, Ph); ^{13}C NMR (75.4 MHz) δ 21.4 (MeCH), 21.7 (MeCH), 32.9 (q, J=4.6 Hz, C-4), 41.5 (NMe), 51.2 (OMe), 67.4 (OCH), 109.1, 109.8 (C-3,5), 125.2 (q, J=278 Hz, CF_3), 126.5 (CH, Ph), 127.0 (m, C–CF_3), 131.6 (CH, Ph), 131.8 (CH, Ph), 138.8 (C-2,6), 146.0 (C, Ph), 166.4, 167.3 (CO); HRMS calcd for $C_{19}H_{20}NO_4F_3$ 383.1344, found 383.1352.

3.9.2. 4-(2-Chlorophenyl)-3-(isopropoxycarbonyl)-5-(methoxycarbonyl)-1-methyl-1,4-dihydropyridine (7c). Elution with 85:15 hexanes–AcOEt; yield 78%; mp 112–113°C; ^{1}H NMR (300 MHz) δ 1.0 (d, J=6.6 Hz, 3H, MeCH), 1.21 (d, J=6.6 Hz, 3H, MeCH), 3.26 (s, 3H, NMe), 3.61 (s, 3H, OMe), 4.95 (h, J=6.6 Hz, 1H, OCH), 5.35 (s, 1H, 4-H), 7.05 (m, 1H, Ph), 7.16 (m, 1H, Ph), 7.17, 7.18 (2s, 2H, 2-H, 6-H), 7.25 (m, 1H, Ph), 7.35 (m, 1H, Ph); ^{13}C NMR (75.4 MHz) δ 21.6 (MeCH), 21.9 (MeCH), 34.5 (C-4), 41.5 (NMe), 51.2 (OMe), 67.4 (OCH), 108.0, 109.0 (C-3,5), 126.7 (CH–Ph), 127.4 (CH, Ph), 129.1 (CH, Ph), 131.5 (CH, Ph), 132.8 (C–Cl), 138.6, 138.8 (C-2,6), 144.7 (C, Ph), 166.4, 167.2 (CO). Anal. calcd for $C_{18}H_{20}ClNO_4$: C, 61.45; H, 6.30; N, 3.98. Found: C, 61.30; H, 6.04; N, 3.75.

3.10. Removal of the *N*-benzhydryl group: Method A

A solution of 1,4-dihydropyridine **11b** or **11d–f** (0.25 mmol) and phenol (0.50 mmol) in TFA (0.87 mL, 0.50 mmol) was stirred at rt overnight. The reaction mixture was poured into a saturated aqueous solution of Na_2CO_3 (10 mL) and extracted with AcOEt (3×10 mL). The solvent was removed and the residue was chromatographed to give **12b** or **12d–f**.

3.10.1. 3,5-Bis(methoxycarbonyl)-4-[2-(trifluoromethyl)-phenyl]-1,4-dihydropyridine (12b, Table 2). Elution with 6:4 hexanes–AcOEt; yield 80%; mp 179°C; ^{1}H NMR (300 MHz) δ 3.58 (s, 6H, OMe), 5.53 (q, J=1.8 Hz, 1H, 4-H), 6.91 (br t, 1H, NH), 7.26 (t, J=8.1 Hz, 1H, Ph), 7.33 (d, J=5.1 Hz, 2H, 2-H, 6-H), 7.44 (t, J=8.1 Hz, 1H, Ph), 7.53 (d, J=8.1 Hz, 2H, Ph); ^{13}C NMR (75.4 MHz) δ 33.2 (q, J=4.6 Hz, C-4), 51.1 (OMe), 108.9 (C-3,5), 125.1 (q, J=275 Hz, CF_3), 126.4 (CH, Ph), 126.5 (CH, Ph), 127.1 (q, J=29 Hz, C–CF_3), 131.5 (CH, Ph), 131.7 (CH, Ph), 134.2 (C-2,6), 146.0 (C, Ph), 167.3 (CO). Anal. calcd for $C_{16}H_{14}F_3NO_4 \cdot 3/4H_2O$: C, 54.17; H, 4.40; N, 3.95. Found: C, 54.15; H, 4.22; N, 3.94.

3.10.2. 4-[2-(Ethoxycarbonyl)phenyl]-3,5-bis(methoxycarbonyl)-1,4-dihydropyridine (12d, Table 2). Elution with 7:3 hexanes–AcOEt; yield 76%; mp 212–213°C; ^{1}H NMR (300 MHz) δ 1.45 (t, J=7.5 Hz, 3H, CH_3), 3.58 (s, 6H, OMe), 4.45 (q, J=7.2 Hz, 2H, OCH_2), 6.0 (s, 1H, 4-H), 6.82 (br s, 1H, NH), 7.20 (m, 1H, Ph), 7.34 (d, J=5.4 Hz, 2H, 2-H, 6-H), 7.40 (m, 2H, Ph), 7.75 (d, J=8 Hz, 1H, Ph); ^{13}C NMR (75.4 MHz) δ 14.3 (CH_3), 32.8 (C-4), 51.2 (OMe), 60.8 (OCH_2), 108.8 (C-3,5), 126.0 (CH, Ph), 129.4 (CH, Ph), 130.1 (C, Ph), 130.4 (CH, Ph), 131.7 (CH, Ph), 134.1 (C-2,6), 147.6 (C–Ph), 167.4, 168.3 (CO). Anal. calcd for $C_{18}H_{19}NO_6 \cdot 1/2CH_2Cl_2$: C, 57.68; H, 5.26; N, 3.63. Found: C, 57.81; H, 5.32; N, 3.65.

