Article

A Green Approach to the Production of 2-pyridone Derivatives Promoted by Infrared Irradiation

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Abstract. An alternative is presented for promoting a reaction with infrared irradiation to obtain different 4-aryl-3-cyano-5-ethoxycarbonyl-6-methyl-2-pyridone derivatives **9a-k**. The process was carried out with a green approach from the corresponding 4*H*-pyrans, using mild reaction conditions and infrared irradiation as the energy source. In the first stage, the reaction produced 1,2,3,4-tetrahydropyridin-2-one derivatives **8a-k**, followed by an oxidative step to afford the target molecules in good yields. The structure of products **9a-k** was confirmed by FT-IR, ^{1}H NMR and ^{13}C NMR spectroscopic techniques and X-ray diffraction. It was found that the efficiency of the reaction depends on the catalyst and the solvent, as well as on the aldehyde substituents.
Key words: 4*H*-pyrans, rearrangement, 2-pyridones, infrared irradiation, green approach.

Resumen. Se reporta el uso de la irradiación infrarroja como un método de activación alternativa para obtener diferentes derivados 4-aril-3-ciano-5-etoxicarbonil-6-metil-2-piridonas **9a-k** con buenos rendimientos. El proceso se lleva a cabo con un enfoque *verde* a partir de los 4*H*-piranos correspondientes, empleando condiciones de reacción suaves y la irradiación infrarroja como el promotor de la reacción, para producir, en una primera etapa, los derivados 1,2,3,4-tetrahidropiridin-2-onas **8a-k**, seguido por un paso de oxidación, para generar las moléculas objetivo. La estructura de los productos **9a-k** se confirmó por las técnicas espectroscópicas de FT-IR, RMN ^{1}H, RMN [13]C y difracción de rayos X. Se encontró que la eficiencia de la reacción depende del catalizador, del disolvente, así como de los sustituyentes del aldehído.
Palabras clave: 4*H*-piranos, transposición, 2-piridonas, irradiación infrarroja, proceso *verde*.

Introduction

The heterocyclic skeleton containing a nitrogen atom is the basis of many essential pharmaceuticals and of many physiologically active natural products. Molecules containing heterocyclic substructures continue to be attractive targets for synthesis, since they often exhibit diverse and important biological properties. One important type of heterocycle that has shown a variety of biological activity is represented by 2-pyridones [1]. They exhibit a specific phosphodiesterase (PDE3) inhibitory activity and are a good alternative to the use of classic digitalis glycosides, such as amrinone and milrinone (Fig. 1), for acute treatment of congestive heart failure (CHF) [2].

Compounds with similar structural motifs exhibit significant pharmacological properties. For example, compounds **1** and **2** were evaluated for their inhibitory activity on the growth of human HT-29 colon tumor cells [3]. Analogues of **3**, tested for inhibitory activity against thrombin, have proved to have an excellent selectivity against trypsin [4]. Likewise, compound **4** has proved to be a nonsteroidal inhibitor of 5*α*-reductase and can be used for the treatment of benign prostatic hyperplasia (Fig. 1) [5]. Compound **5** has been used for the treatment of seborrheic dermatitis (Fig. 1) [6]. Compound **6** modulates serine hydrolase activity and also inhibits the activity of BuChE or AChE, while stimulating the activity of trypsin [7].

Currently, the preferred method for the preparation of 2-pyridones is the Michael addition of acetonitrile derivatives
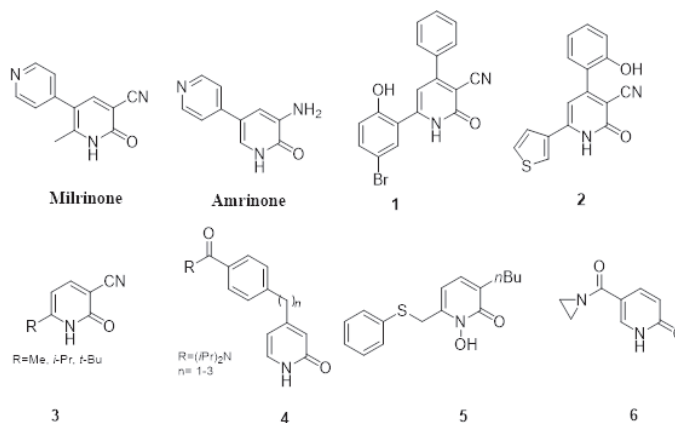

