Synthesis of methyl 4-aryl-6-methyl-4,7-dihydro-1*H*-pyrazolo-[3,4-*b*]pyridine-5-carboxylates from methyl 4-aryl-6-methyl-2-oxo-1,2,3,4-tetrahydropyridine-5-carboxylates

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Novel methyl 4,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylates 3a–e have been prepared in a two step procedure from the readily available 2-oxo-1,2,3,4-tetrahydropyridine-5-carboxylates 1a–e by treatment with the Vilsmeier–Haack reagent. Further treatment of the novel *o*-chloroformyl substituted methyl 1,4-dihydropyridine-5-carboxylates 2a–e with hydrazine affords the corresponding methyl pyrazolo[3,4-*b*]pyridine-5-carboxylates in good yields. Semiempirical calculations reveal a favoured geometry with a boat conformation in the dihydropyridine system and a planar pyrazole ring.

Introduction

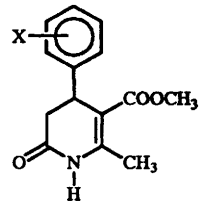
Much effort has been devoted to the synthesis of 1,4-dihydropyridines (1,4-DHPs) due to their calcium antagonist effect useful in the treatment of cardiovascular diseases.[1] The presence of an aryl group on C-4 and ester groups on C-3 and C-5 of the 1,4-DHP ring has proved to be a fundamental requirement for the pharmacological activity.[2] The presence of the five membered lactone fused to the 1,4-DHP ring results in a promotion of the calcium ions into the intracellular space thus exhibiting an agonist effect.[3]

In spite of the widely developed chemistry of the 1,4-DHPs,[4] much less is known about the synthesis of 1,4-DHPs bearing substituents other than hydrogen atoms or alkyl groups at C-2 and C-6.[5]

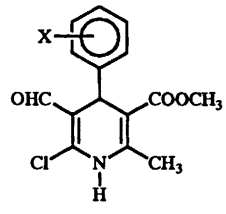
Recently, we have reported the synthesis and conformational study of acridine derivatives related to 1,4-DHPs[6] and other difuro[3,4-*b*:3′,4′-*e*]pyridines related to other structures showing cardiotonic properties.[7] In this paper we report the synthesis of novel 4-aryl-2-chloro-3-formyl-6-methyl-5-methoxycarbonyl 1,4-DHPs **2** from 4-aryl-6-methyl-2-oxo-1,2,3,4-tetrahydropyridine-5-carboxylates **1** by reaction with the Vilsmeier–Haack reagent. The chloro-substituted 1,4-DHPs **2** proved to be excellent candidates for further transformations into other heterocyclic-fused 1,4-DHPs. Thus, methyl 4-aryl-6-methyl-4,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylates **3** were easily prepared from **2** by treatment with hydrazine hydrate.

Pyrazolo[3,4-*b*]pyridines have been previously prepared in a multistep reaction involving the formation of either the pyrazole or pyridine ring and the further construction of the other heterocyclic system.[8] In addition to the effect on the calcium channels, pyrazolo[3,4-*b*]pyridines proved to be active against Gram positive and negative bacteria,[9] as cholesterol formation-inhibiting compounds,[10] pesticides, aldose reductase inhibitors and for the treatment of cataracts associated with diabetes.[11]

Although some pyrazolo[3,4-*b*]pyridines have been prepared from 2-chloropyridines bearing a carbohydrazide group[12] or a dichloromethyl function on C-3 as a masked formyl group,[13] the procedure now reported is, to the best of our knowledge, a new approach to the synthesis of substituted pyrazolo[3,4-*b*]pyridines **3**.



1



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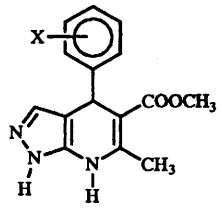

