Synthesis of Some New Unsymmetrically Substituted 1,4-Dihydropyridines

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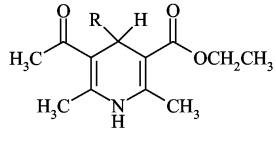
A series of some new 3,5-unsymmetrically substituted 1,4-dihydropyridines have been synthesized, which have ethoxycarbonyl and acetyl groups on 3- and 5-positions, respectively. A three-step procedure has been examined to increase the yield of the desired products, by suppressing the formation of the symmetrically substituted 3,5-diacetyl-1,4-dihydropyridines and 3,5-diethoxycarbonyl-1,4-dihydropyridines.

Key words: 1,4-Dihydropyridines, Heterocycles, 2-Benzylidene-1,3-dicarbonyl Compounds

Introduction

The preparation of symmetrically substituted 1,4-dihydropyridines by classical Hantzsch synthesis [1], involving the condensation of an aldehyde, ammonia and acetoacetic ester or other 1,3-dicarbonyl compounds, was modified by Beyer [2], Knoevenagel [3] to allow the preparation of unsymmetrical 1,4-dihydropyridines by condensation of an alkylidene or arylidene 1,3-dicarbonyl compound with a β-amino-a,β-unsaturated carbonyl compound, which is known as Hantzsch-Beyer synthesis. Symmetrically substituted 1,4-dihydropyridine drugs are achiral molecules, but when the ester groups bear different alkoxy groups, a chiral center is established in the 4-position of the dihydropyridine ring. Chiral 1,4-dihydropyridines [4 – 6] have been employed as synthetic intermediates for a wide variety of compounds such as natural products [7], calcium channel blockers [8], and NADH models [9]. Nifedipine, with symmetrical substituents on its dihydropyridine ring, is achiral; while second generation derivatives, such as felodipine, nitrendipine, nivadipine, nimodipine, nicardipine, and amoldipine, with unsymmetrical substitution (different ester groups on 3- and 5-positions), are chiral. Because of the importance of C-4 chirality with respect to the pharmacological activity of 4-aryl-1,4-dihydropyridines, the availability of asymmetric synthesis of this class of compounds is highly desirable. Various studies have been devoted to the preparation of unsymmetrical 1,4-dihydropyridine-3,5-diesters, such as nitrendipine [10], felodipine [11, 12] and others [13 – 16]. Some studies have also been devoted to the preparation of unsymmetrical 1,4-dihydropyridines, in which an alkoxycarbonyl (ester) group and a alkanoyl (keto) group are located on 3- and 5-positions, respectively [14, 17 – 21]. In the course of our studies on the chemistry of 1,4-dihydropyridines, especially their photochemical reactions, we have prepared various 1,4-dihydropyridine-3,5-diesters, known as Hantzsch dihydropyridine and also 3,5-diacetyl-1,4-dihydropyridines and investigated their photooxidation and oxidation to elucidate the effect of nature and type of 4-substituent and also the presence of ester or keto groups on 3- and 5-position on the rate of reaction [22, 23]. In continuation of these studies we were interested in the synthesis of 5-acyl-1,4-dihydropyridine-3-carboxylates, with the general structure **1**. The aim of this work was to find out the best procedure for the preparation of these compounds by suppressing the formation of undesired by-products.



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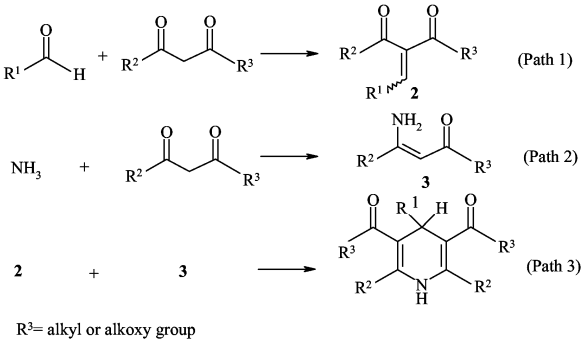
Results and Discussion

The Hantzsch dihydropyridine synthesis provides normally a convenient route to the preparation of all symmetrical dihydropyridines. Although the mechanism for the Hantzsch dihydropyridine synthesis has been followed by NMR [24], the known mechanism for this reaction consists of three reaction paths, which occur simultaneously (Scheme 1): a) the Knoevenagel condensation between aliphatic or aromatic aldehyde with a 1,3-dicarbonyl compound yields an alkylidene- or arylidene-1,3-dicarbonyl compound (path 1); b) the condensation between ammonia and a 1,3-dicarbonyl compound leading to the β-amino-a,β-unsaturated carbonyl compound (path 2); c) the reaction between both condensation products leading to the formation of a 1,4-dihydropyridine (path 3).



Scheme 1.

For the formation of 1,4-dihydropyridines unsymmetrically substituted at 3- and 5-positions it is important to select one of the two different 1,3-dicarbonyl compounds for use in path 1 or path 2 to increase the yields of both reaction paths and especially the yield of dihydropyridine in path 3. Since the formation of symmetrical dihydropyridines has been observed during the reaction path 3 [10, 16], we have tried to synthesise some new and also some known 1,4-dihydropyridines which have a carboethoxy group and an acetyl group in 3- and 5-positions, respectively. It should be noted that in many reports on the preparation of unsymmetrical 1,4-dihydropyridines, the formation of symmetrical dihydropyridines was not mentioned [10–21]. At first, as a test experiment, we have tried the synthesise ethyl 5-acetyl-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (**1f**) in two different ways (Scheme 2).