Fig. 1 The 2-pyridone moiety in various compounds with biological activity.

to an appropriate *α,β*-unsaturated carbonyl substrate, and the subsequent hydrolytic cyclization followed by oxidative aromatization [8]. Alternatively, the treatment of *β*-oxo amides under Vilsmeier conditions yields 2-pyridones [9]. Other noteworthy methods have been reported, such as starting from the Blaise reaction intermediate [10], or the cyclization between Baylis-Hillman acetates and enamino esters or nitriles [11]. However, many of the established methods are carried out under harsh reaction conditions. For example, Degani *et al*. reported the

synthesis of 3-cyano-2-pyridones using a guanidine based ionic liquid as catalyst [12].

The modification of fundamental synthetic reactions by using different energy sources represents one of the main focuses of our research group. In order to contribute to the development of environmentally benign methods, several reactions have been studied by our group, including the Knoevenagel condensation [13], the formation of *N*-benzylideneanilines [14], the use of 4*H*-pyran [15], and Diels-Alder reactions [16].

Encouraged by the aforementioned reports on the preparation of active pyridine compounds, we aimed to obtain some 2-pyridone derivatives through a more environmentally friendly method. In the current contribution, we investigated infrared irradiation as a promoter of reactions to produce a variety of 4-aryl and (heteroaryl)-3-cyano-5-ethoxycarbonyl-6-methyl-2-pyridones in good yields.
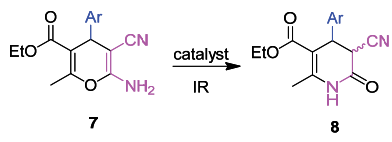
Results and Discussion

The ring opening/closing process of 7a-k

The synthesis of 4*H*-pyrans **7** has been previously reported [15], and we hypothesized that a rearrangement of **7** and the subsequent oxidation reaction would provide a synthetic route for yielding 4-aryl-3-cyano-5-ethoxycarbonyl-6-methyl-2-pyridones **9** under infrared irradiation. It was envisaged that for 4*H*-pyran **7a** a sequential ring opening would be followed by a ring closing process. It was necessary to find a suitable catalyst for this rearrangement, for which purpose *p*-toluenesulfonic acid was initially tested [17], using IR irradiation as the energy source at 90 °C (50 V, OSRAM R-20 bulb, 127 V, 250 W, λ = 1255.6 nm) [18] for 60 min in the absence of solvent. The desired pyridone **8a** was obtained as a mixture of diastereoisomers *trans/cis* in low yield (29%), as observed from the ^{1}H NMR (300 MHz) analysis of the crude reaction mixture (Table 1, entry 1).

The reaction was carried out with different solvents in order to determine their effect. As shown in Table 1, the reaction was performed in CHCl$_3$, THF, CH$_3$CN, dioxane, water and ethanol (entries 2-7) to analyze the catalytic activity of the acid and the medium best suited for the transformation. It was found that the reaction using ethanol as the solvent (Table 1, entry 7) resulted in the highest yields.

It is known that ultrasound can perform chemical transformations [19]. To demonstrate the efficiency and applicability of IR irradiation, we compared its use to that of other sources of energy. Previous reports [17] describe the ring opening followed by ring closure during the hydration and dehydration of the 4*H*-pyran nucleus at 70 °C for 7 h, leading to 3, 4-dihydropyridone derivatives. With these thermal conditions, the results were similar to those found in the present study (Table 2, entry 2), in which the same conditions prevailed but with IR irradiation as the reaction promoter. An analysis of yields and reaction times shows that compared with the thermal method, with IR irradiation the reaction time is shortened and the product yield

Table 1. A comparative study of the effect of different solvents on the ring opening/closing of **7a**.[a]

Entry	Solvent	Reaction time	Yield (%)[b]
1	None	1.0 h	29
2	CHCl$_3$	12 h	0
3	THF	12 h	0
4	CH$_3$CN	12 h	0
5	Dioxane	6 h	55
6	Water	2 h	65
7	Ethanol	10 min	87

[a]Reaction conditions: **7a** (1.5 mmol), *p*-toluenesulfonic acid (0.15 mmol), and solvent (3.0 mL) under IR irradiation at 90 °C (50V). [b]After the recrystallization procedure, isolated yields were determined by NMR and correspond to the mixture of *trans/cis* adducts.