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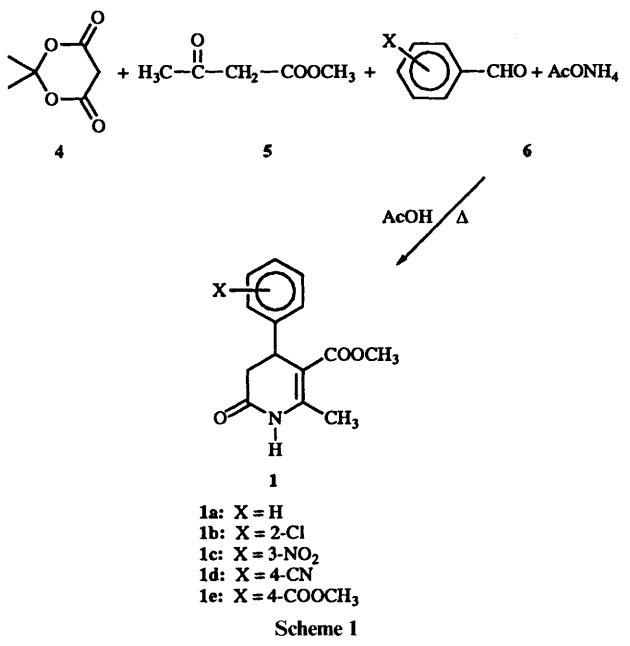
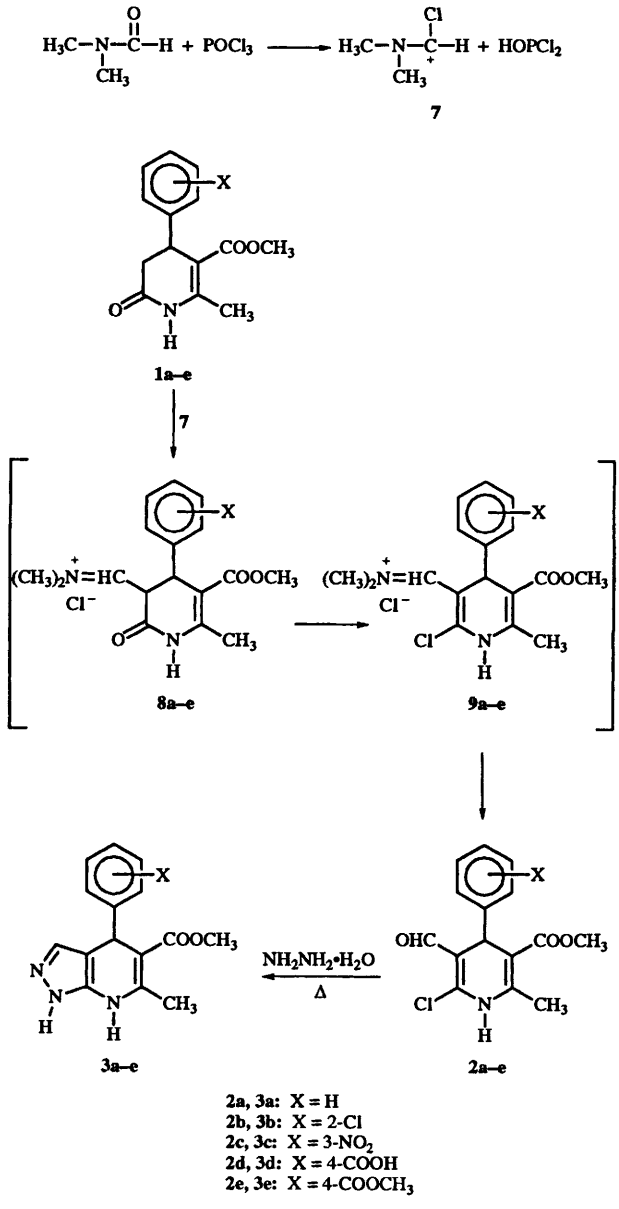
Results and discussion

Methyl 2-oxo-1,2,3,4-tetrahydropyridine-5-carboxylates **1a–e** were prepared from Meldrum's acid by following a modified procedure to that previously reported (Scheme 1).[14] Thus, equimolar amounts of Meldrum's acid **4**, methyl acetoacetate **5** and the corresponding substituted aromatic aldehyde **6** were refluxed in the presence of ammonium acetate, in acetic acid as the solvent. In addition to the catalytic effect, the higher boiling point of this solvent facilitates the decarboxylation step resulting in significantly higher yields than those previously reported.[14] It is worth mentioning that the acidic character of Meldrum's acid **4** (pK_a = 9.97), higher than the β-keto ester **5** (pK_a = 11.0), is responsible for blocking formation of the 1,4-DHP ring. 1,4-Dihydropyridines **2a–e** were prepared from **1a–e** by reaction with the Vilsmeier–Haack reagent ($POCl_3$, DMF).[15] The reaction was monitored by TLC and the final compounds **2a–e** were obtained in good yields.

The reaction was shown to proceed through a mechanism involving several steps (Scheme 2). It begins with the formation of the electrophilic reagent **7** from *N*,*N*-dimethylformamide and



Scheme 1



Scheme 2

phosphorous oxychloride.[16] Reaction of **7** with the enolic form of the 2-pyridone **1** could proceed through the intermediate **8**,[5] followed by reaction with $POCl_3$ to give the chloro-derivative intermediate **9**. Further basic hydrolysis by treatment with sodium acetate leads to compounds **2a–e** as pale yellow stable crystalline solids. It is worthy of mention that compound **1d** (X = CN) undergoes the Vilsmeier–Haack reaction to form compound **2d** in which the cyano group on the aromatic ring is fully hydrolysed to the corresponding carboxylic acid.