The data shown in Scheme 2 indicated that the results obtained according to the procedure A are better, therefore, this procedure has been chosen for the preparation of all unsymmetrical dihydropyridines in this work. The preparation of benzylidene intermediates was successful only in the cases of **4a**–**e**, which were isolated and fully characterized. But in the cases of **4f**–**l**, since the reaction in path 4 was not completed and the yields were low, ethyl 3-aminocrotonate (**5**) was added to the reaction mixture of path 4 after it had been refluxed before for 4 h. Table 1 shows the yields of **4a**–**e** and **1a**–**e**.

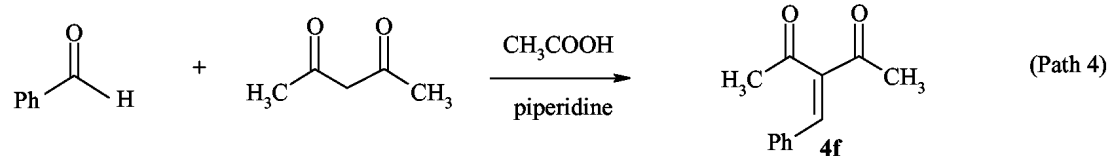
Table 1. Isolated yields of **4a**–**e** and **1a**–**e**.

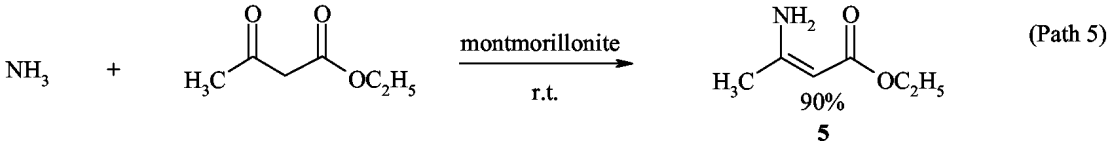
R-Substituent	4			1		
		Yield (%)	Time (h)		Yield (%)	Time (h)
2-NO_2-C_6H_4	**a**	90	0.75	**a**	42	13
3-NO_2-C_6H_4	**b**	70	1.5	**b**	40	15
3,4-$(CH_3O)_2$-C_6H_3	**c**	75	5	**c**	45	20
5-methyl-2-furyl	**d**	72	1.5	**d**	40	15
3-(CH_3O)-4-(OH)-C_6H_3	**e**	65	2	**e**	34	15

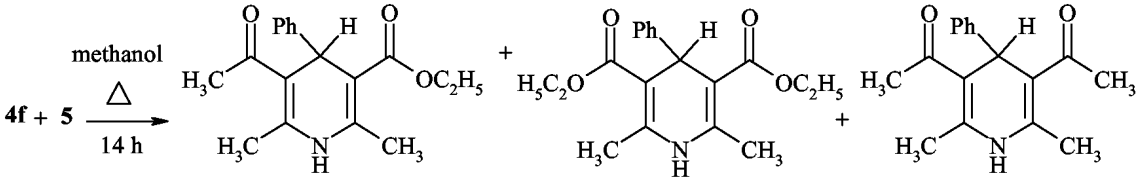
Formation of symmetrically substituted dihydropyridines, namely 1,4-dihydropyridine-3,5-diester **6** and 3,5-diacetyl-1,4-dihydropyridine **7** has been observed in some of our reactions (Table 2). These products can be obtained by a retro Michael process of the reaction intermediate followed by condensation of enaminoester **5** or enaminoketone **9** with the 2-benzylidene-1,3-dicarbonyl compound **4** or **8** to the symmetrical dihydropyridines. Formation of symmetrical dihydropyridine ester has been observed during the synthesis of unsymmetrical dihydropyridine ester [16]. The authors explain that the transformation of the benzylidene alkyl ester (with bulky substituent) to the benzylidene methyl ester according to the retro Michael process favors the formation of less hindered compound, which leads to the formation of symmetrical dihydropyridine methyl ester.

IR, ^{1}H NMR, MS and UV data gave useful information about the structural assignment of unsymmetrical 1,4-dihydropyridines (**1a**–**l**). This was supported by the following observations: a) A NH and two different CO absorption bands are found in the IR spectra corresponding to the acetyl and ester groups, respectively, and also the presence of dihydropyridine ring. b) The ^{1}H NMR spectra show two different absorptions around $\delta = 2.4$ ppm for the CH_3CO group as singlet and also triplet around 1.3 ppm for the methyl group of the $CO_2CH_2CH_3$ moiety. The interesting point is that due to presence of a chiral center at C-4, the CH_2 moiety of the $CO_2CH_2CH_3$ group is diastereotopic and appears as two quartet of quartets and in most cases as two partially overlapped quartet of quartets. c) The

Procedure A:







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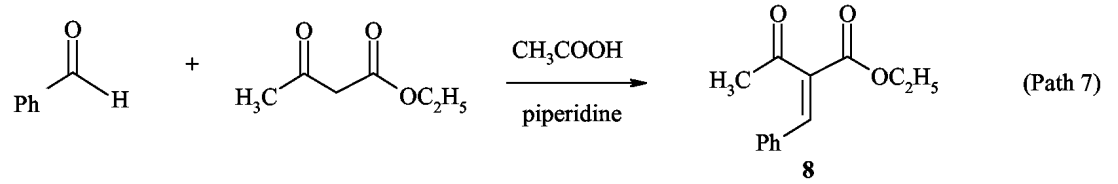

