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MILD, SELECTIVE, AND HIGH-YIELD OXIDATION OF HANTZSCH 1,4-DIHYDROPYRIDINES WITH LEAD(IV) ACETATE

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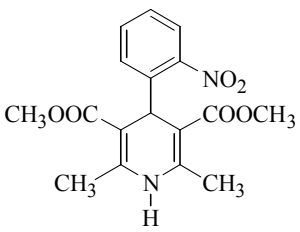
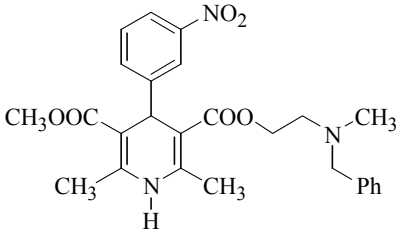
Abstract – Aromatization of 1,4-dihydropyridines with lead(IV) acetate under mild reaction conditions is described. The method is very selective, mild and versatile in the synthesis of different substituted pyridines.

INTRODUCTION

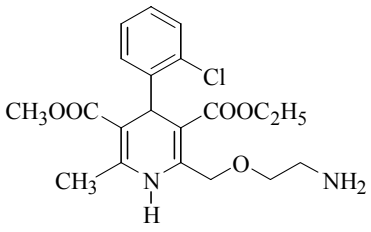
1,4-Dihydropyridines (1,4-DHPs) are very important class of compounds because of their pharmacological activity as a calcium antagonist or agonist.[1] The 1,4-DHP compounds cause vasorelaxation by blocking voltage-operated calcium channel in smooth muscle cells and also by increasing NO release from the intact endothelium.[2] Some representatives like nifedipine, nicardipine or amlodipine are widely used for treatment of hypertension.



nifedipine



nicardipine



amlodipine

1,4-DHPs have also been extensively utilised as the analogs of NAD(P)H coenzymes to study the mechanism and synthetic methods to obtain various NAD and NADH analogues. During the redox processes[3] and in the course of drug metabolism[4] 1,4-DHP systems are oxidatively transformed into the corresponding 4-arylpyridine derivatives, which are found to be of use in the treatment of arteriosclerosis.[5] Similarly, 1,4-DHPs are slowly oxidised with air oxygen during storage. Therefore, oxidised 1,4-DHPs are

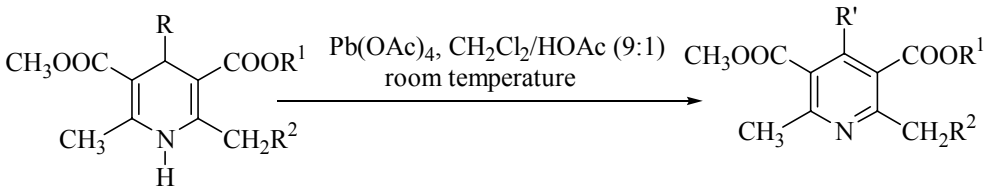
important either for pharmacological studies or as analytical standards in analysis of pharmacologically active 1,4-DHPs. Consequently, oxidation of 1,4-DHPs has been the subject in a large number of studies and a plethora of reagents are used for this purpose. The oldest and the most used reagents for aromatization of 1,4-DHPs is nitric acid of different concentrations, 20% HNO_3,[6,7] 50% HNO_3,[8,9] 2M HNO_3,[10] 5M HNO_3[11] and 6M HNO_3.[12] Nitrous acid is also used *in situ* prepared from sodium nitrite and different acids; $NaNO_2$/HOAc,[12-14] $NaNO_2$/HCl,[15] $NaNO_2$/$NaHSO_4$,[16] $NaNO_2$/$Mg(HSO_4)_2$[17] or $NaNO_2$/oxalic acid dihydrate.[18] Gaseous nitrogen monoxide is also employed for that purpose.[19,20] Metal nitrates such as $Bi(NO_3)_3 \cdot 5H_2O$,[21] $Fe(NO_3)_3/SiO_2$,[22] $(NH_4)_2[Ce(NO_3)_6]$; (CAN),[23] and recently $Zr(NO_3)_4$[24] are described as mild aromatization reagents. Additionally, the aromatization of 1,4-DHPs has been efficiently conducted with chromium compounds such as CrO_3,[25] CrO_2,[26] H_2CrO_4,[27] pyridinium dichromate,[28] nicotinium dichromate,[29] pyridinium chlorochromate[30] and $Zn(ClCrO_3)_2 \cdot 9H_2O$,[31] as well as other metal salts such as $Mn(OAc)_3$,[32] $BaMnO_4$,[33] $FeCl_3 \cdot 6H_2O$,[34] $K_3[Fe(CN)_6]$,[35] $RuCl_3/O_2$(g),[36] $KMnO_4$[37] $Hg(OAc)_2$[38] and $SnCl_4$.[39] Other non-metallic reagents which are able to oxidise 1,4-DHPs include DDQ,[40] chloranil,[41] *tert*-butylhydroperoxide,[42] dibenzoyl peroxide,[43] and molecular iodine.[44] Microwave promoted aromatization of 1,4-DHPs is also described.[45] The main drawback for the most of these methods is prolonged heating needed to complete the conversion that cause lowering of the yield. Only few reagents are able to complete the reaction at room temperature. On the other hand, almost all reagents are tested only for model 1,4-DHPs that lack of the presence of functional groups sensitive to oxidation. The main problem when metal nitrates or nitrites are used as oxidants is possible formation of carcinogenic *N*-nitroso side-products. Therefore, it is still necessary to find milder and especially selective oxidant for the Hantzsch 1,4-DHPs. In this course we attempt to find strong and selective oxidant to complete oxidation under mild conditions (room or lower temperature) but also to be tolerant to a variety of functionalities present in some commercial 1,4-DHPs.