Compounds **2a–e** showed the presence of the NH group in the IR spectra (3280–3220 cm^{-1}) and also in the ^1H NMR spectra as a singlet at δ 10.5–10.4. The 1,4-DHP proton on C-4 appears as a singlet at δ 5.3–4.9. The push–pull effect present in the olefinic double bonds of the 1,4-DHP ring is responsible for the higher δ values found in the ^{13}C NMR spectra for the C-2 and C-6 atoms and the lower δ values for the C-5 and C-3 atoms. This finding has been previously observed in other related molecules.[6]

Pyrazolo[3,4-*b*]pyridines **3a–e** were formed from compounds **2a–e** by treatment with hydrazine hydrate in ethanol as solvent (Scheme 2). Compounds **3a–e** were thus obtained as stable high melting point crystalline solids in good yields (see Experimental section).

The reported procedure, utilizing little-known *o*-chloroformyl 1,4-DHP derivatives, is a new and expeditious procedure for the synthesis of these compounds containing an unsubstituted pyrazole ring. The reaction takes place by the attack of the nucleophilic nitrogen either at the chloro or formyl groups, followed by further heterocyclization to the bicyclic system. Some evidence suggests that the first step involves substitution of the amino group for the chlorine atom.[5]

The novel compounds **3a–e** were fully characterized by their analytical and spectroscopic data. Thus, the NH stretching vibration appears at *ca.* 3280 cm^{-1} in the IR spectra, while the protons on the pyrazole and pyridine rings appear as two singlets at δ 8.3–8.2 and 5.4–5.2 respectively (see Experimental section).

The determination of the favoured conformation has been used to account for the pharmacological effect of the 1,4-DHP ring.[2] Theoretical calculations and X-ray data have also supported these findings.[17] We have carried out the determination of the favoured geometry for compound **3a** using the quantum chemical AM1 method (Fig. 1). The 1,4-DHP ring presents a boat conformation with C-4 and the nitrogen atoms out of the plane defined by the olefinic carbons of the pyridine ring. The phenyl substituent on C-4 is in a pseudoaxial position bisecting the dihydropyridine ring. The pyrazole ring is essentially planar and forms a dihedral angle with the pyridine ring as is shown in Table 1. The calculated heat of formation for

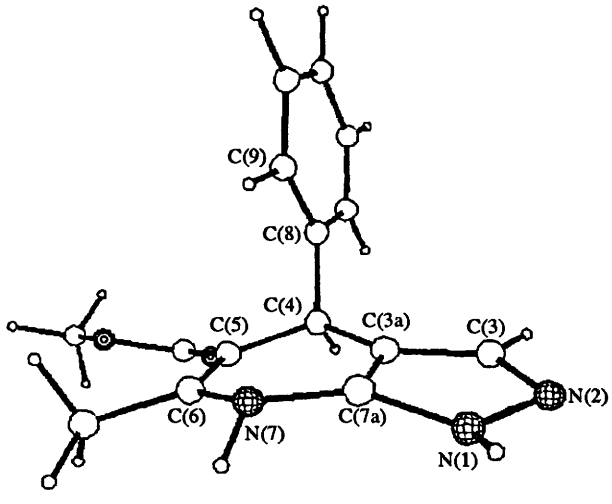


Fig. 1 Minimum energy conformation for compound **3a**

Table 1 Relevant geometric data (°) for compound **3a**

C(6)–N(7)–C(7a)	115.00
C(5)–C(4)–C(3a)	109.51
C(5)–C(4)–C(8)–C(9)	54.08
C(6)–C(5)–C(3a)–C(7a)	−0.52
C(6)–C(7a)–C(3a)–C(4)	9.02
C(5)–C(3a)–C(7a)–N(7)	8.55
C(5)–C(3a)–C(7a)–N(1)	168.71
C(6)–C(7a)–C(3a)–C(3)	−171.12
C(3a)–C(3)–N(2)–N(1)	3.25
C(3a)–C(7a)–N(1)–N(2)	4.89
C(7a)–N(1)–N(2)–C(3)	−5.06

Table 2 Net atomic charges (in e) calculated for the olefinic carbons of compound **3a**

Olefinic carbon	Charge
C(3a)	−0.211
C(5)	−0.213
C(6)	0.105
C(7a)	0.102

the favoured conformation of compound **3a** was 29.74 kcal mol^{-1} with a theoretical dipole moment of 4.51 D.†

The atomic charges calculated for the olefinic carbons are shown in Table 2. The values obtained confirm the push–pull effect observed by ^{13}C NMR spectroscopy. The C-3a and C-5 atoms show a high electron density whereas C-6 and C-7a reveal an electron-deficient character.

In conclusion, we have carried out the synthesis of novel 4,7-dihydropyrazolo[3,4-*b*]pyridines **3a–e** from the readily available methyl 2-oxo-1,2,3,4-tetrahydropyridine-5-carboxylates **1a–e** by the Vilsmeier–Haack reaction and subsequent treatment with hydrazine in good overall yield. The novel 1,4-DHPs bearing the chlorine and formyl group proved to be useful intermediates for the synthesis of other pyridine-fused heterocycles. Theoretical calculations, performed on compound **3a**, show a favoured geometry with a planar pyrazole ring and a boat conformation for the 1,4-DHP system.