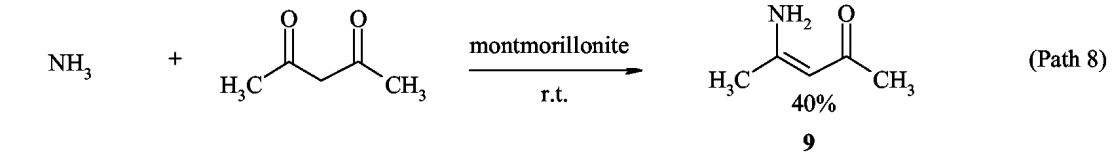

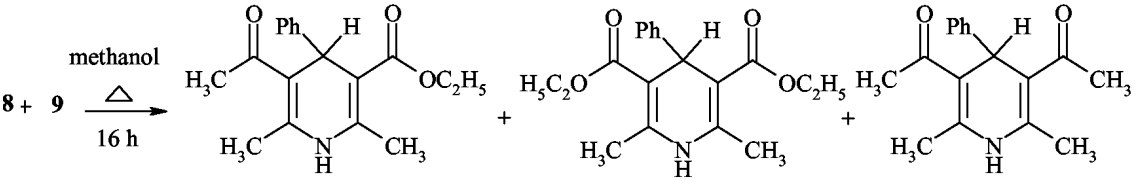

Scheme 2.

R	Unsymmetrical DHP (%)		Symmetrical DHP-Ester (%)		Symmetrical DHP-Keto (%)		Time (h)
2-NO_2-C_6H_4	**1a**	42	**6a**	trace		–	13
3-NO_2-C_6H_4	**1b**	40		–		–	15
3,4-$(CH_3O)_2$-C_6H_3	**1c**	45	**6c**	trace		–	20
5-Methyl-2-furyl	**1d**	40	**6d**	5	**7d**	7	15
3-(CH_3O)-4-(OH)-C_6H_3	**1e**	34	**6e**	5		–	15
C_6H_5	**1f**	34	**6f**	trace		–	14
4-Cl-C_6H_4	**1g**	24	**6g**	15	**7g**	4	13
4-CH_3-C_6H_4	**1h**	32		–	**7h**	23	12
3-Pyridyl	**1i**	27	**6i**	22		–	16
4-Pyridyl	**1j**	25	**6j**	14		–	15
2-Furyl	**1k**	30	**6k**	trace		–	14
2-Thienyl	**1l**	32	**6l**	trace		–	17

Table 2. Isolated yields of products obtained by preparation of unsymmetrical dihydropyridines.

mass spectra show molecule ion peaks of each compound and also several peaks due to characteristic fragmentation. d) The UV spectra show characteristic absorption above 300 nm for the dihydropyridine ring.

Experimental Section

Melting points were determined using a Stuart Scientific SMP2 capillary apparatus and are uncorrected. IR spectra were recorded from KBr discs on Philips PU 9716. ^{1}H NMR spectra were recorded with a Bruker DRX 500 (500 MHz) instrument. They are reported as follows: Chemical shifts δ, [multiplicity, number of protons, coupling constants J (Hz), and assignment]. Mass spectra were obtained on Sisonn, TRIO 1000, EI-mode at 70 eV. Elemental analysis were run on Euro EA-CHNS analyzer. UV spectra were measured on a Shimadzu UV-160 spectrometer. Preparative layer chromatography (PLC) was carried out on 20×20 cm^2 plates, coated with a 1 mm layer of Merck silica gel PF_{254}, prepared by applying the silica as slurry and drying in air.

*General procedure for the preparation of benzylidene intermediates **4a – e** [25]*

A mixture of the appropriate benzaldehyde (1 mmol) and acetylacetone (0.110 g, 1.1 mmol) was stirred for approximately 1 min at 65 °C in a pre-heated oil bath until a homogeneous viscous liquid has been obtained. After that piperidine (0.015 g, 0.18 mmol) and glacial acetic acid (0.011 g, 0.18 mmol) were added to the stirred mixture and the progress of reaction was followed by TLC. After the reaction was completed, the mixture was cooled to room temperature, ether was added and the solid products were recrystallized from an appropriate solvent.

Physical and spectroscopic data

3-(2-Nitrobenzylidene)pentane-2,4-dione (**4a**): Recrystallized from petroleum ether/ethyl acetate (12 : 1). – M. p. 74 – 75 °C (lit. [14]: m. p. 63 – 63.5 °C). – UV/vis (MeOH): $\lambda_{max}(\lg\varepsilon) = 242$ nm (3.87). – IR (KBr): $\tilde{\nu} = 1697$ and 1662 (CO), 1525 and 1351 (NO_2) cm^{-1}. – MS (EI, 70 eV): m/z (%) = 233(2) [M$^+$], 191(5) [M$^+$-$COCH_2$], 187(58) [M$^+$-NO_2], 173(44), 149(59), 148(43), 131(66), 103(79), 102(28).

3-(3-Nitrobenzylidene)pentane-2,4-dione (**4b**): Recrystallized from petroleum ether/ethyl acetate (5 : 1) – M. p. 95 – 97 °C. – UV/vis (MeOH): $\lambda_{max}(\lg\varepsilon) = 347$ (3.28), 230 nm (3.69) – IR (KBr): $\tilde{\nu} = 1708$ and 1667 (CO), 1528 and 1359 (NO_2) cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.36$ (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 7.53 (s, 1H, vinylic H), 7.64 (m, 1H, 5'-H), 7.76 (d, 1H, J = 7.8 Hz, 6'-H), 8.30 (m_c, 2H, 2'-H and 4'-H). – MS (EI, 70 eV): m/z (%) = 233(84) [M$^+$], 218(88) [M$^+$-Me], 216(96) [M$^+$-OH], 191(66) [M$^+$-$COCH_2$], 190(64) [M$^+$-Ac], 187(16) [M$^+$-NO_2], 186(43), 176(100), 144(41), 131(84), 118(38), 101(88). – $C_{12}H_{11}NO_4$ (233.23): calcd. C 61.80, H 4.75, N 6.01, O 27.44; found C 61.91, H 4.71, N 6.08.