Table 2. Comparison of different sources of energy for the conversion of **7a** to **8a**.[a]

Entry	Energy source	T/°C	t/h	yield (%)[b]
1	IR (50V)	90	0.1	86
2	Thermal	70	0.5	72
3	Ultrasound	70	0.4	80
4	r.t	25	7	8

[a]Reaction conditions: **7a** (1.5 mmol), *p*-toluenesulfonic acid (0.15 mmol), and ethanol (3.0 mL). [b]After the recrystallization procedure, isolated yields were determined by NMR and correspond to the mixture of *trans/cis* adducts.

is increased (Table 2, entry 1). It is important to mention that at 90 °C (50 V) decomposition of the raw material and product begins.

On the other hand, several Brönsted-Lowry acids were screened, including sulfuric and hydrochloric acid, to assess their efficiency in the ring opening/closing of **7a** (Table 3). We also studied the catalytic activity of iodine on the reaction. Hydrochloric acid was found somewhat better than iodine (yield 80%), but the best results were obtained with sulfuric acid (yield 94%). The latter catalyst at 10 mol% was enough to push the reaction forward. Increasing the amount of catalyst (30%) did not result in significant improvement in the yield (Table 3, entry 5), while reducing the amount of catalyst below 10 mol% resulted in a lower yield (Table 3, entry 4). Iodine resulted in poor conversion of **8a** (Table 3, entry 6).

The use of these optimal experimental conditions (IR irradiation, 90 °C, H$_2$SO$_4$-EtOH) for the reactions of different 6-amino-5-cyanopyrans **7b-k** afforded good yields of 4-aryl-3-cyano-5-ethoxycarbonyl-6-methyl-3,4-dihydro-2-pyridones

Table 3. Catalyst optimization for the conversion of **7a** into **8a**.[a]

entry	catalyst	catalyst (mol%)	t (min)	yield(%)[b]
1	*p*-TsOH (99%)	10	10	87
2	HCl (35%)	10	10	80
3	H_2SO_4 (99%)	10	5	94
4	H_2SO_4 (99%)	5	20	65
5	H_2SO_4 (99%)	30	7	95
6	I_2 (99%)	10	30	57

[a]All entries were carried out using catalysts in ethanol as solvent, under IR irradiation. [b] Determined by ^{1}H NMR of the crude reaction mixtures, corresponding to the mixture of *trans*/*cis* adducts.

8b-k. The results (Table 4) indicate that both aryl and heteroaryl functional groups are suitable for the reaction.

Compounds **8a-k** were isolated as a *trans*/*cis* mixture of adducts. Like their precursors, these compounds showed the same number of signals in the proton-decoupled ^{13}C NMR spectrum as with the ^{1}H NMR spectrum. The latter spectrum shows two new sets of signals at ~10.80-10.40 ppm, corresponding to the NH protons (*trans/cis*), ~5.05-4.57 ppm (*trans J* = 7.5Hz) and 4.67-4.35 ppm (*cis J* = 5.5 Hz). Furthermore, the infrared spectra of **8a-k** displayed carbonyl absorptions at ~1721 and 1662 cm^{−1}, in contrast to the carbonyl absorption at ~1676 cm^{−1} for **7a-k**.

The proposed mechanism of rearrangement of 4*H*-pyrans is described in Scheme 1, involving a hydration process to produce the intermediary **II**, which then undergoes a condensation reaction to yield **8a-k** [18].