Experimental

Melting points were determined in capillary tubes in an Electrothermal C14500 apparatus and are uncorrected. The NMR spectra were recorded on a Bruker AC spectrometer [250 MHz (^1H) and 62.0 MHz (^{13}C)]. Chemical shifts are given as δ values against tetramethylsilane as the internal standard and J values are given in Hz. The IR spectra were measured with a Bruker IRS48 instrument as potassium bromide pellets. Mass spectra were obtained with a Hewlett Packard 5890 machine. Microanalyses were performed by the Servicio de Microanálisis of Universidad Complutense de Madrid. The reactions were monitored by TLC performed on silica gel plates (Merck $60F_{250}$) and using benzene–methanol (8:2) as the eluent.

Meldrum's acid, methyl acetoacetate, ammonium acetate, *N*,*N*-dimethylformamide, phosphorus oxychloride, sodium acetate and hydrazine hydrate were obtained from commercial sources (Aldrich and Merck) and were used without further purification. Aromatic aldehydes were distilled before use. The geometry optimization was carried out with the semiempirical AM1 method by using the MOPAC molecular orbitals set. Previously, the molecular geometry was optimized by using Allinger's Molecular Mechanics with PCMODEL program. Calculations were performed on a PC 486/33 computer.

† 1 cal = 4.184 J; 1 D ≈ 3.335 64 × 10^{-30} C m.

Methyl 4-aryl-6-methyl-2-oxo-1,2,3,4-tetrahydropyridine-5-carboxylate 1

General procedure. A mixture of the appropriate aromatic aldehyde (40 mmol), Meldrum's acid (40 mmol), methyl acetoacetate (40 mmol) and ammonium acetate (42 mmol) in acetic acid (40 cm^3) was heated at reflux for a variable length of time (10–14 h, monitored by TLC) and then poured into ice–water. The solid that precipitated was collected by filtration. Futher purification was accomplished by recrystallization from ethanol.

Methyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyridine-5-carboxylate 1a. Following the general procedure (reaction time 10 h) gave **1a** (59%), mp 197–198 °C (lit.,[14] 197–198 °C).

Methyl 4-(2-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyridine-5-carboxylate 1b. Following the general procedure (reaction time 10 h) gave **1b** (60%), mp 198–200 °C (Found: C, 60.3; H, 5.2; N, 5.2. $C_{14}H_{14}ClNO_3$ requires C, 60.11; H, 5.04; N, 5.01%); ν_{max}/cm^{-1} 3217 (NH), 1708 (CO, ester), 1687 (C=O) and 1615 (C=C); $\delta_H(CDCl_3)$ 8.81 (1 H, br s, NH), 7.38 (1 H, m), 7.15 (2 H, m), 7.04 (1 H, m), 4.69 (1 H, dd, H-4, J 8.3 and 1.7, X part of ABX), 3.60 (3 H, s, OCH_3), 2.95 (1 H, dd, H-3, J 16.5 and 8.3, A part of ABX), 2.68 (1 H, dd, H-3′, J 16.5 and 1.9, B part of ABX) and 2.45 (3 H, s, CH_3); $\delta_C(CDCl_3)$ 171.0 (C2), 167.0 (CO_2), 147.9 (C6), 138.2, 133.3, 130.2, 128.3, 127.2 and 127.1 (aryl), 105.9 (C5), 51.5 (OCH_3), 36.3 (C3), 34.9 (C4) and 18.8 (CH_3).

Methyl 6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyridine-5-carboxylate 1c. Following the general procedure (reaction time 10 h) gave **1c** (63%), mp 204–205 °C (lit.,[14] 206–207 °C).

Methyl 4-(4-cyanophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyridine-5-carboxylate 1d. Following the general procedure (reaction time 14 h) gave **1d** (55%), mp 258–259 °C (Found: C, 66.7; H, 5.3; N, 10.5. $C_{15}H_{14}N_2O_3$ requires C, 66.66; H, 5.22; N, 10.36%); ν_{max}/cm^{-1} 3225 (NH), 2225 (CN), 1700 (CO, ester), 1637 (C=O) and 1612 (C=C); $\delta_H(CDCl_3)$ 8.38 (1 H, s, NH), 7.62 (2 H, d, J 8.1), 7.31 (2 H, d, J 8.1), 4.33 (1 H, dd, H-4, J 8.2 and 1.0, X part of ABX), 3.69 (3 H, s, OCH_3), 3.01 (1 H, dd, H-3, J 16.6 and 8.2, A part of ABX), 2.69 (1 H, dd, H-3′, J 16.6 and 1.0, B part of ABX) and 2.46 (3 H, s, CH_3); $\delta_C(CDCl_3)$ 170.2 (C2), 166.9 (CO_2), 147.4 (C6), 147.3, 132.7 (2C), 127.6 (2C) and 118.7 (aryl), 111.0 (CN), 105.8 (C5), 51.6 (OCH_3), 38.0 (C3), 37.6 (C4) and 19.2 (CH_3).