3-(3,4-Dimethoxybenzylidene)pentane-2,4-dione (**4c**): Recrystallized from petroleum ether/ethyl acetate (10 : 1) – M. p. 101 – 102 °C. – UV/vis (MeOH): $\lambda_{max}(\lg\varepsilon) =$ 336 (4.40), 247(4.20), 226 nm (4.15). – IR (KBr): $\tilde{\nu} = 1714$ and 1678 (CO) cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.36$ (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.91 (d, 1H, $J = 8.3$ Hz, 5'-H), 6.96 (d, 1H, $J = 2.0$ Hz, 2'-H), 7.07 (dd, 1H, $J =$ 8.3 Hz and 2.0 Hz, 6'-H), 7.46 (s, 1H, vinylic H). – MS (EI, 70 eV): m/z (%) = 248(92) [M$^+$], 247(63) [M$^+$-H], 233(89) [M$^+$-Me], 217(83) [M$^+$-OMe], 205(77) [M$^+$-Ac], 191(100), 163(75), 148(58). – $C_{14}H_{16}O_4$ (248.28): calcd. C 67.73, H 6.50, O 25.78; found C 67.73, H 6.45.

3-[(5-Methyl-2-furyl)methylene]pentane-2,4-dione (**4d**): Recrystallized from petroleum ether/ethyl acetate (15 : 1). – M. p. 90 – 91 °C. – UV/vis (MeOH): $\lambda_{max}(\lg\varepsilon) = 335$(4.27), 240(3.63), 214 nm(3.64). – IR (KBr): $\tilde{\nu} = 1706$ and 1646 (CO) cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.37$ (br s, 3H, 5'-CH_3), 2.39 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 6.18 (dd, 1H, $J = 3.3$ Hz and 0.8 Hz, 4'-H), 6.73 (d, 1H, $J = 3.3$ Hz, 3'-H), 7.13 (s, 1H, vinylic H). – MS (EI, 70 eV): m/z (%) = 192(97) [M$^+$], 177(95) [M$^+$-Me],

150(43) [M^+-$COCH_2$], 149(76) [M^+-Ac], 135(100), 107(86), 79(76). – $C_{11}H_{12}O_3$ (192.22): calcd. C 68.74, H 6.29, O 24.97; found C 68.84, H 6.29.

3-(4-Hydroxy-3-methoxybenzylidene)pentane-2,4-dione (**4e**): Recrystallized from petroleum ether/ethyl acetate (2 : 1). – M. p. 131 – 132 °C. – UV/vis (MeOH): $\lambda_{max}(\lg\varepsilon) =$ 340(14.30), 249(4.00), 225 nm(3.95). – IR (KBr): $\tilde{\nu} =$ 3377 (OH), 1691 and 1643 (CO) cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): $\delta = 2.36$ (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 6.20 (s, 1H, OH), 6.95 (m_c, 2H, 2'-H and 6'-H), 7.01 (dd, 1H, $J = 8.2$ Hz and 1.8 Hz, 5'-H), 7.44 (s, 1H, vinylic H). – MS (EI, 70 eV): m/z (%) = 234(88) [M^+], 219(83) [M^+-Me], 217(60) [M^+-OH], 203(47) [M^+-OMe], 191(86) [M^+-Ac], 177(97), 149(53), 145(100), 117(64), 105(58). – $C_{13}H_{14}O_4$ (234.25): calcd. C 66.66, H 6.02, O 27.32; found C 66.62, H 5.98.

General procedure for the preparation of unsymmetrical 1,4-dihydropyridines **1a** – **l**

A mixture of ethyl 3-aminocrotonate [26] (0.129 g, 1 mmol) and pure benzylidene **4a** – **e** (1 mmol) or the reaction mixture of not completed benzylidene reaction and glacial acetic acid (0.009 g, 0.15 mmol) in methanol (5 ml) was refluxed with stirring under protection from light for the time given in Table 3. The solvent was evaporated, the residue was dissolved in ethyl acetate and cooled in a refrigerator. The precipitated products were purified either by recrystallization or column chromatography.

Ethyl-5-acetyl-2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (**1a**): Recrystallized from petroleum ether/ethyl acetate (15 : 1). – M. p. 175 – 176 °C (lit. [14]: m. p. 175 – 175.4 °C). – UV/vis (MeOH): $\lambda_{max}(\lg\varepsilon) =$ 366(3.72), 250 nm(4.22). – IR (KBr): $\tilde{\nu} =$ 3333 (NH), 1675 ($CO_2C_2H_5$) and 1655 ($COCH_3$) cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.26$ (t, 3H, $J = 7.1$ Hz, $CO_2CH_2CH_3$), 2.32 (s, 3H, 2-CH_3), 2.36 (s, 3H, 6-CH_3), 2.37 (s, 3H, $COCH_3$), 4.04 (qq, 1H, $J = 7.1$ Hz, $CO_2CH_2CH_3$), 4.24 (qq, 1H, $J = 7.1$ Hz, $CO_2CH_2CH_3$), 5.79 (br s, 1H, NH), 5.88 (s, 1H, 4-H), 7.33 (m_c, 1H, 6'-H), 7.52 (m_c, 2H, 4'- and 5'-H), 7.74 (d, 1H, $J = 8.1$ Hz, 3'-H). – MS (EI, 70 eV): m/z (%) = 344(15) [M^+], 328(50) [M^+-O], 327(93) [M^+-OH], 284(69) [M^+-$COCH_2$-H_2O], 282(100), 268(71), 255(49), 254(70), 222(59), 194(49).