Table 4. Relation between diasteroisomers *cis/trans* in **8a-k**, determined by NMR.

product	R_1	R_2	R_3	Ratio *trans/cis*	yield (%)[a]
8a	4-FC$_6$H$_4$	-CO$_2$Et	-CH$_3$	82/18	85
8b	4-BrC$_6$H$_4$	-CO$_2$Et	-CH$_3$	91/9	91
8c	3-NO$_2$C$_6$H$_4$	-CO$_2$Et	-CH$_3$	82/18	86
8d	2-NO$_2$C$_6$H$_4$	-CO$_2$Et	-CH$_3$	84/16	90
8e	C$_6$H$_5$	-CO$_2$Et	-CH$_3$	84/16	86
8f	*n*-propyl	-CO$_2$Et	-CH$_3$	95/5	72
8g	4-CH$_3$OC$_6$H$_4$	-CO$_2$Et	-CH$_3$	89/11	86
8h	2,4-Cl$_2$C$_6$H$_3$	-CO$_2$Et	-CH$_3$	86/14	93
8i	3-NO$_2$C$_6$H$_4$	-COCH$_3$	-CH$_3$	84/16	80
8j	3-NO$_2$C$_6$H$_4$	-CO$_2$CH$_3$	-CH$_2$CO$_2$CH$_3$	84/16	85
8k	4-NO$_2$C$_6$H$_4$	-CO$_2$Et	-CH$_3$	84/16	87

[a]Determined after recrystallization by ^{1}H NMR, corresponding to the mixture of *trans/cis* adducts.
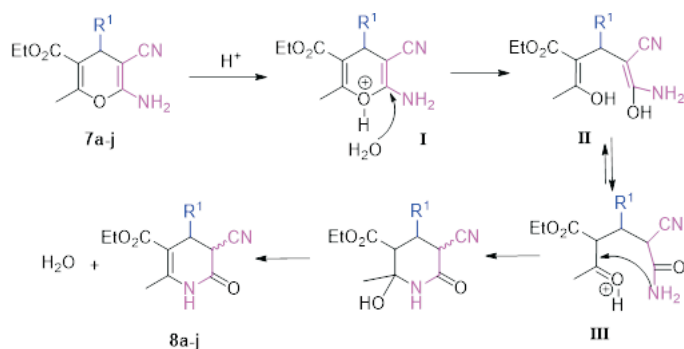
Scheme 1. Plausible mechanistic course for the synthesis of 3,4-dihydropyridin-2-ones.

Oxidation of 4-aryl-3-cyano-5-ethoxycarbonyl-6-methyl-3,4-dihydro-2-pyridones 8a-k

The ring opening/closing of **7a** proved to be an efficient process for building the 4-aryl-3-cyano-5-ethoxycarbonyl-6-methyl-3,4-dihydro-2-pyridone scaffold. 3,4-dihydro-2-pyridones **8a-k** possess a core that may be expected to undergo an oxidation reaction.
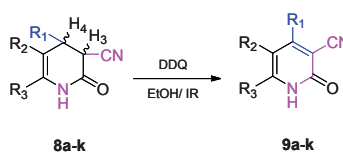
In the course of the current study, an initial attempt was made to oxidize the adduct **8a** with nitric acid on silica gel under solvent-free conditions with infrared irradiation at 100 °C (60 V). The starting material began to decompose after 10 min of reaction (Table 5, entry 1). Thereafter, we employed nitric acid on silica gel in EtOH as the solvent at reflux (60 V) and at 70 °C (30 V) for 2-3 h to give **9a** in low yields after purification on column chromatography (Table 5, entries 2 and 3). In order to induce aromatization, adduct **9a** was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), employing ethanol as the solvent, under infrared irradiation for 10 min to give **9a** in good yield (80%; Table 5, entry 4).

In order to investigate the scope and limitations of this oxidation reaction, as well as to identify the possible effect induced by other substrates on the formation of compounds **9b-k**, the reaction was carried out with substrates **9b-k** under the same reaction conditions. The behavior observed was similar to

Table 5. Oxidation of **8a** using various reaction conditions.

entry	conditions	yield (%)[a]
1	HNO$_3$/silica gel/solventless/100 °C (60 V)/10 min, IR.	0
2	HNO$_3$/silica gel/EtOH/reflux (60 V)/2 h, IR.	18
3	HNO$_3$/silica gel/EtOH/70 °C (30 V)/3 h, IR.	20
4	DDQ/EtOH/reflux (50 V)/10 min, IR.	80

[a]Yields refer to the pure isolated product.