RESULTS AND DISCUSSION

It is known from the literature[46] that lead(IV) acetate, $Pb(OAc)_4$, is a very strong oxidant used specially in sugar chemistry for the cleavage of carbon-carbon bond or decarboxylation, and for rearrangement of aliphatic or cyclic ethers. Lead(IV) acetate is also used as a mild and selective oxidant in dihydroacridine chemistry.[47,48] To our knowledge this reagent has not yet been used for aromatization of 1,4-DHPs. We wish to report here that lead(IV) acetate readily and selectively oxidises substituted 1,4-DHPs in high yields.[49] Study of this reaction is performed on model compound but also on commercial 1,4-DHPs, such as amlodipine (**11**), with protected (compound (**10**)) and free amino group. The selectivity obtained from the reaction with $Pb(OAc)_4$ increased the importance of this oxidant because it was reported that only CAN[23] has a similar selectivity for the aromatization of 1,4-DHPs. Many oxidants published in the literature cause

polymerisation of starting material without a trace of the product. We have also noticed that $Pb(OAc)_4$ dealkylates 4-alkyl-1,4-DHPs similarly to other metal oxidants. The results of oxidation presented by Scheme 1 are summarised in Table 1.

Scheme 1



1-15 **16-28**

Table 1. The oxidation of 1,4-DHPs with lead(IV) acetate, Scheme 1

1,4-DHP	R	R^1	R^2	Product[a]	R'	time/min	Yield/%[b]
1	H	CH_3	H	**16**	H	120	90
2	$CH(CH_3)_2$	"	"	**16**	"	60	93
3	CH_2Ph	"	"	**16**	"	15	71
4	Ph	"	"	**17**	Ph	15	90
5	*m*-Cl-C_6H_4	"	"	**18**	*m*-Cl-C_6H_4	20	76
6	*p*-Cl-C_6H_4	"	"	**19**	*p*-Cl-C_6H_4	20	75
7	*o*-NO_2-C_6H_4	"	"	**20**	*o*-NO_2-C_6H_4	60	89
8	*m*-NO_2-C_6H_4	C_2H_5	"	**21**	*m*-NO_2-C_6H_4	60	96
9	*o*-NO_2-C_6H_4	$CH_2CH(CH_3)_2$	"	**22**	*o*-NO_2-C_6H_4	45	76
10	*o*-Cl-C_6H_4	C_2H_5	OCH_2CH_2Pht[c]	**23**	*o*-Cl-C_6H_4	1140	97
11	"	"	$OCH_2CH_2NH_2$	**24**	"	30	92[d]
12	"	"	$OCH_2CH_2NBz_2$[e]	**25**	"	15	95
13	"	"	OCH_2CH_2NHAc[f]	**26**	"	1200	91
14	"	"	OCH_2CH_2X[g]	**27**	"	720	86
15	*m*-NO_2-C_6H_4	$(CH_2)_2NCH_3Bz$[e]	H	**28**	*m*-NO_2-C_6H_4	5	-[h]

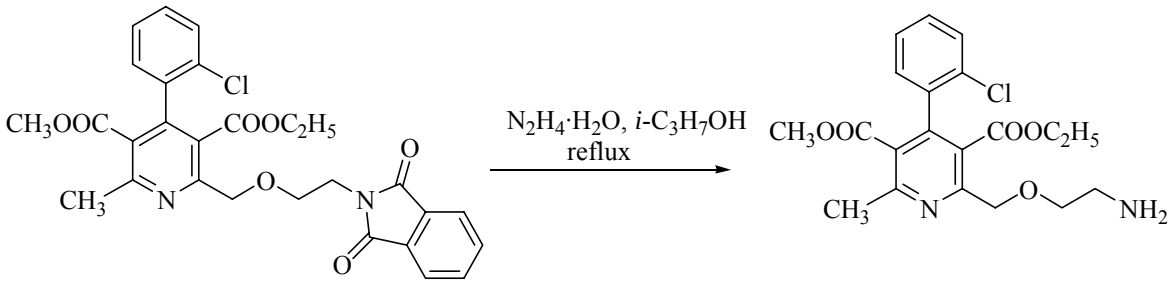
[a] Pyridine derivatives (**16-27**) were fully characterised (EXPERIMENTAL) since the data present in the literature are not complete.

[b] Yield after purification in isopropyl ether. [c] Pht = phthalimido group. [d] Isolated as acetate salt. [e] Bz = CH_2Ph. [f] Ac = CH_3CO. [g] X = 3,4,5,6-tetrachlorophthalimido group. [h] Decomposition of starting material.

The best solvent for oxidation of 1,4-DHPs using $Pb(OAc)_4$ is proved to be a mixture of dichloromethane and acetic acid (9:1, v/v). Usually, the common reaction medium used for oxidation of 1,4-DHPs with metal salts is acetic acid,[12-14,21,24,32] but such conditions required the complete neutralisation during the work-up procedure. The employed mixture of solvents allows the precipitation of lead(II) acetate during the reaction and almost quantitative removal of lead salts by filtration in the work-up procedure. This minimise the toxic water waste usually present when other metal salts are used, such as chromium compounds,[25-31] CAN,[23] $Mn(OAc)_3$,[32] $Bi(NO_3)_3$,[21] $Zr(NO_3)_4$,[24] $SnCl_4$[39] etc.