Methyl 4-(4-methoxycarbonylphenyl)-6-methyl-2-oxo-1,2,-3,4-tetrahydropyridine-5-carboxylate 1e. Following the general procedure (reaction time 14 h) gave **1e** (61%), mp 186–188 °C (Found: C, 63.75; H, 5.6; N, 4.6. $C_{16}H_{17}NO_5$ requires C, 63.36; H, 5.65; N, 4.62%); ν_{max}/cm^{-1} 3225 (NH), 1725 (CO, ester), 1637 (C=O) and 1612 (C=C); $\delta_H(CDCl_3)$ 8.91 (1 H, s, NH), 7.97 (2 H, d, J 8.3), 7.27 (2 H, d, J 8.3), 4.32 (1 H, dd, H-4, J 8.2 and 1.0, X part of ABX), 3.91 (3 H, s, OCH_3), 3.66 (3 H, s, OCH_3), 2.98 (1 H, dd, H-3, J 16.5 and 8.2, A part of ABX), 2.69 (1 H, dd, H-3′, J 16.5, 1.0, B part of ABX) and 2.44 (3 H, s, CH_3); $\delta_C(CDCl_3)$ 171.0 (C2), 167.1 (CO_2), 166.1 (CO_2), 147.4 (C6), 147.2 (2C), 130.1, 128.9 and 126.7 (2C) (aryl), 106.1 (C5), 52.0 (OCH_3), 51.4 (OCH_3), 37.8 (C3, C4) and 19.0 (CH_3).

Methyl 4-aryl-6-chloro-5-formyl-2-methyl-1,4-dihydropyridine-3-carboxylate 2

General procedure. A solution of anhydrous *N*,*N*-dimethylformamide (40 mmol, 3.1 cm^3) in dry chloroform (10 cm^3) was added dropwise to a stirred solution of phosphorus oxychloride (40 mmol, 3.85 cm^3) under a nitrogen atmosphere at room temp. After 30 min, a solution of the appropriate methyl 4-aryl-6-methyl-2-oxo-1,2,3,4-tetrahydropyridine-5-carboxylate **1** (10 mmol) in 40 cm^3 of dry chloroform was added. After 18 h stirring at room temperature, a solution of sodium acetate (40 g) in water (60 cm^3) was slowly added. After 0.5 h, the mixture was partitionated between water and chloroform, and the

aqueous phase was extracted with ethyl acetate. The organic phases were mixed and dried with anhydrous magnesium sulfate. The organic solvent was removed *in vacuo* and the solid recrystallized from ethanol.

Methyl 6-chloro-5-formyl-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate 2a. Following the general procedure gave **2a** (80%), mp 181–182 °C (Found: C, 61.9; H, 4.9; N, 4.9. $C_{15}H_{14}ClNO_3$ requires C, 61.76; H, 4.84; N, 4.80%); ν_{max}/cm^{-1} 3225 (NH), 2850 (HCO), 1706 (CO, ester), 1637 (C=O) and 1612 (C=C); δ_H([$^2H_6$]-DMSO) 10.36 (1 H, s, NH), 9.69 (1 H, s, HCO), 7.23–7.12 (5 H, m, Ph), 4.95 (1 H, s, CH), 3.55 (3 H, s, OCH_3) and 2.34 (3 H, s, CH_3); δ_C([$^2H_6$]-DMSO) 186.5 (CHO), 166.6 (CO_2), 145.6 (C6), 142.7 (C2), 145.5, 128.3 (2C), 127.1 (2C) and 126.5 (aryl), 111.2 (C5), 104.5 (C3), 51.1 (OCH_3), 37.6 (C4) and 17.7 (CH_3); *m/z* 291 (M^+, 13%), 216 (32), 214 (100), 182 (14), 154 (6), 118 (7), 115 (6) and 77 (15).

Methyl 6-chloro-4-(2-chlorophenyl)-5-formyl-2-methyl-1,4-dihydropyridine-3-carboxylate 2b. Following the general procedure gave **2b** (82%), mp 197–198 °C (Found: C, 55.3; H, 4.1; N, 4.4. $C_{15}H_{13}Cl_2NO_3$ requires C, 55.23; H, 4.02; N, 4.29%); ν_{max}/cm^{-1} 3250 (NH), 2850 (HCO), 1712 (CO, ester), 1637 (C=O) and 1612 (C=C); δ_H([$^2H_6$]-DMSO) 10.35 (1 H, s, NH), 9.65 (1 H, s, HCO), 7.30–7.19 (4 H, m, Ph), 5.27 (1 H, s, CH), 3.49 (3 H, s, OCH_3) and 2.26 (3 H, s, CH_3); δ_C([$^2H_6$]-DMSO) 186.4 (CHO), 166.5 (CO_2), 144.9 (C6), 143.4 (C2), 143.3, 131.9, 131.3, 129.2, 128.0 and 127.2 (aryl), 110.8 (C5), 104.5 (C3), 50.8 (OCH_3), 36.8 (C4) and 17.6 (CH_3); *m/z* 325 (M^+, 5%), 327 (M + 2, 4%), 214 (100), 182 (14), 154 (5) and 139 (7).