Table 6. Synthesis of 5-cyano-pyridin-2-ones **9a-k**.

Product	R_1	R_2	R_3	Yield (%)
9a	4-FC$_6$H$_4$	-CO$_2$Et	-CH$_3$	82
9b	4-BrC$_6$H$_4$	-CO$_2$Et	-CH$_3$	84
9c	3-NO$_2$C$_6$H$_4$	-CO$_2$Et	-CH$_3$	83
9d	2-NO$_2$C$_6$H$_4$	-CO$_2$Et	-CH$_3$	85
9e	C$_6$H$_5$	-CO$_2$Et	-CH$_3$	81
9f	*n*-propyl	-CO$_2$Et	-CH$_3$	70
9g	4-CH$_3$OC$_6$H$_4$	-CO$_2$Et	-CH$_3$	75
9h	2,4-Cl$_2$C$_6$H$_3$	-CO$_2$Et	-CH$_3$	83
9i	3-NO$_2$C$_6$H$_4$	-COCH$_3$	-CH$_3$	80
9j	3-NO$_2$C$_6$H$_4$	-CO$_2$CH$_3$	-CH$_2$CO$_2$CH$_3$	82
9k	4-NO$_2$C$_6$H$_4$	-CO$_2$Et	-CH$_3$	91

that found with **8a**, resulting in the formation of adducts **9b-k** as single products in comparable yields (Table 6). It is evident that the reaction proceeded smoothly for both electron rich and electron deficient aryl and heteroaryl aldehydes that have a 1,3-dicarbonylic moiety. There was reasonably good yield after purification with column chromatography.

The compounds were analyzed by various spectroscopic methods. The IR spectrum of **9a** exhibited bands at 3079, 2228 and 1662 cm^{-1}, indicating the presence of NH, C≡N and C=O functionalities, respectively. The ^{1}H NMR spectrum evidenced the disappearance of the multiplicity of H-3 and H-4, the characteristic singlet at δ 3.81 ppm due to a methyl group, and the presence of an ethoxy group at 0.72 and 2.46 ppm. The spectral data and physical properties of **9a-k** can be seen in the experimental and supplementary information sections.

A single-crystal X-ray diffraction crystallography of compound **9b** allowed us to confirm its structure (Fig. 2.) [20].

Conclusions

In summary, we have developed a simple, efficient and rapid method for the synthesis of 2-pyridone derivatives in moderate to excellent yields using IR irradiation. This simple procedure with some aspects of a green approach has the advantage of requiring only mild conditions during the reaction, using a catalytic quantity of H$_2$SO$_4$ for the first stage and DDQ.

Experimental Section

Melting points were determined on an electrothermal digital 90100 melting point apparatus and were uncorrected. IR spectra

were recorded on a Perkin-Elmer Spectrum 100 FT-IR spectrophotometer. NMR spectra were recorded on Varian Gemini (300 MHz) and Varian VNMR System (500 MHz) instruments, using solutions in DMSO-d$_6$ and CDCl$_3$ with Me$_4$Si as internal standard. High-resolution mass spectra (HRMS) were obtained with a JSM-GCMate II mass spectrometer, and electron impact techniques (70 eV) were employed. X-ray data were collected on an Oxford Diffraction Xcalibur S single-crystal X-ray diffractometer. For reactions with ultrasound heating, Bransonic equipment was used (Branson model 1510). TLC analyses were performed using silica plates and were visualized using UV (254 nm) or iodine.