The oxidation is accomplished within 15-120 min except in the cases of imido derivatives (**10** and **14**) and *N*-acetyl derivative (**13**). Although, the conversion of about 50% in all three *N*-acyl derivatives is reached in approximatelly 30 min, the complete consumption of starting material is observed only after prolonged stirring. It is also important to note that during oxidation of this three compounds (**10**), (**13**) and (**14**) lead(II) acetate does not precipitate from the reaction mixture, suggesting that it remains complexed with a product. On the contrary, free amino or dibenzylamino group present in compounds (**11**) and (**12**) increases oxidation power of lead(IV) and does not complex lead(II). The presence of *N*-acyl group in molecule seems to be crucial for decreasing of reaction speed probably *via* complexation of lead(IV) by the product formed as the reaction proceeds. The conversion of starting material in all cases is quantitative. Only compound (**15**) was not succesfully oxidised probably due to oxidative dealkylation of an activated ester group present in molecule. The compound (**24**) is prepared independently in the form of a free base starting from compound (**23**) by deprotection of phthalimido group in reaction with hydrazine hydrate, according to Scheme 2.

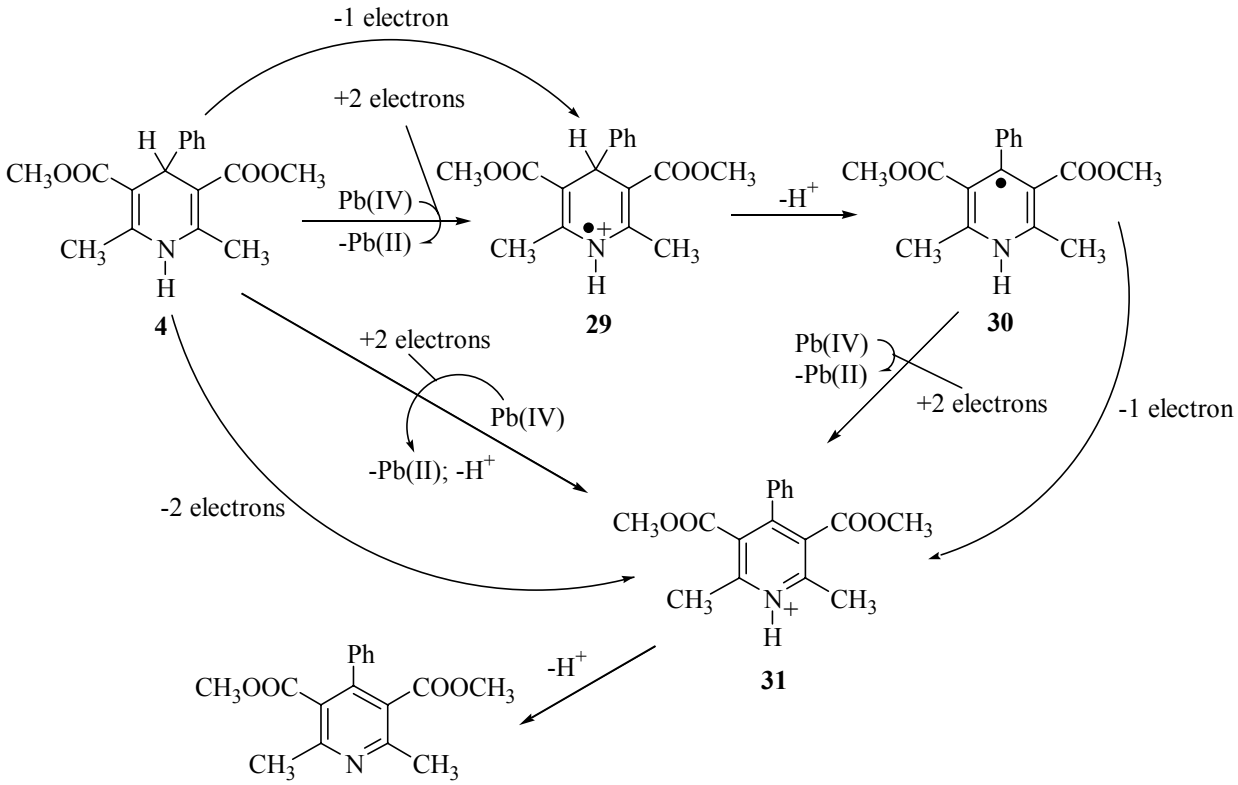
Scheme 2



23 **24**

The mechanism (Scheme 3, described on the model compound (**4**)) of lead(IV)-promoted oxidation probably includes the formation of radical cation (**29**), which subsequently loses proton to generate the radical (**30**) that is further oxidised to protonated derivative (**31**), similarly to manganese(III)-promoted oxidation.[32] Finally, deprotonation leads to pyridine derivative (**17**). It is also possible to predict the direct oxidation of 1,4-DHP (**4**) to pyridinium salt (**31**) due to the fact that reduction of lead(IV) to lead(II) requires two electron transfers from 1,4-DHP.

Scheme 3



In summary, new aromatization method of 1,4-DHPs using lead(IV) acetate allows fast, simple, practical and efficient way of preparation of a wide variety of substituted pyridine derivatives. The highest advantage of this method is the tolerance to various functional groups, such as free and substituted amino group that allows one-step synthesis of valuable amlodipine oxidation product.

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer Spectrum One spectrophotometer, and ^{1}H-NMR and ^{13}C-NMR spectra on a Bruker 600 for $CDCl_3$ solution, shifts are given in ppm downfield from TMS as an internal standard. All the mass spectra were obtained on FTMS Finigen 2001 DD spectrometer. TLC analyses were performed on Merck's (Darmstadt, Germany) DC-alufolien with Kieselgel 60_{254}. Elemental analyses were done in Central Analytical Service (CAS) at Ruđer Bošković Institute. 1,4-DHPs (**4**-**7**), (**12**) and (**13**) are prepared according to literature method.[50-52] Amlodipine (**11**) as a free base is prepared from appropriate besylate salt by acid-base extraction. Nitrendipine (**8**) was donated from Shijiazhuang Pharm., China, while nisoldipine (**9**) from Triquimsat Co., Argentina.