Methyl 6-chloro-5-formyl-2-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate 2c. Following the general procedure gave **2c** (75%), mp 213–214 °C (Found: C, 53.6; H, 3.9; N, 8.55. $C_{15}H_{13}ClN_2O_5$ requires C, 53.50; H, 3.89; N, 8.32%); ν_{max}/cm^{-1} 3252 (NH), 2830 (HCO), 1687 (CO, ester), 1625 (C=O), 1600 (C=C), 1525 and 1387 (NO_2); δ_H([$^2H_6$]-DMSO) 10.53 (1 H, s, NH), 9.67 (1 H, br s, HCO), 8.05 (1 H, d), 8.00 (1 H, s), 7.60 (2 H, m), 5.05 (1 H, s, CH), 3.54 (3 H, s, OCH_3) and 2.36 (3 H, s, CH_3); δ_C([$^2H_6$]-DMSO) 186.5 (CHO), 166.2 (CO_2), 147.7 (C6), 147.5 (C2), 146.5, 143.2, 134.0, 129.9, 121.7 and 121.6 (aryl), 110.4 (C5), 103.6 (C3), 51.2 (OCH_3), 37.9 (C4) and 17.9 (CH_3); *m/z* 336 (M^+, 4%), 338 (M + 2, 2), 319 (10), 214 (100), 182 (17), 154 (7) and 118 (8).

Methyl 4-(4-carboxyphenyl)-6-chloro-5-formyl-2-methyl-1,4-dihydropyridine-3-carboxylate 2d. Following the general procedure gave **2d** (73%), mp 263–265 °C (Found: C, 57.4; H, 4.3; N, 4.3. $C_{16}H_{14}ClNO_5$ requires C, 57.24; H, 4.20; N, 4.17%); ν_{max}/cm^{-1} 3225 (NH), 2787 (HCO), 1700 (CO, ester), 1637 (C=O) and 1600 (CO_2H); δ_H([$^2H_6$]-DMSO) 10.41 (1 H, s, NH), 9.69 (1 H, s, HCO), 7.72 (2 H, d), 7.20 (2 H, d), 4.98 (1 H, s, CH), 3.55 (3 H, s, OCH_3) and 2.34 (3 H, s, CH_3); δ_C([$^2H_6$]-DMSO) 186.5 (CHO), 167.8 (CO_2H), 166.5 (CO_2), 145.8 (C6), 142.9 (C2), 148.5, 132.7, 127.6 (2C) and 127.0 (2C) (aryl), 110.7 (C5), 104.1, (C3), 51.2 (OCH_3), 37.7 (C4) and 17.8 (CH_3); *m/z* 335 (M^+, 10), 318 (15), 214 (100), 182 (20), 154 (8) and 118 (6).

Methyl 6-chloro-5-formyl-4-(4-methoxycarbonylphenyl)-2-methyl-1,4-dihydropyridine-3-carboxylate 2e. Following the general procedure gave **2e** (75%), mp 202–204 °C (Found: C, 58.6; H, 4.7; N, 4.4. $C_{17}H_{16}ClNO_5$ requires C, 58.38; H, 4.61; N, 4.00%); ν_{max}/cm^{-1} 3280 (NH), 2787 (HCO), 1706 (CO, ester), 1695 (CO_2CH_3) and 1655 (C=O); δ_H([$^2H_6$]-DMSO) 10.46 (1 H, s, NH), 9.67 (1 H, s, HCO), 7.84 (2 H, d), 7.29 (2 H, d), 5.00 (1 H, s, CH), 3.79 (3 H, s, OCH_3), 3.53 (3 H, s, OCH_3) and 2.34 (3 H, s, CH_3); δ_C([$^2H_6$]-DMSO) 186.5 (CHO), 166.4 (CO_2), 166.0 (CO_2), 146.1 (C6), 143.1 (C2), 150.7, 129.3 (2C), 127.9 and 127.6 (2C) (aryl), 110.5 (C5), 103.8 (C3), 52.0 (OCH_3), 51.1 (OCH_3), 38.0 (C4) and 17.8 (CH_3); *m/z* 349 (M^+, 10%), 318 (20), 214 (100), 182 (15), 154 (6) and 118 (12).

Methyl 4-aryl-6-methyl-4,7-dihydro-1*H*-pyrazolo[3,4-*b*]-pyridine-5-carboxylates 3

General procedure. A mixture of the corresponding dihydropyridine **2** (2 mmol) and hydrazine hydrate 99% (2 mmol) in ethanol (20 cm^3) was heated at reflux for 6 h. The reaction mixture was then cooled to 0 °C and the solid that precipitated was collected by filtration. Further purification was accomplished by recrystallization from ethanol.