General procedure for the preparation of ethyl-5-cyano-4-(aryl)-2-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylates (8a-k) using IR irradiation

A mixture of 4*H*-pyran **7a-k** (1.50 mmol) and concentrated sulfuric acid (10 mol%) in EtOH (3 mL) was IR irradiated at 80 °C (50 V) for 15 minutes. The progress of the reaction was monitored by TLC (hexane/EtOAc, 7/3). The reaction was purified by recrystallization using a 95/5 ratio of H$_2$O/EtOH to obtain the mixture of the two diastereoisomers. The solid obtained was collected by vacuum filtration, and then the product was allowed to dry before quantification.

Procedure for the preparation of ethyl-5-cyano-4-(aryl)-2-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (8a) using ultrasound

A mixture of 4*H*-pyran **7a** (1.50 mmol) and *p*-toluenesulfonic acid (15 mol%) in EtOH (3 mL) was heated to 50 °C and
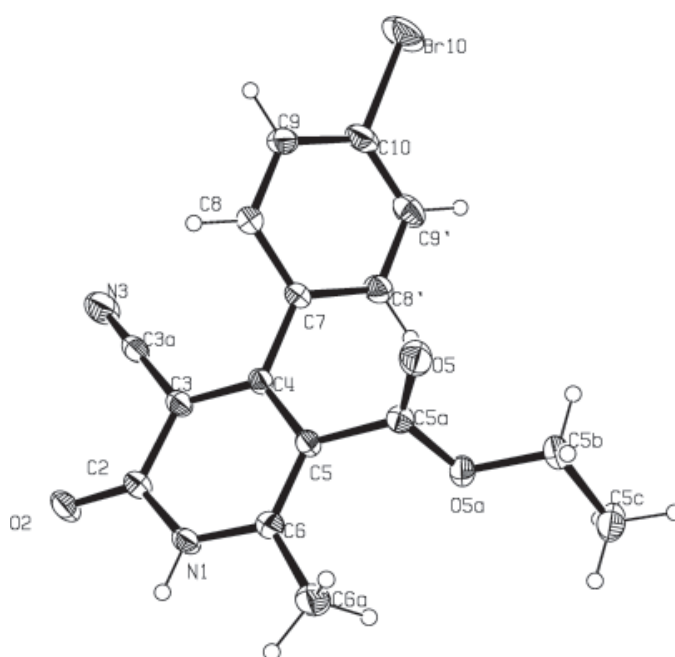
Fig. 2. The X-ray structure of **9b**.

maintained at that temperature for 25 minutes. The progress of the reaction was monitored by TLC (hexane/EtOAc, 7/3). The reaction was purified by recrystallization using a 95/5 ratio of H$_2$O/EtOH to obtain the mixture of the two diastereoisomers. The solid obtained was collected by vacuum filtration, and then the product was allowed to dry before quantification.

Procedure for the preparation of ethyl-5-cyano-4-(aryl)-2-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (8a) by conventional heating

A mixture of 4*H*-pyran **7a** (1.50 mmol) and *p*-toluenesulfonic acid (15 mol%) in EtOH (3 mL) was heated at reflux for 25 minutes. The progress of the reaction was monitored by TLC (hexane/EtOAc, 7/3). The reaction was purified by recrystallization using a 95/5 ratio of H$_2$O/EtOH to obtain the mixture of the two diastereoisomers. The solid obtained was collected by vacuum filtration, and then the product was allowed to dry before quantification.

General procedure for the preparation of ethyl-5-cyano-2-methyl-6-oxo-4-hetero and carboaryl-1,6-dihydropyridine-3-carboxylates (9a-k)

A mixture of 1,2,3,4-tetrahydropyridin-2-ones **(8a-k)** (1.52 mmol), ethanol (3 mL) and DDQ (1.52 mmol) was IR irradiated at 90 °C (50 V) for 10 minutes. The progress of the reaction was monitored by TLC (EtOAc/hexane 5/5). The reaction was purified by column chromatography (hexane/AcOEt, 1/1). The solid obtained was collected under vacuum.