General procedure for the oxidation of 1,4-DHP with $Pb(OAc)_4$. To a solution of 1,4-DHP (2.0 mmol) in CH_2Cl_2/HOAc (9:1, 6 mL) at rt $Pb(OAc)_4$ (0.89 g, 2.0 mmol) was added in small portions during 15 min. The reaction mixture was stirred for the time indicated in the Table 1. The precipitated solid was removed

by filtration, dichloromethane (20 mL) was added, and then reaction mixture was neutralised with 5% aqueous $NaHCO_3$. The organic layer was dried over Na_2SO_4 and evaporated. The crude product was additionally purified by recrystallisation from isopropyl ether.

2,6-Dimethyl-3,5-dimethoxycarbonylpyridine (16). Colorless plates; mp 103.0-104.0°C (lit.,[53] 100°C); yields: Entry 1 (0.41 g, 90%), Entry 2 (0.41 g, 93%), Entry 3 (0.32 g, 71%). R_f (10% C_2H_5OAc/CH_2Cl_2) 0.38; IR ν (KBr) 1722, 1435, 1363, 1285, 1107, 772 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.86 (6H, s, CH_3), 3.93 (6H, s, OCH_3), 8.71 (1H, s, CH). ^{13}C-NMR ($CDCl_3$) δ: 24.65, 52.16, 122.61, 141.01, 162.42, 166.03. MS (m/z, %) 224 ($M,^+$ 100), 192 (5), 183 (5), 179 (6), 170 (21). Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.1; H, 5.7; N, 6.1.

2,6-Dimethyl-3,5-dimethoxycarbonyl-4-phenylpyridine (17). Pale yellow plates; mp 128.0-132.0°C (from isopropyl ether); yield 0.54 g (90%). R_f (10% C_2H_5OAc/CH_2Cl_2) 0.26; IR ν (KBr): 2956, 1733, 1563, 1439, 1288, 1243, 702 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.69 (6H; s, CH_3), 3.55 (6H, s, OCH_3), 7.22-7.26 (2H, m, Ph), 7.41-7.43 (3H, m, Ph). ^{13}C-NMR ($CDCl_3$) δ: 21.38, 52.36, 127.86, 127.35, 128.27, 128.95, 135.42, 154.58, 166.98. MS (m/z, %) 300 ($MH,^+$ 100), 268 (47), 236 (23), 224 (34), 194 (19), 170 (20). Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.1; H, 5.8; N, 4.6.

2,6-Dimethyl-3,5-dimethoxycarbonyl-4-(*m*-chlorophenyl)pyridine (18). Colorless prisms; mp 112.5-114.0°C (from isopropyl ether); yield 0.51 g (76%). R_f (10% C_2H_5OAc/CH_2Cl_2) 0.30; IR ν (KBr): 2961, 1732, 1559, 1423, 1238, 1210, 1108, 1033 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.61 (6H, s, CH_3), 3.59 (6H, s, OCH_3), 7.14 (1H, d, J = 7.5 Hz, Ph), 7.26 (1H, t, J = 1.8 Hz, Ph), 7.30–7.38 (2H, m, Ph). ^{13}C-NMR ($CDCl_3$) δ: 22.75, 52.06, 125.98, 126.36, 127.76, 128.55, 129.31, 134.03, 137.94, 144.52, 155.65, 167.76. MS (m/z, %) 334 ($MH,^+$ 100), 301 (16), 270 (39). Anal. Calcd for $C_{17}H_{16}NO_4Cl$: C, 61.18; H, 4.83; N, 4.20; Cl, 10.62. Found: C, 61.2; H, 4.7; N, 4.1; Cl, 10.4.

2,6-Dimethyl-3,5-dimethoxycarbonyl-4-(*p*-chlorophenyl)pyridine (19). Colorless needles; mp 140.0-143.0°C (from isopropyl ether) (lit.,[53] 137-139°C); yield 0.50 g (75%). R_f (10% C_2H_5OAc/CH_2Cl_2) 0.28; IR ν (KBr): 2953, 1733, 1557, 1492, 1435, 1241, 1039, 1020, 857 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.60 (6H, s, CH_3) 3.58 (6H, s, OCH_3), 7.19 (2H, d, J = 2.0 Hz, Ph), 7.36 (2H, d, J = 2.0 Hz, Ph). ^{13}C-NMR ($CDCl_3$) δ: 32.45, 51.79, 126.13, 128.00, 128.77, 134.29, 144.48, 155.23, 167.60. MS (m/z, %) 334 ($MH,^+$ 100), 302 (65), 270 (18), 179 (17), 170 (20), 123 (21). Anal. Calcd for $C_{17}H_{16}NO_4Cl$: C, 61.18; H, 4.83; N, 4.20; Cl, 10.62. Found: C, 61.1; H, 4.7; N, 4.1; Cl, 10.5.

2,6-Dimethyl-3,5-dimethoxycarbonyl-4-(*o*-nitrophenyl)pyridine (20). Yellow powder; mp 103.0-105.0°C (from isopropyl ether); yield 0.61 g (89%). R_f (10% C_2H_5OAc/CH_2Cl_2) 0.31; IR ν (KBr) 2954, 1727, 1615, 1562, 1531, 1437, 1355, 1253, 1114, 1039, 968, 870, 842, 811, 794, 755, 703 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.66 (s, 6H, CH_3), 3.51 (s, 6H, OCH_3), 7.19–7.22 (1H, m, Ph), 7.55–7.67 (2H, m, Ph), 8.21 (1H, d, J = 8.0 Hz, Ph). ^{13}C-NMR ($CDCl_3$) δ: 23.61, 52.18, 124.32, 124.78, 129.59, 130.59, 131.94,

132.94, 145.20, 147.56, 157.02, 167.18. Anal. Calcd for $C_{17}H_{16}N_2O_6$: C, 59.30; H, 4.68; N, 8.14. Found: C, 59.1; H, 4.5; N, 8.0.