Ethyl 5-acetyl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (**1b**): Recrystallized from petroleum ether/ethyl acetate (15 : 1). – M. p. 160 – 161 °C (lit. [19]: m. p. 168 – 169 °C). – UV/vis (MeOH): $\lambda_{max}(\lg\varepsilon) =$ 369(3.49), 245 nm(4.04). – IR (KBr): $\tilde{\nu} =$ 3289 (NH), 1700 ($CO_2C_2H_5$) and 1645 ($COCH_3$) cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.33$ (t, 3H, $J = 7.1$ Hz, $CO_2CH_2CH_3$), 2.24 (s, 3H, 2-CH_3), 2.38 (s, 3H, 6-CH_3), 2.43 (s, 3H, $COCH_3$), 4.21 (two partially overlapped quartet of quartets, 2H, $J = 7.1$ Hz, $CO_2CH_2CH_3$), 5.20 (s, 1H, 4-H), 5.99 (s, 1H, NH), 7.44 (t, 1H, $J = 7.9$ Hz, 5'-H), 7.69 (br d, 1H, $J = 7.7$ Hz, 6'-H), 8.06 (dd, 1H, $J = 8.1$ Hz and 1.2 Hz, 4'-H), 8.15 (br s, 1H, 2'-H). – MS (EI, 70 eV): m/z (%) = 344(10) [M^+], 327(11) [M^+-OH], 315(12) [M^+-Et], 301(15) [M^+-Ac], 271(7) [M^+-CO_2Et], 222(100) [M^+-Ar], 194(71), 106(7). – $C_{18}H_{20}N_2O_5$ (344.37): calcd. C 62.78, H 5.85, N 8.13, O 23.23; found C 62.7, H 5.8, N 7.5.

Ethyl-5-acetyl-4-(3,4-dimethoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3-carboxylate (**1c**): Recrystallized from ethyl acetate/methanol (20 : 1). – M. p. 162 – 163 °C. – UV/vis (MeOH): $\lambda_{max}(\lg\varepsilon) =$ 369(3.88), 230 nm(4.26). – IR (KBr): $\tilde{\nu} =$ 3333 (NH), 1675 ($CO_2C_2H_5$) and 1662 ($COCH_3$) cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.35$ (t, 3H, $J = 7.1$ Hz, $CO_2CH_2CH_3$), 2.21 (s, 3H, 2-CH_3), 2.33 (s, 3H, 6-CH_3), 2.42 (s, 3H, $COCH_3$), 3.87 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.24 (two partially overlapped quartet of quartets, 2H, $J = 7.1$ Hz, $CO_2CH_2CH_3$), 5.02 (s, 1H, 4-H), 5.71 (s, 1H, NH), 6.80 (m_c, 2H, 5'-H and 6'-H), 6.92 (d, 1H, $J = 1.5$ Hz, 2'-H). – MS (EI, 70 eV): m/z (%) = 359(55) [M^+], 344(16) [M^+-Me], 330(45) [M^+-Et], 316(49) [M^+-Ac], 314(19) [M^+-OEt], 296(41), 286(26) [M^+-CO_2Et], 222(100) [M^+-Ar], 194(93), 106(17). – $C_{20}H_{25}NO_5$ (359.43): calcd. C 66.84, H 7.01, N 3.90, O 22.26; found C 66.85, H 7.06, N 3.82.

Ethyl-5-acetyl-2,6-dimethyl-4-(5-methyl-2-furyl)-1,4-dihydropyridine-3-carboxylate (**1d**): Column chromatography with petroleum ether/ethyl acetate (4 : 1). – M. p. 142 – 143 °C. UV/vis (MeOH): $\lambda_{max}(\lg\varepsilon) =$ 362(3.80), 239 nm(4.06). – IR (KBr): $\tilde{\nu} =$ 3307 (NH), 1691 ($CO_2C_2H_5$) and 1646 ($COCH_3$) cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.34$ (t, 3H, $J = 7.1$ Hz, $CO_2CH_2CH_3$), 2.24 (s, 3H, 2-CH_3), 2.35 and 2.36 (6H, two singlets, 6-CH_3, 5'-CH_3), 2.37 (s, 3H, $COCH_3$), 4.22 (qq, 1H, $J = 7.1$ Hz, $CO_2CH_2CH_3$), 4.29 (qq, 1H, $J = 7.1$ Hz, $CO_2CH_2CH_3$), 5.14 (s, 1H, 4-H), 5.81 (m_c, 2H, 3'-H and 4'-H), 5.86 (s, 1H, NH). – MS (EI, 70 eV): m/z (%) = 303(97) [M^+], 288(12) [M^+-Me], 274(47) [M^+-Et], 260(68) [M^+-Ac], 230(93) [M^+-CO_2Et], 222(16), 194(38), 188(45), 149(56), 106(14). – $C_{17}H_{21}NO_4$ (303.36): calcd. C 67.31, H 6.98, N 4.62, O 21.10; found C 67.44, H 7.05, N 4.57.