Ethyl-5-cyano-4-(4-fluorophenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (9a)

White solid, m.p. 215-216 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 13.12 (s, 1H), 7.40-7.36 (m, 4H), 3.87 (q, *J* = 7.1 Hz, 2H), 2.43 (s, 3H), 0.78 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 164.79, 163.66, 161.70, 158.47, 153.44, 132.33, 129.68, 115.55, 115.37, 112.01, 100.87, 60.95, 18.27, 13.19. IR (KBr, cm^{-1}): *v* 2996, 2230, 1708, 1650, 1284. HRMS (EI$^+$) calculated for C$_{16}$H$_{13}$FN$_2$O$_3$ 300.0910, found (M$^+$) 300.0904 (2.0 ppm error).

Ethyl 4-(4-bromophenyl)-5-cyano-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (9b)

Yellow crystal, m.p. 228-229 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.74 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 3.87 (q, *J* = 7.2 Hz, 2H), 2.44 (s, 3H), 0.76 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 164.64, 159.78, 158.29, 153.96, 135.25, 131.47, 129.36, 122.92, 115.36, 111.51, 100.56, 60.94, 18.41, 13.09. IR (KBr, cm^{-1}): *v* 2996, 2230, 1708, 1650, 1284. HRMS (EI$^+$) calculated for C$_{16}$H$_{13}$BrN$_2$O$_3$ 360.0110, found (M$^+$) 360.0103 (2.0 ppm error).

Ethyl 5-cyano-2-methyl-4-(3-nitrophenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (9c)

Red solid, m.p. 227-228 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.28 (s,1H), 8.41 (m, 1H) 8.24 (s, 1H), 7.88 (s, 2H), 3.88 (q, *J* = 7.2 Hz, 2H), 2.51 (s, 3H), 0.74 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 164.29, 159.51, 157.21, 154.79, 147.50, 137.75, 134.07, 130.41, 124.13, 122.10, 115.15, 111.17, 101.39, 60.96, 18.64, 13.12. IR (KBr, cm^{-1}): *v* 2901, 2229, 1728, 1671, 1288. HRMS (EI$^+$) calculated for C$_{16}$H$_{13}$N$_3$O$_5$ 327.0855, found (M$^+$) 327.0850 (1.5 ppm error).

Ethyl 5-cyano-2-methyl-4-(2-nitrophenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (9d)

Brown solid, m.p. 225-226 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 13.29 (s,1H), δ 8.35 (d, *J* = 8.3 Hz, 1H), 7.93 (t, *J* = 7.6 Hz, 1H), 7.82 (td, *J* = 8.0, 0.9 Hz, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 3.82 (q, *J* = 7.1 Hz, 2H), 2.56 (s, 3H), 0.74 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 163.62, 159.28, 158.57, 156.18, 146.07, 134.81, 131.80, 130.87, 129.78, 124.71, 114.77, 109.74, 100.78, 60.90, 19.33, 13.13. IR (KBr, cm^{-1}): *v* 2941, 2230, 1720, 1660, 1284. HRMS (EI$^+$) calculated for C$_{16}$H$_{13}$N$_3$O$_5$ 327.0855, found (M$^+$) 327.0850 (1.5 ppm error).

Ethyl 5-cyano-2-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxylate (9e) [21]

Brown solid, m.p. 217-218 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.52-7.48 (m, 3H), 7.33-7.30 (m, 2H), 3.81 (q, *J* = 7.1 Hz, 2H), 0.70 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 164.87, 159.76, 159.42, 153.11, 135.88, 129.45, 128.45, 127.14, 115.37, 112.06, 100.56, 60.86, 30.66, 18.19. IR (KBr, cm^{-1}): *v* 3210, 2229, 1728, 1641, 1285.

Ethyl 5-cyano-2-methyl-6-oxo-4-propyl-1,6-dihydropyridine-3-carboxylate (9f)

White solid, m.p. 161-162 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.28 (q, *J* = 7.1 Hz, 1H), 2.69-2.61 (m, 1H), 2.31 (s, 3H), 1.59-1.47 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 1H), 0.91 (t, *J* = 7.4 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.21, 161.60, 159.77, 152.78, 115.34, 111.79, 100.65, 61.48, 34.80, 22.74, 18.48, 13.82, 13.78. IR (KBr, cm^{-1}): *v* 2977, 2229, 1720, 1658, 1287. HRMS (EI$^+$) calculated for C$_{13}$H$_{16}$N$_2$O$_3$ 248.1161, found (M$^+$) 248.1155 (2.4 ppm error).