2,6-Dimethyl-3-methoxycarbonyl-4-(*m*-nitrophenyl)-5-ethoxycarbonylpyridine (21). Yellow oil; yield 0.69 g (96%). R_f (10% C_2H_5OAc/CH_2Cl_2) 0.36; IR ν (liquid film): 2983, 1721, 1560, 1438, 1373, 1293, 1214, 1108 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, t, J = 7.1 Hz, CH_3), 2.63 (3H, s, CH_3), 2.64 (3H, s, CH_3), 3.59 (3H, s, OCH_3), 4.07 (2H, q, J = 14.3 Hz, CH_2), 7.57–7.63 (2H, m, Ph), 8.17–8.18 (1H, m, Ph), 8.23–8.30 (1H, m, Ph). ^{13}C-NMR ($CDCl_3$) δ: 13.55, 22.94, 22.98, 52.25, 61.54, 123.03, 123.29, 129.12, 134.06, 137.90, 143.45, 147.70, 155.97, 156.09, 167.00, 167.55. MS (m/z, %) 359 (MH^+ 100), 341 (19), 327 (9), 313 (10). Anal. Calcd for $C_{18}H_{18}N_2O_6$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.2; H, 5.0; N, 7.7.

2,6-Dimethyl-3-isobutyloxycarbonyl-4-(*o*-nitrophenyl)-5-methoxycarbonylpyridine (22). Yellow oil; yield 0.59 g (76%). R_f (10% C_2H_5OAc/CH_2Cl_2) 0.37; IR ν (liquid film): 2962, 1729, 1559, 1532, 1349, 1236, 1110, 1042 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.67 (6H, d, J = 6.9 Hz, (CH_3)$_2$CH), 1.52–1.59 (1H, m, CH), 2.56 (3H, s, CH_3), 2.58 (3H, s, CH_3), 3.41 (3H, s, OCH_3), 3.52–3.55 (1H, m, CH_2CH), 3.69–3.72 (1H, m, CH_2CH), 7.13–7.15 (1H, m, Ph), 7.47–7.50 (1H, m, Ph), 7.54–7.57 (1H, m, Ph), 8.11–8.13 (1H, dd, J_1 = 8.1 Hz, J_2 = 1.2 Hz, Ph). ^{13}C-NMR ($CDCl_3$) δ: 18.71, 18.76, 23.42, 23.52, 27.27, 51.93, 71.56, 124.20, 124.49, 125.04, 129.36, 130.06, 131.87, 132.73, 144.62, 147.42, 156.56, 156.70, 166.82, 167.08. Anal. Calcd for $C_{20}H_{22}N_2O_6$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.0; H, 5.6; N, 7.1.

2-[2-(*N*-Phthalimido)ethoxymethyl]-3-ethoxycarbonyl-4-(*o*-chlorophenyl)-5-methoxycarbonyl-6-methylpyridine (23). Pale yellow plates; mp 121.0-123.0°C (from izopropyl ether); yield 1.04 g (97%). R_f (10% C_2H_5OAc/CH_2Cl_2) 0.25; IR ν (KBr): 1772, 1717, 1563, 1392, 1231, 1114, 717 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, J = 7.1 Hz, CH_2CH_3), 2.61 (3H, s, CH_3), 3.53 (3H, s, OCH_3), 3.72 (2H, t, J = 5.8 Hz, CH_2), 3.88 (2H, t, J = 5.8 Hz, CH_2), 4.01 (2H, q, J = 13.9 Hz, CH_2), 4.82–4.90 (2H, m, CH_2), 7.14 (1H, dt, J_1 = 7.3 Hz, J_2 = 1.6 Hz, Ph), 7.23–7.33 (2H, m, Ph), 7.39 (1H, d, J = 7.4, Ph), 7.70 (2H, dd, J_1 = 3.0 Hz, J_2 = 5.4 Hz, Ph), 7.83 (2H, dd, J_1 = 3.0 Hz, J_2 = 5.4 Hz, Ph). ^{13}C-NMR ($CDCl_3$) δ: 13.45, 23.18, 37.33, 52.17, 61.36, 67.60, 72.84, 123.19, 126.05, 126.42, 128.20, 129.05, 129.77, 130.29, 132.17, 132.89, 133.83, 134.97, 144.93, 156.09, 166.29, 167.35, 168.13. MS (m/z, %) 537 (MH^+ 100), 407 (16), 347 (12), 345 (16), 268 (16), 260 (17), 174 (10). Anal. Calcd for $C_{28}H_{25}N_2O_7Cl$: C, 62.63; H, 4.69; N, 5.22; Cl, 6.60. Found: C, 62.5; H, 4.6; N, 5.1; Cl, 6.5.