Ethyl-5-acetyl-4-(4-hydroxy-3-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3-carboxylate (**1e**): Recrystallized from ethyl acetate/methanol (10 : 1). – M. p. 192 – 193 °C. – UV/vis (MeOH): $\lambda_{max}(\lg\varepsilon) =$ 370(3.88), 231 nm(4.18). – IR (KBr): $\tilde{\nu} =$ 3291 (NH), 1677 ($CO_2C_2H_5$) and 1640 ($COCH_3$) cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.35$ (t, 3H, $J = 7.1$ Hz, $CO_2CH_2CH_3$), 2.20 (s, 1H, 2-CH_3), 2.32 (s, 3H, 6-CH_3), 2.41 (s, 3H, $COCH_3$), 3.89 (s, 3H, 3'-OCH_3), 4.22 (two partially overlapped quartet of quartets, 2H, $J = 7.1$ Hz, $CO_2CH_2CH_3$), 4.99 (s, 1H, 4-H), 5.53 (s, 1H, 4'-OH), 5.70 (s, 1H, NH),

6.76 (dd, 1H, $J = 8.2$ Hz and 1.75 Hz, 6'-H), 6.81 (d, 1H, $J = 8.1$ Hz, 5'-H), 6.89 (d, 1H, $J = 1.7$ Hz, 2'-H). – MS (EI, 70 eV): m/z (%) = 345(24) [M^+], 330(10) [M^+-Me], 316(23) [M^+-Et], 302(29) [M^+-Ac], 272(11) [M^+-CO_2Et], 258(11), 222(100), 194(69), 106(8). – $C_{19}H_{23}NO_5$ (345.40): calcd. C 66.07, H 6.71, N 4.06, O 23.16; found C 66.13, H 6.70, N 3.95.

Ethyl-5-acetyl-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (**1f**): Recrystallized from petroleum ether/ethyl acetate (10 : 1). – M. p. 163 – 164 °C (lit. [14]: m. p. 165 – 166 °C). – UV/vis (MeOH): $\lambda_{max}(\lg\varepsilon) =$ 370(3.63), 247 nm(3.91). – IR (KBr): $\tilde{\nu} = 3300$ (NH), 1663 ($CO_2C_2H_5$) and 1640 ($COCH_3$) cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.33$ (t, 3H, $J = 7.1$ Hz, $CO_2CH_2CH_3$), 2.20 (s, 3H, 2-CH_3), 2.32 (s, 3H, 6-CH_3), 2.40 (s, 3H, $COCH_3$), 4.21 (two partially overlapped quartet of quartets, 2H, $J = 7.1$ Hz, $CO_2CH_2CH_3$), 5.05 (s, 1H, 4-H), 5.87 (s, 1H, NH), 7.19 (m_c, 1H, *p*-H), 7.28 (m_c, 4H, *o* and *m*-H). – MS (EI, 70 eV): m/z (%) = 299(5) [M^+], 298(7) [M^+-H], 282 [M^+-Me-H_2] (15), 270(4) [M^+-Et], 254(11) [M^+-Et], 236(50), 226(4) [M^+-CO_2Et], 222 [M^+-Ph](20), 194(20).

Ethyl-5-acetyl-4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3-carboxylate (**1g**): Column chromatography with petroleum ether/ethyl acetate (4 : 1). – M. p. 174 – 175 °C. – UV/vis (MeOH): $\lambda_{max}(\lg\varepsilon) = 369(3.82)$, 245 nm(4.20). – IR (KBr): $\tilde{\nu} = 3341$ (NH), 1700 ($CO_2C_2H_5$) and 1654 ($COCH_3$) cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.33$ (t, 3H, $J = 7.1$ $CO_2CH_2CH_3$), 2.20 (s, 3H, 2-CH_3), 2.33 (s, 3H, 6-CH_3), 2.40 (s, 3H, $COCH_3$), 4.20 (two partially overlapped quartet of quartets, 2H, $J = 7.1$ Hz, $CO_2CH_2CH_3$), 5.03 (s, 1H, 4-H), 5.84 (s, 1H, NH), 7.24 (m_c, 4H, C_6H_4Cl). – MS (EI, 70 eV): m/z (%) = 333(17) [M^+], 304(15) [M^+-Et], 290(17) [M^+-Ac], 260(12) [M^+-CO_2Et], 222(100) [M^+-Ar], 194(64), 149(9), 106(5). – $C_{18}H_{20}ClNO_3$ (333.82): calcd. C 64.77, H 6.04, N 4,20, Cl 10.62, O 14.38; found C 64.06, H 6.23, N 4.02.

Ethyl-5-acetyl-2,6-dimethyl-4-(p-tolyl)-1,4-dihydropyridine-3-carboxylate (**1h)**: Column chromatography with petroleum ether/ethyl acetate (4 : 1). – M. p. 155 °C. – UV/vis (MeOH): $\lambda_{max}(\lg\varepsilon) = 371(3.94)$, 249 nm(4.16).- IR (KBr): $\tilde{\nu} = 3290$ (NH), 1692 ($CO_2C_2H_5$) and 1648 ($COCH_3$) cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.34$ (t, 3H, $J =$ 7.1 Hz, $CO_2CH_2CH_3$), 2.20 (s, 3H, 2-CH_3), 2.31 (s, 3H, 6-CH_3), 2.32 (s, 3H, 4'-CH_3), 2.40 (s, 3H, $COCH_3$), 4.22 (two partially overlapped quartet of quartets, 2H, $J =$ 7.1 Hz, $CO_2CH_2CH_3$), 5.02 (s, 1H, 4-H), 5.87 (s, 1H, NH), 7.08 (d, 2H, $J = 7.8$ Hz, 3'-H and 5'-H), 7.20 (d, 2H, $J = 7.9$ Hz, 2'-H and 6'-H). – MS (EI, 70 eV): m/z (%) = 313(18) [M^+], 312(7) [M^+-H], 298(4) [M^+-Me], 284(15) [M^+-Et], 270(19) [M^+-Ac], 240(13) [M^+-CO_2Et], 222(100) [M^+-Ar], 194(64), 149(10), 106(6). – $C_{19}H_{23}NO_3$ (313.40): calcd. C 72.82, H 7.40, N 4.47, O 15.32; found C 72.98, H 7.47, N 4.45.