Methyl 6-methyl-4-phenyl-4,7-dihydro-1*H*-pyrazolo[3,4-*b*]-pyridine-5-carboxylate 3a. Following the general procedure gave **3a** (61%), mp 278–279 °C (Found: C, 67.0; H, 5.8; N, 15.7. $C_{15}H_{15}N_3O_2$ requires C, 66.90; H, 5.61; N, 15.60%); ν_{max}/cm^{-1} 3283 (NH), 1656 (C=O) and 1631 (C=N); δ_H([$^2H_6$]-DMSO) 10.01 (1 H, s, NH), 9.98 (1 H, s, NH), 8.35 (1 H, s, CH=N), 7.22–7.13 (5 H, m, Ph), 5.18 (1 H, s, CH), 3.55 (3 H, s, OCH_3) and 2.31 (3 H, s, CH_3); δ_C([$^2H_6$]-DMSO) 166.9 (CO_2), 156.4 (C3), 146.2 (C6), 133.0 (C7a), 146.0, 128.0 (2C), 127.2 (2C) and 126.2 (aryl), 107.7 (C3a), 102.5 (C5), 50.8 (OCH_3), 38.4 (C4) and 18.0 (CH_3).

Methyl 4-(2-chlorophenyl)-6-methyl-4,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate 3b. Following the general procedure gave **3b** (60%), mp 268–270 °C (Found: C, 59.6; H, 4.7; N, 13.9. $C_{15}H_{14}ClN_3O_2$ requires C, 59.31; H, 4.65; N, 13.83%); ν_{max}/cm^{-1} 3304 (NH), 1653 (C=O) and 1631 (C=N); δ_H([$^2H_6$]-DMSO) 10.28 (1 H, s, NH), 9.96 (1 H, s, NH), 8.31 (1 H, s, CH=N), 7.33–7.10 (4 H, m, Ph), 5.40 (1 H, s, CH), 3.48 (3 H, s, OCH_3) and 2.24 (3 H, s, CH_3); δ_C([$^2H_6$]-DMSO) 166.8 (CO_2), 156.6 (C3), 145.5 (C6), 133.4 (C7a), 144.6, 131.8, 131.0, 129.1, 127.7 and 127.1 (aryl), 108.0 (C3a), 102.0 (C5), 50.5 (OCH_3), 37.8 (C4) and 17.8 (CH_3); *m/z* 303 (M^+, 8%), 305 (M + 2, 3), 288 (14), 268 (25), 244 (11), 192 (100), 160 (23), 158 (13), 132 (13) and 105 (12).

Methyl 6-methyl-4-(3-nitrophenyl)-4,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate 3c. Following the general procedure gave **3c** (86%) mp 280–281 °C (Found: C, 57.5; H, 4.6; N, 18.0. $C_{15}H_{14}N_4O_4$ requires C, 57.32; H, 4.49; N, 17.83%); ν_{max}/cm^{-1} 3299 (NH), 1654 (C=O), 1631 (C=N), 1529 and 1345 (NO_2); δ_H([$^2H_6$]-DMSO) 10.41 (1 H, s, NH), 9.77 (1 H, s, NH), 8.24 (1 H, s, CH=N), 7.96 (1 H, s), 7.75 (1 H, d), 7.36 (2 H, m), 5.20 (1 H, s, CH), 3.46 (3 H, s, OCH_3) and 2.24 (3 H, s, CH_3); δ_C([$^2H_6$]-DMSO) 166.2 (CO_2), 155.7 (C3), 147.7 (C6), 133.5 (C7a), 147.3, 146.4, 133.3, 129.0, 121.8 and 120.7 (aryl), 106.7 (C3a), 101.1 (C5), 50.4 (OCH_3), 39.3 (C4) and 17.5 (CH_3).

Methyl 4-(4-carboxyphenyl)-6-methyl-4,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate 3d. Following the general procedure gave **3d** (65%), mp 256–258 °C (Found: C, 61.5; H, 5.0; N, 13.7. $C_{16}H_{15}N_3O_4$ requires C, 61.34; H, 4.83; N, 13.41%); ν_{max}/cm^{-1} 3314 (NH), 1662 (CO, ester), 1646 (CO, acid) and 1625 (C=N); δ_H([$^2H_6$]-DMSO) 10.38 (1 H, s, NH), 10.03 (1 H, s, NH), 8.33 (1 H, s, CH=N), 7.70 (2 H, d, *J* 8.1), 7.26 (2 H, d, *J* 8.1), 5.20 (1 H, s, CH), 3.54 (3 H, s, OCH_3) and 2.31 (3 H, s, CH_3); δ_C([$^2H_6$]-DMSO) 167.8 (CO_2H), 166.8 (CO_2), 156.0 (C3), 146.5 (C6), 133.7 (C7a), 149.0, 132.5, 127.3 (2C) and 127.1 (2C) (aryl), 107.3 (C3a), 101.6 (C5), 50.9 (OCH_3), 38.8 (C4) and 18.0 (CH_3); *m/z* 313 (M^+, 2%), 291 (12), 214 (100), 184 (10), 182 (17), 158 (46), 150 (32), 105 (33) and 77 (26).