2-(2-Aminoethoxy)methyl-3-ethoxycarbonyl-4-(*o*-chlorophenyl)-5-methoxycarbonyl-6-methylpyridine as acetate salt (24). Pale yellow powder; mp 100.0-103.0°C (from isopropyl ether); yield 0.86 g (92%). R_f (3% NH_3(aq)/17% CH_3OH/40% CH_3CN/40% dioxane) 0.54; IR ν (KBr): 2988, 2952, 1727, 1555, 1434, 1415, 1236 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J = 7.1 Hz, CH_2CH_3), 1.92 (3H, s, CH_3), 2.65 (3H, s, CH_3CO), 3.08 (2H, t, J = 4.8 Hz, CH_2), 3.54 (3H, s, OCH_3), 3.72 (2H, t, J = 4.9 Hz, CH_2), 4.00 (2H, q, J = 7.1 Hz, CH_2CH_3), 4.81 (1H, d, J = 13.4 Hz, CH_2O), 4.84 (1H, d, J = 13.4 Hz, CH_2O), 7.17 (1H,

dd, J_1 = 7.2 Hz, J_2 = 1.6 Hz, Ph), 7.28 (1H, dt, J_1 = 7.3 Hz, J_2 = 1.1 Hz, Ph), 7.33 (1H, dt, J_1 = 7.7 Hz, J_2 = 1.6 Hz, Ph), 7.41 (1H, dd, J_1 = 7.8 Hz, J_2 = 0.9 Hz, Ph), 7.65 (3H, br s, D_2O exchangeable, NH_3). ^{13}C-NMR ($CDCl_3$) δ: 13.23, 22.76, 22.92, 39.69, 52.01, 61.46, 68.74, 72.29, 125.99, 128.06, 128.95, 129.73, 130.07, 132.68, 134.75, 145.01, 155.54, 156.37, 166.36, 166.93, 176.97. Anal. Calcd for $C_{22}H_{27}N_2O_7Cl$: C, 56.59; H, 5.83; N, 6.00; Cl, 7.59. Found: C, 56.5; H, 5.7; N, 5.9.

2-(2-Aminoethoxy)methyl-3-ethoxycarbonyl-4-(*o*-chlorophenyl)-5-methoxycarbonyl-6-methyl-pyridine as free base (24). To a suspension of 2-[2-(*N*-phthalimido)ethoxymethyl]-3-ethoxycarbonyl-4-(*o*-chlorophenyl)-5-methoxycarbonyl-6-methylpyridine (**23**) in 10 mL of 96% ethanol at rt hydrazine monohydrate (0.24 mL, 5.0 mmol) was added at once. The resulting solution was stirred for 20 h. The formed precipitate was filtered and washed with 5 mL of 96% ethanol. The organic solvent was evaporated and the residue dissolved in 40 mL of dichloromethane. The resulting suspension was stirred for 15 min, filtered and obtained crystals washed with 15 mL of dichloromethane. Dichloromethane extracts were evaporated and the residue was purified by chromatography on silica column with 10% CH_3OH/dichloromethane as eluent. After evaporation of selected fractions, R_f 0.14, compound (**24**) was isolated as yellow oil; yield 0.40 g (98%). R_f (3% NH_3(aq)/17% CH_3OH/40% CH_3CN/40% dioxane) 0.54; IR ν (liquid film): 3376, 2951, 1731, 1595, 1436, 1232, 1109, 1043 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, t, J = 7.1 Hz, CH_2CH_3), 2.65 (3H, s, CH_3), 2.75 (2H, br s, D_2O exchangeable, NH_2), 2.83 (2H, t, J = 4.9 Hz, CH_2), 3.49-3.54 (5H, m, CH_2+CH_3), 4.00 (2H, q, J = 14.22 Hz, CH_2), 4.78 (1H, d, J = 12.7 Hz, CH_2O), 4.84 (1H, d, J = 12.6 Hz, CH_2O), 7.18 (1H, dd, J_1 = 7.3 Hz, J_2 = 1.7 Hz, Ph), 7.27-7.35 (2H, m, Ph), 7.42 (1H, d, J = 7.3 Hz, Ph). ^{13}C-NMR ($CDCl_3$) δ: 13.37, 23.16, 41.69, 52.11, 61.24, 73.09, 73.31, 126.04, 128.10, 129.03, 129.75, 130.19, 132.81, 134.90, 156.02, 156.26, 166.54, 167.28. Anal. Calcd for $C_{20}H_{23}N_2O_5Cl$: C, 59.04; H, 5.70; N, 6.89; Cl, 8.71. Found: C, 59.0; H, 5.6; N, 6.8.

2-[2-(*N*,*N*-Dibenzylamino)ethoxymethyl]-3-ethoxycarbonyl-4-(*o*-chlorophenyl)-5-methoxycarbonyl-6-methylpyridine (25). Yellow oil; yield 0.56 g (95%). R_f (10% C_2H_5OAc/CH_2Cl_2) 0.50; IR ν (liquid film): 3028, 2950, 1732, 1559, 1480, 1453, 1436, 1297, 1230, 1108, 1043, 750 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 0.83 (3H, t, J = 7.0 Hz, CH_2CH_3), 2.66 (3H, s, CH_3), 3.56 (3H, s, OCH_3), 3.59-3.61 (4H, m, CH_2CH_2), 3.64 (4H, s, 2xCH_2Ph), 3.83-3.85 (2H, m, CH_2CH_3), 4.77 (1H, d, J = 12.5 Hz, CH_2O), 4.80 (1H, d, J = 12.6 Hz, CH_2O), 7.18 (1H, d, J = 6.5 Hz, Ph), 7.24 (1H, d, J = 6.9 Hz, Ph), 7.29-7.32 (5H, m, Ph), 7.34-7.41 (6H, m, Ph), 7.43 (1H, d, J = 7.9 Hz, Ph). ^{13}C-NMR ($CDCl_3$) δ: 13.44, 23.28, 52.17, 52.50, 58.89, 61.10, 69.70, 73.24, 126.09, 126.50, 128.17, 128.34, 128.76, 129.10, 129.77, 130.31, 132.95, 135.12, 139.64, 144.84, 156.02, 156.56, 166.41, 167.43. MS (m/z, %) 587 (MH^+, 100), 498 (26), 364 (21), 224 (61), 132 (33). Anal. Calcd for $C_{34}H_{35}N_2O_5Cl$: C, 69.56; H, 6.01; N, 4.77; Cl, 6.04. Found: C, 69.7; H, 5.9; N, 4.9, Cl, 6.2.