3.10.3. 4-[3-(Ethoxycarbonyl)phenyl]-3,5-bis(methoxycarbonyl)-1,4-dihydropyridine (12e, Table 2). Elution with 7:3 hexanes–AcOEt; yield 73%; mp 144–145°C; ^{1}H NMR (300 MHz) δ 1.38 (t, J=7.2 Hz, 3H, CH_3), 3.62 (s, 6H, OMe), 4.35 (q, J=7.2 Hz, 2H, OCH_2), 4.97 (s, 1H, 4-H), 6.75 (br t, 1H, NH), 7.33 (t, J=7.6 Hz, 1H, Ph), 7.37 (d, J=5.7 Hz, 2H, 2-H, 6-H), 7.59 (d, J=7.8 Hz, 1H, Ph), 7.85 (d, J=7.8 Hz, 1H, Ph), 7.98 (s, 1H, Ph); ^{13}C NMR (75.4 MHz) δ 14.4 (CH_3), 37.5 (C-4), 51.3 (OMe), 60.9 (OCH_2), 107.9 (C-3,5), 127.7 (CH, Ph), 127.8 (CH, Ph), 129.2 (CH, Ph), 130.4 (C, Ph), 132.9 (CH, Ph), 134.0 (C-2,6), 147.1 (C–Ph), 167.0, 167.2 (CO). Anal. calcd for $C_{18}H_{19}NO_6 \cdot 1/2CH_2Cl_2$: C, 57.68; H, 5.26; N, 3.63. Found: C, 57.79; H, 5.29; N, 3.62.

3.10.4. 3,5-Bis(methoxycarbonyl)-4-[2-[2-(methoxycarbonyl)vinyl]phenyl]-1,4-dihydropyridine (12f, Table 2). Elution with 1:1 hexanes–AcOEt; yield 70%; ^{1}H NMR (400 MHz) δ 3.55 (s, 6H, OMe), 3.82 (s, 3H, OMe), 5.27 (s, 1H, 4-H), 6.36 (d, J=16 Hz, 1H, CH=C*H*–CO_2), 6.55 (br t, 1H, NH), 7.16 (dt, J=1.2, 7.2 Hz, 1H, Ph), 7.31 (dt, J=1.2, 7.8 Hz, 1H, Ph), 7.33 (d, J=5.2 Hz, 2H, 2-H, 6-H), 7.39 (dd, J=1.2, 7.8 Hz, 1H, Ph), 7.47 (dd, J=1.2, 7.8 Hz, 1H, Ph), 8.60 (d, J=16 Hz, 1H, C*H*=CH–CO_2); ^{13}C NMR (100.6 MHz) δ 33.9 (C-4), 51.2 (OMe), 51.7 (OMe), 108.8 (C-3,5), 118.9 (CH=*C*H–CO_2), 125.9 (CH, Ph), 126.8 (CH, Ph), 130.2 (CH, Ph), 130.6 (CH, Ph), 132.7 (C, Ph), 133.9 (C-2,6), 144.5 (*C*H=CH–CO_2), 146.9 (C, Ph), 167.2, 167.9 (CO).

3.11. Method B

3.11.1. 4-(2-Chlorophenyl)-3,5-bis(methoxycarbonyl)-1,4-dihydropyridine (12c, Table 2). A mixture of 1,4-dihydropyridine **11c** (75 mg, 0.16 mmol) and $AlCl_3$ (127 mg, 0.95 mmol) in C_6H_6 (4 mL) was heated at 60°C for 6 h. The reaction mixture was poured into a saturated aqueous solution of Na_2CO_3 (10 mL) and extracted with AcOEt (3×10 mL). The solvent was removed and the residue was chromatographed (8:2 hexanes–AcOEt) to give **12c** (49 mg, 98%). Mp 175°C; ^{1}H NMR (300 MHz) δ 3.61 (s, 6H, OMe), 5.38 (s, 1H, 4-H), 6.40 (br s, 1H, NH), 7.08 (td, J=1.8, 7.8, 8 Hz, 1H, Ph), 7.18 (td, J=1.8, 7.4, 7.8 Hz, 1H, Ph), 7.28 (d, J=7.8 Hz, 1H, Ph), 7.33 (d, J=5.1 Hz, 2H, 2-H, 6-H), 7.38 (d, J=7.6 Hz, 1H, Ph); ^{13}C NMR (75.4 MHz) δ 34.8 (C-4), 51.2 (OMe), 108.0 (C-3,5), 126.7 (CH, Ph), 127.4 (CH, Ph), 129.1 (CH, Ph), 131.3 (CH, Ph), 132.5 (C–Cl), 134.0 (C-2,6), 144.5 (C–Ph), 167.2 (CO). Anal. calcd for $C_{15}H_{14}ClNO_4 \cdot 1/3CH_2Cl_2$: C, 54.84; H, 4.40; N, 4.17. Found: C, 54.50; H, 4.12; N, 3.91.

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