Ethyl-5-acetyl-2,6-dimethyl-4-(3-pyridyl)-1,4-dihydropyridine-3-carboxylate (**1i**): Column chromatography with petroleum ether/ethyl acetate (6 : 5). – M. p. 197 – 198 °C, (lit. [20]), m. p. 188 °C. – UV/vis (MeOH): $\lambda_{max}(\lg\varepsilon) =$ 370(3.95), 243 nm(4.39). – IR (KBr): $\tilde{\nu} = 3033$ (NH), 1691 ($CO_2C_2H_5$) and 1662 ($COCH_3$) cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.31$ (t, 3H, $J = 7.1$ Hz, $CO_2CH_2CH_3$), 2.23 (s, 3H, 2-CH_3), 2.35 (s, 3H, 6-CH_3), 2.39 (s, 3H, $COCH_3$), 4.19 (two partially overlapped quartet of quartets, 2H, $J = 7.2$ Hz, $CO_2CH_2CH_3$), 5.08 (s, 1H, 4-H), 6.69 (s, 1H, NH), 7.24 (dd, 1H, $J = 7.5$ Hz and 4.9 Hz, 5'-H), 7.70 (d, 1H, $J = 7.7$ Hz, 4'-H), 8.43 (d, 1H, $J = 3.9$ Hz, 6'-H), 8.57 (s, 1H, 2'-H). – MS (EI, 70 eV): m/z (%) = 300(8) [M^+], 299(12) [M^+-H], 285(3) [M^+-Me], 271(13) [M^+-Et], 257(9) [M^+-Ac], 227(7) [M^+-CO_2Et], 222(100) [M^+-Ar], 194(62), 106(9). – $C_{17}H_{20}N_2O_3$ (300.36): calcd. C 67.98, H 6.71, N 9.33, O 15.98, found C 67.69, H 6.68, N 9.25.

Ethyl-5-acetyl-2,6-dimethyl-4-(4-pyridyl)-1,4-dihydropyridine-3-carboxylate (**1j**): Column chromatography with petroleum ether/ethyl acetate (6 : 5). – M. p. 168 – 169 °C. – UV/vis (MeOH): $\lambda_{max}(\lg\varepsilon) = 370(4.21)$, 242 nm(4.65). – IR (KBr): $\tilde{\nu} = 3162$ (NH), 1643 ($CO_2C_2H_5$) and 1632 ($COCH_3$) cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): $\delta_H = 1.33$ (t, 3H, $J = 7.0$ Hz, $CO_2CH_2CH_3$), 2.22 (s, 3H, 2-CH_3), 2.36 (s, 3H, 6-CH_3), 2.42 (s, 3H, $COCH_3$), 4.21 (two partially overlapped quartet of quartets, 2H, $CO_2CH_2CH_3$), 5.11 (s, 1H, 4-H), 6.06 (s, 1H, NH), 7.23 (d, 2H, $J = 4.6$ Hz, 3'-H and 5'-H), 8.50 (d, 2H, $J = 4.6$ Hz, 2'-H and 6'-H). – MS (EI, 70 eV): m/z (%) = 300(14) [M^+], 271(9) [M^+-Et], 257(5) [M^+-Ac], 222(100) [M^+-Ar], 194(62), 149(5), 106(9). – $C_{17}H_{20}N_2O_3$ (300.36): calcd. C 67.98, H 6.71, N 9.33, O 15.98; found C 67.21, H 7.08, N 9.03.

Ethyl-5-acetyl-4-(2-furyl)-2,6-dimethyl-1,4-dihydropyridine-3-carboxylate (**1k**): Recrystallized from petroleum ether/ethyl acetate (10 : 1). – M. p. 116 – 117 °C (lit. [21]: m. p. 118 – 120 °C). – UV/vis (MeOH): $\lambda_{max}(\lg\varepsilon) =$ 361(4.09), 244 nm(4.34). – IR (KBr): $\tilde{\nu} = 3231$ (NH), 1676 ($CO_2C_2H_5$) and 1660 ($COCH_3$) cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.33$ (t, 3H, $J = 7.1$ Hz, $CO_2CH_2CH_3$), 2.34 (s, 3H, 2-CH_3), 2.36 (s, 6H, 6-CH_3 and $COCH_3$), 4.24 (two partially overlapped quartet of quartets, 2H, $J = 7.1$, $CO_2CH_2CH_3$), 5.20 (s, 1H, 4-H), 5.96 (d, 1H, $J = 2.7$ Hz, 3'-H), 6.08 (s, 1H, NH), 6.26 (dd, 1H, $J = 2.8$ Hz and 2.0 Hz, 4'-H), 7.28 (d, 1H, $J = 1.7$ Hz, 5'-H). – MS (EI, 70 eV): m/z (%) = 289(69) [M^+], 288(3) [M^+-H], 274(7) [M^+-Me], 260 [M^+-Et] (85), 247(9) [M^+-$COCH_2$], 246(100) [M^+-Ac], 244(28) [M^+-OEt], 222(14) [M^+-Ar], 218(38), 194(37), 174(48), 149(47). – $C_{16}H_{19}NO_4$ (289.33): calcd. C 66.42, H 6.62, N 4.84, O 22.12; found C 66.26, H 6.60, N 4.84.