2-[2-(*N*-Acetylamino)ethoxymethyl]-3-ethoxycarbonyl-4-(*o*-chlorophenyl)-5-methoxycarbonyl-6-methylpyridine (26). Yellow cubes; mp 66.0-68.0°C (from isopropyl ether); yield 0.40 g (91%). R_f (10% CH_3OH/CH_2Cl_2) 0.56; IR ν (KBr): 2949, 1732, 1657, 1559, 1430, 1286, 1227, 1042 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.01 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 1.98 (3H, s, CH_3), 2.68 (3H, s, CH_3CO), 3.42 (2H, t, *J* = 4.8 Hz, CH_2), 3.56 (3H, s, OCH_3), 3.57-3.58 (2H, m, CH_2), 4.06 (2H, q, *J* = 7.1, CH_2CH_3), 4.79 (1H, d, *J* = 12.7, CH_2O), 4.84 (1H, d, *J* = 12.8, CH_2O), 6.40 (1H, br s, D_2O exchangeable, NH), 7.17 (1H, dd, J_1 = 7.5, J_2 = 1.3, Ph), 7.29-7.32 (1H, m, Ph), 7.36 (1H, t, *J* = 7.5, Ph), 7.44 (1H, d, *J* = 7.9, Ph). ^{13}C-NMR ($CDCl_3$) δ: 13.50, 23.07, 23.20, 39.17, 52.24, 61.62, 69.96, 73.09, 126.18, 126.50, 128.43, 129.21, 130.02, 130.21, 132.89, 134.73, 145.19, 155.90, 156.28, 167.09, 167.15, 170.24. MS (m/z, %) 449 (MH^+ 100), 364 (16), 347 (14), 179 (26), 170 (70), 123 (41). Anal. Calcd for $C_{22}H_{25}N_2O_6Cl$: C, 58.86; H, 5.61; N, 6.24; Cl, 7.90. Found: C, 58.7; H, 5.8; N, 6.4, Cl, 7.8.

2-[2-*N*-(3,4,5,6-Tetrachlorophthalimido)ethoxymethyl]-3-ethoxycarbonyl-4-(2-chlorophenyl)-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine (27). Yellow cubes; mp 131.0-133.0°C (from 20% *i*-C_3H_7OH/isopropyl ether); yield 0.58 g (86%). R_f (10% C_2H_5OAc/CH_2Cl_2) 0.53; IR ν (KBr): 1721, 1559, 1423, 1396, 1234, 1103, 1044 cm^{-1}.^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 2.63 (3H, s, CH_3), 3.53 (3H, s, OCH_3), 3.66-3.69 (2H, m, CH_2), 3.85-3.93 (2H, m, CH_2), 4.00 (2H, q, *J* = 14.1 Hz, CH_2), 4.74 (1H, d, *J* = 13.1, CH_2O), 4.89 (1H, d, *J* = 13.1, CH_2O), 7.09 (1H, dd, J_1 = 7.5 Hz, J_2 = 1.5 Hz, Ph), 7.24–7.30 (2H, m, Ph), 7.36 (1H, d, *J* = 7.2, Ph). ^{13}C-NMR ($CDCl_3$) δ: 13.49, 22.87, 38.28, 52.16, 61.44, 66.99, 73.20, 125.95, 126.23, 128.01, 128.31, 128.99, 129.38, 129.73, 130.21, 132.80, 134.78, 139.60, 145,10, 156.02, 156.10, 163.46, 166.08, 167.29. MS (m/z, %) 672 (M^+ 20), 363 (18), 347 (100), 318 (39), 268 (96). Anal. Calcd for $C_{28}H_{25}N_2O_7Cl_5$: C, 49.84; H, 3.14; N, 4.15; Cl, 26.27. Found: C, 49.8; H, 3.0; N, 4.2; Cl, 26.4.

Synthesis of model 1,4-DHPs by modified Hantzsch condensation

2,6-Dimethyl-3,5-dimethoxycarbonyl-1,4-dihydropyridine (1). To a solution of methyl acetoacetate (116.12 g, 1 mol) and 37% formaldehyde solution (40 mL, 15.55 g, 0.52 mol), cooled to 3°C, 1 mL of triethylamine was added. The reaction mixture was stirred for 44 h and then extracted with distilled water (200 mL). Water layer (upper) was additionally extracted with three portions of ether (100 mL). Organic layers were gathered, dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The residue was dissolved in absolute ethanol (80 mL). Gaseous ammonia was introduced to that solution, previously cooled to 0°C, during 2 h by keeping the temperature between 0-5°C. Reaction mixture was stirred for 48 h at rt. After that the crystals were removed by filtration and washed with 96% ethanol (3x20 mL). Crude product was additionally purified in refluxing isopropyl ether (200 mL) during 1 h, cooled to 3°C and left at that temperature for 20 h. Crystals were filtered and washed with cold isopropyl ether (3x50 mL). After

drying in vacuum, product (**1**) was isolated as pale yellow powder; mp 211-219°C (from isopropyl ether); yield 38.33 g (34%). R_f (10% C_2H_5OAc/CH_2Cl_2) 0.33; IR ν (KBr): 3346, 1698, 1646, 1505, 1432, 1219, 1183 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.25 (6H, s, CH_3), 3.27 (2H, s, CH_2), 3.71 (6H, s, OCH_3), 5.20 (1H, s, NH), ppm; ^{13}C-NMR ($CDCl_3$) δ: 19.00, 24.71, 50.88, 99.28, 144.95, 168.24. Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22. Found: C, 58.4; H, 6.6; N, 6.1.