Methyl 4-(4-methoxycarbonylphenyl)-6-methyl-4,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate 3e. Following the general procedure gave **3e** (60%), mp 295–296 °C (Found: C, 62.6; H, 5.5; N, 12.9. $C_{17}H_{17}N_3O_4$ requires C, 62.38; H, 5.23; N, 12.84%); ν_{max}/cm^{-1} 3287 (NH), 1726 (CO, ester), 1655 (CO, ester) and 1631 (C=N); δ_H([$^2H_6$]-DMSO) 10.37 (1 H, s, NH), 10.10 (1 H, s, NH), 8.31 (1 H, s, CH=N), 7.82 (2 H, d, *J* 8.3), 7.35 (2 H, d, *J* 8.3), 5.22 (1 H, s, CH), 3.80 (3 H, s, OCH_3), 3.53 (3 H, s, OCH_3) and 2.30 (3 H, s, CH_3); δ_C([$^2H_6$]-DMSO) 166.6 (CO_2), 164.8 (CO_2), 151.3 (C3), 146.7 (C6), 133.4 (C7a), 148.3, 129.0 (2C), 127.8 and 127.7 (2C) (aryl), 107.5 (C3a), 101.4 (C5), 51.9 (OCH_3), 50.8 (OCH_3), 39.2 (C4) and 18.2 (CH_3).

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References

1 F. Bossert and W. Vater, *Med. Res. Rev.*, 1989, **9**, 291.
2 S. Goldmann and J. Stoltefuss, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1559.
3 M. Schramm, G. Thomas, R. Towart and G. Franckowiak, *Nature*, 1983, **303**, 535; V. Rose, *Arch. Pharm. (Weinheim, Ger.)*, 1990, **323**, 281.
4 J. Kuthan and A. Kurfurst, *Ind. Eng. Chem. Prod. Res. Dev.*, 1982, **21**, 191.
5 A. Guzman, M. Romero, A. Maddox and J. Muchowski, *J. Org. Chem.*, 1990, **55**, 5793.
6 N. Martín, M. Quinteiro, C. Seoane, J. L. Soto, A. Mora, M. Suárez, E. Ochoa, A. Morales and J. R. del Bosque, *J. Heterocycl. Chem.*, 1995, **32**, 235.
7 N. Martín, J. L. Segura, C. Seoane, J. L. Soto, M. Morales and M. Suárez, *Liebigs Ann. Chem.*, 1991, 827.
8 G. P. Ellis, *Synthesis of Fused Heterocycles*, Wiley, 1992, vol. 47, part 2.
9 A. M. El-Dean, A. A. Aralla, T. A. Mohamed and A. A. Geies, *Z. Naturforsch., Teil B*, 1991, **46**, 541 (*Chem. Abstr.*, 1991, **115**, 49498a).
10 Y. Fujikawa, M. Suzuki, H. Iwasaki, M. Sakashita and M. Kitahara, *Eur. Pat. Appl.*, EP 339 358, 1989 (*Chem. Abstr.*, 1990, **113**, 23903n).
11 A. Abdel Hafez, I. Awad and R. Ahmed, *Collect. Czech. Chem. Commun.*, 1993, **58**, 1198.
12 P. Bellani, E. Lauria and G. Zoni, *Farmaco, Ed. Sci.*, 1971, **26**, 872.
13 M. H. Elnagdi, M. R. H. Elmoghayer and K. U. Sadek, *Adv. Heterocycl. Chem.*, 1990, **48**, 65.
14 J. Svetlik, I. Goljer and F. Turecek, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1315.
15 G. Hazebroucq, *Ann. Pharm. Fr.*, 1916, **24**, 793 (*Chem. Abstr.*, 1969, **67**, 10854d); C. Jutz, *Adv. Org. Chem.*, 1976, **9**, 225.
16 Y. Kantlemner, *Adv. Org. Chem.*, 1979, **9**, 5; H. Jugie, K. Smith and G. Martin, *J. Chem. Soc., Perkin Trans. 2*, 1975, 925.
17 S. Goldman, L. Born, S. Kazda, B. Pittel and M. Schramm, *J. Med. Chem.*, 1990, **33**, 1413; R. Fossheim, K. Suarteng, A. Mostad, C. Romming, E. Shefter and D. T. Triggle, *J. Med. Chem.*, 1982, **25**, 1229; R. Fossheim, A. Joslyn, A. L. Solo, E. Luchowski, A. Rutledge and D. T. Triggle, *J. Med. Chem.*, 1988, **31**, 300. See also ref. 2 and references cited therein.

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