Ethyl-5-acetyl-2,6-dimethyl-4-(2-thienyl)-1,4-dihydropyridine-3-carboxylate (**1l**): Recrystallized from petroleum ether/ethyl acetate (10 : 1). – M. p. 134 – 135 °C. – UV/vis (MeOH): $\lambda_{max}(\lg\varepsilon) = 363(3.80)$, 238 nm(4.15). – IR (KBr): $\tilde{\nu} = 3264$ (NH), 1675 ($CO_2C_2H_5$) and 1643 ($COCH_3$) cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.39$ (t, 3H, $J =$ 7.1 Hz, $CO_2CH_2CH_3$), 2.26 (s, 3H, 2-CH_3), 2.34 (s, 3H, 6-CH_3), 2.42 (s, 3H, $COCH_3$), 4.28 (two partially overlapped quartet of quartets, 2H, $J = 7.1$, $CO_2CH_2CH_3$), 5.35 (s, 1H, 4-H), 6.07 (s, 1H, NH), 6.84 (d, 1H, $J =$ 3.4 Hz, 3'-H), 6.91 (dd, 1H, $J = 5.0$ and 3.5 Hz, 4'-H), 7.13 (dd, 1H, $J = 5.6$ and 1.1 Hz, 5'-H). – MS (EI, 70 eV): m/z (%) = 305(75) [M^+], 304(9) [M^+-H], 277(11) [M^+-C_2H_4], 276(92) [M^+-Et], 262(100) [M^+-Ac], 232(38) [M^+-CO_2Et], 222(31) [M^+-Ar], 218(45), 194(89), 149(23). – $C_{16}H_{19}NO_3S$ (305.40): calcd. C 62.93, H 6.27, N 4.59, O 23.37, S 10.50; found C 62.86, H 6.32, N 4.61, S 10.37.

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[1] A. Hantzsch, Ber. Dtsch. Chem. Ges. **17**, 1315 (1884); ibid. **18**, 1774 and 2379 (1885).
[2] C. Beyer, Ber. Dtsch. Chem. Ges. **24**, 1662 (1891).
[3] E. Knoevenagel, W. Ruschhaupt, Ber. Dtsch. Chem. Ges. **31**, 1025 (1898).
[4] U. Eisner, J. Kuthan, Chem. Rev. **72**, 1 (1972).
[5] D. M. Stout, A. I. Meyers, Chem. Rev. **82**, 223 (1982).
[6] J. Kuthan, A. Kurfürst, Ind. Eng. Chem. Prod. Res. Dev. **21**, 191 (1982).
[7] M. L. Bennasai, E. Zulaica, Y. Alonso, L. Mata, E. Molins, J. Bosch, Chem. Commun. 1166 (2001), and references cited therein
[8] S. Goldmann, J. Stoltefuss, Angew. Chem. Int. Ed. Engl. **30**, 1559 (1991).
[9] M. Fujii, K. Nakamura, A. Ohno, Trends Heterocycl. Chem. **5**, 17 (1997).
[10] P. Naab, W. Lange, W. Teller, Eur. Pat. Appl. EP 319814 (1989); Chem. Abstr. **122**, 7381 (1990).
[11] A. Gustavsson, A. Kallstrom, S. Palma, PCT Int. App. WO 9725313 (1997); Chem. Abstr. **127**, 149077 (1997).
[12] R. Desai, D. Aguilar, M. Aslam, N. Gallegos, PCT Int. App. WO 9724326 (1997); Chem. Abstr. **127**, 135726 (1997).
[13] W. Teller, W. Koebernick, A. Haaf, P. Naab, M. Preiss, Ger. Offen DE 3312216 (1984); Chem. Abstr. **102**, 95543 (1985).
[14] J. A. Berson, E. Brown, J. Am. Chem. Soc. **77**, 444 (1955).
[15] R. Alajarin, P. Jordán, J. J. Vaquero, J. Alvarez-Builla, Synthesis 389 (1995).
[16] R. Alajarin, J. J. Vaquero, J. Alvarez-Builla, M. Pastor, C. Sunhel, M. F. de Gasa-Juana, J. Priego, P. R. Statkow, J. Sanz-Aparicio, I. Fonseca, J. Med. Chem. **38**, 2830 (1995).
[17] M. Mahendra, B. H. Doreswamy, M. A. Sridhar, J. Shashidhara Prasad, G. R. Patel, J. A. Patel, A. Shah, J. Chem. Crystallog. **34**, 441 (2004).
[18] N. Tewari, N. Dwivedi, R. P. Tripathi, Tetrahedron Lett. **45**, 9011 (2004).
[19] A. P. Philips, J. Am. Chem. Soc. **73**, 2248 (1951).
[20] F. Bossert, W. Vater, Ger. Offen DE 2003146 (1971); Chem. Abstr. **75**, 98457 (1971).
[21] D. Ilavsky, V. Milata, Collect. Czech. Chem. Commun. **61**, 1233(1996).
[22] H. R. Memarian, M. Bagheri, D. Döpp, Monatsh. Chem. **135**, 833 (2004), and references cited therein.
[23] H. R. Memarian, I. Mohammadpoor-Baltork, M. Javaheri, J. Chin. Chem. Soc., in press.
[24] A. R. Katritzky, D. L. Ostercamp, T. L. Yousaf, Tetrahedron **42**, 5729 (1986).
[25] Benzylidene intermediates have been prepared by adoption of the reported procedure: W. H. Correa, J. L. Scott, Green Chem. **3**, 296 (2001).
[26] Ethyl 3-aminocrotonate has been prepared according to the known procedure: M. E. F. Braibante, H. S. B. Braibante, L. Missio, A. Andricopulo, Synthesis 898 (1994).