2,6-Dimethyl-3,5-dimethoxycarbonyl-4-isopropyl-1,4-dihydropyridine (2). To a solution of methyl acetoacetate (232.24 g, 2.0 mol) and ammonium acetate (385.41 g, 5.0 mol) in 96% ethanol (1300 mL), isobutyraldehyde (72.11 g, 1.0 mol) was added during 30 min. Reaction mixture was stirred at rt for 140 h. After that solvent was evaporated and to the residue dichloromethane (1000 mL) and water (800 mL) were added. The mixture was stirred for 15 min and the layers were separated. Water layer was additionally extracted with dichloromethane (200 mL). Organic layers were collected, dried over anhydrous sodium sulfate, filtered and evaporated. Crude product was crystallised from hot isopropyl ether (600 mL). After drying in vacuum, product (**2**) was isolated as a colorless needles; mp 168.0-169.5°C; yield 90.38 g (38%). R_f (10% C_2H_5OAc/CH_2Cl_2) 0.33; IR ν (KBr): 3338, 2954, 1706, 1651, 1490, 1218, 1077 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.73 (6H, d, J = 6.9, CH_3), 1.52–1.61 (1H, m, CH), 2.31 (6H, s, CH_3), 3.71 (6H, s, OCH_3), 3.89 (1H, d, J = 5.4, CH), 6.09 (1H, br, NH). ^{13}C-NMR ($CDCl_3$) δ: 18.09, 19.05, 35.29, 38.61, 50.68, 101.16, 144.93, 169.07. Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 62.7; H, 7.9; N, 5.1.

2,6-Dimethyl-3,5-dimethoxycarbonyl-4-benzyl-1,4-dihydropyridine (3). To a solution of methyl acetoacetate (58.06 g, 0.5 mol) and ammonium acetate (96.35 g, 1.25 mol) in 96% ethanol (300 mL), a solution of phenylacetaldehyde (60.08 g of solution, 30.04 g of aldehyde, 0.25 mol) in diethyl phtalate diluted with 96% ethanol (100 mL) was added during 30 min. Reaction mixture was stirred at rt for 140 h. After that the solvent was evaporated to dryness and to the residue dichloromethane (500 mL) and water (300 mL) were added. The layers were stirred for 15 min and separated. Water layer was additionally extracted with dichloromethane (200 mL). Organic layers were collected, dried over anhydrous sodium sulfate, filtered and evaporated. Crude product was crystallised from hot isopropyl ether (300 mL). After drying in vacuum product (**3**) was isolated as a pale yellow powder; mp 156.0-159.0°C; yield 10.79 g (13.7%). R_f (10% C_2H_5OAc/CH_2Cl_2) 0.45; IR ν (KBr): 3335, 1700, 1659, 1647, 1491, 1435, 1215 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.19 (6H, s, CH_3), 2.58 (2H, d, J = 5.5, CH_2Ph), 3.60 (6H, s, OCH_3), 4.19 (1H, t, J = 5.5, CH), 5.50 (1H, br, NH), 7.01-7.04 (2H, m, Ph), 7.11-7.22 (3H, m, Ph). ^{13}C-NMR ($CDCl_3$) δ: 19.01 35.28, 42.22, 50.74, 101.38, 125.50, 127.08, 129.97, 138.96, 145.62, 168.10. Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.4; H, 6.6; N, 4.4.

2-[2-*N*-(3,4,5,6-Tetrachlorophthalimido)ethoxymethyl]-3-ethoxycarbonyl-4-(*o*-chlorophenyl)-5-met-hoxycarbonyl-6-methyl-1,4-dihydropyridine (14). To a solution of amlodipine (**11**, 2.05 g, 5 mmol) in glacial acetic acid (20 mL) 3,4,5,6-tetrachlorophtalanhydride (1.43 g, 5 mmol) was added. The

reaction mixture was heated at reflux temperature during 2 h. After cooling to rt reaction mixture was poured in water (100 mL), neutralised with solid $NaHCO_3$ and extracted with dichloromethane (3 x 50 mL). Combined organic layers were collected, dried over anhydrous sodium sulfate, filtered and evaporated. Crude product was crystallised from hot methanol (50 mL). After drying in vacuum product (**14**) was isolated as a yellow cubes; mp 185.0-187.0°C; yield 1.80 g (53%). R_f (10% C_2H_5OAc/CH_2Cl_2) 0.74; IR ν (KBr): 3360, 3061, 2982, 1775, 1720, 1693, 1641, 1614, 1482, 1429, 1395, 1365, 1309, 1281 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.16 (3H, t, J = 7.18, CH_2CH_3), 2.45 (3H, s, CH_3), 3.60 (3H, s, OCH_3), 3.74–3.78 (2H, m, CH_2CH_3), 3.98–4.05 (4H, m, CH_2CH_2), 4.61 (1H, d, J = 15.64, CH_2O), 4.73 (1H, d, J = 15.64, CH_2O), 5.29 (1H, s, CH), 5.35 (1H, s, NH), 6.99–7.12 (2H, m, Ph), 7.21 (1H, dd, J_1 = 7.7 Hz, J_2 = 1.3 Hz, Ph), 7.35 (1H, dd, J_1 = 7.7 Hz, J_2 = 1.7 Hz, Ph). ^{13}C-NMR ($CDCl_3$) δ: 13.96, 18.93, 36.70, 38.59, 50.53, 59.55, 68.03, 68.44, 100.83, 103.58, 126.72, 127.22, 127.43, 129.06, 129.80, 131.41, 132.20, 140.35, 144.58, 144.70, 145.85, 163.82, 167.12, 168.03. Anal. Calcd for $C_{28}H_{23}N_2O_7Cl_5$: C, 49.69; H, 3.43; N, 4.14; Cl, 26.19. Found: C, 49.5; H, 3.3; N, 4.2; Cl, 26.3.

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