Ethyl 5-cyano-4-(4-methoxyphenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (9g) [21]

White solid, m.p. 217-218 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.03 (s, 1H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.06 (d, *J* = 8.7 Hz, 2H), 3.89 (q, *J* = 6.9 Hz, 2H), 3.89 (s, 3H), 2.40 (s, 3H), 0.79 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 165.18, 160.30, 159.94, 159.08, 152.58, 128.87, 127.82, 115.71, 113.90, 111.37, 101.24, 60.95, 55.32, 18.06, 13.26. IR (KBr, cm^{-1}): *v* 3009, 2226, 1722, 1666, 1295.

Ethyl 5-cyano-4-(2,4-dichlorophenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (9h)

Brown solid, m.p. 235-237 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.33 (s, 1H), 7.83 (d, J = 1.5 Hz, 1H), 7.585 (dd, J = 8.4, 1.5 Hz, 1H), 7.43(d, J = 8.4 Hz, 1H), 3.90 (q, J = 7.2 Hz, 2H), 2.54 (s, 3H), 0.80 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.67, 159.34, 156.54, 156.03, 134.64, 134.49, 131.87, 130.43, 128.89, 127.59, 114.63, 110.72, 101.63, 60.84, 19.10, 13.07. IR (KBr, cm^{-1}): v 2988, 2230, 1722, 1655, 1284. HRMS (EI$^+$) calculated for $C_{16}H_{12}Cl_2N_2O_3$ 350.0225, found (M$^+$) 350.0220 (1.4 ppm error).

5-acetyl-6-methyl-4-(3-nitrophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (9i)

White solid, m.p. 258-260 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.18 (s,1H), 8.40 (m, 1H) 8.27 (d, J = 1.2 Hz, 1H), 7.89 (s, 2H), 2.38 (s, 3H), 1.87 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 200.75, 160.27, 156.62, 152.56, 147.37, 137.31, 135.36, 131.50, 125.53, 123.57, 116.03, 112.17, 32.74, 18.91. HRMS (EI$^+$) calculated for $C_{15}H_{11}N_3O_4$ 297.0750, found (M$^+$) 297.0743 (2.4 ppm error).

Ethyl-5-cyano-2-methyl-4-(4-nitrophenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (9k) [21]

Brown solid; mp 208-210 °C; IR (KBr): 2254, 1651, 1283 cm^{-1}; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 13.13 (s, 1H), 8.46 (d, J = 8.4 Hz, 2H), 7.74 (d, 2H, J = 8.4Hz), 3.92 (q, 2H, J = 7 Hz), 2.54 (s, 3H), 0.80 (t, 3H, J = 7 Hz); ^{13}C NMR (CDCl$_3$, 50 MHz): δ 164.2, 159.4, 157.8, 154.9, 147.9, 142.8, 128.9, 123.6, 115.0, 110.9, 101.0, 61.05, 18.7, 13.1.

X-ray Structure Study of 9b. A single crystal, obtained by the slow evaporation of a concentrated solution of **9b** (*n*-hexane/AcOEt, pale yellow), was mounted on glass fibers. Crystallographic measurements were performed on an Oxford Diffraction Xcalibur S single-crystal X-ray diffractometer using MoK\α radiation (graphite crystal monochromator, λ = 0.71073 Å) at room temperature. Three standard reflections, which were monitored periodically, showed no change during data collection. Unit cell parameters were obtained from least-squares refinement of 26 reflections in the range $2° < 2\theta < 20°$. Intensities were corrected for Lorentz and polarization effects. No absorption correction was applied. Anisotropic temperature factors were introduced for all non-hydrogen atoms. Hydrogen atoms were placed in idealized positions and their atomic coordinates refined. Structures were solved using the SHELXTL, [22] SHELX97, [23] or SIR92, [24] programs implemented in the WinGX suite[25], and refined using SHELXTL or SHELX97 within WinGX on a personal computer. In all cases ORTEP and packing diagrams were made with PLATON and ORTEP-3 [26].

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