



Solvent-free, two-step synthesis of some unsymmetrical 4-aryl-1,4-dihydropyridines

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4-Aryl-1,4-dihydropyridines are efficiently synthesised under solvent-free conditions in high yield. The use of volatile solvents is restricted to recrystallisation of the product, which, due to the high degree of conversion, is kept to a minimum. Optimisation of reaction conditions by careful consideration of the reaction rate and extent of conversion is demonstrated. This is yet another example of how readily solvent-free reactions may be implemented in the highly reproducible and efficient preparation of pure therapeutic agents with minimal production of waste and optimised use of energy.

Introduction

4-Aryl-1,4-dihydropyridines **5** are potent blockers and activators of L-type calcium channels¹ and are extensively used in the treatment of cardiovascular disease (CVD) which is a leading cause of death the world over (41.4% of deaths in the USA in 1996 were a result of CVD).² Second generation calcium channel blockers such as Amlodipine,[†] the world's best selling drug for the treatment of hypertension (marketed as Norvasc by Pfizer with sales of \$2.6 billion in 1998),² sustained release calcium antagonists such as Nisoldipine[‡] and older products such as Felodipine[§] and Nifedipine[¶] are all members of the 1,4-dihydropyridine class and, together with other calcium antagonists accounted for 3.1% of the total world pharmaceutical market of \$297.6 billion at the end of the 3rd quarter 2000.³

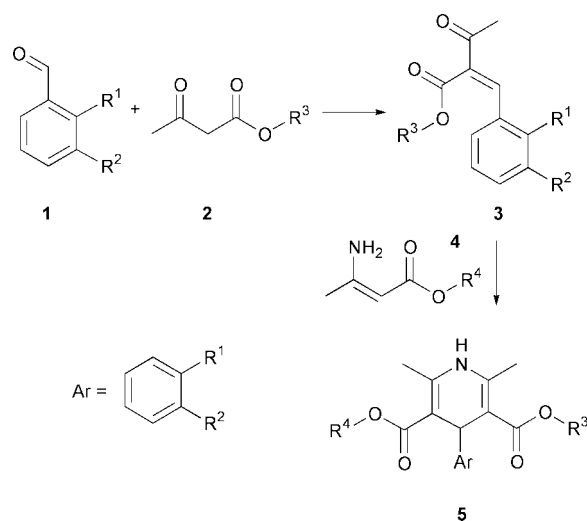
The Hantzsch pyridine synthesis⁴ described in 1882 provides a convenient route to the preparation of all symmetrical dihydropyridines. This reaction consists in essence in the condensation of an aromatic aldehyde with an excess of an acetoacetate ester and ammonia.^{5,6} Unsymmetrically 3,5- (or 2,6-) substituted dihydropyridines are usually synthesised by a two-step process such as that illustrated in the Scheme 1.

While this has been described as a one-pot procedure,⁷ it is more common to react the aromatic aldehyde **1** with an appropriate acetoacetate ester **2** to produce the benzylidene intermediate **3** which is further reacted with 3-aminocrotonic acid ester **4** yielding the unsymmetrical 1,4-dihydropyridine **5**.^{8,9–15}

Various strategies have been employed to maximise conversion and minimise reaction time and these include azeotropic removal of water,^{9–11} catalyst optimisation,^{9,12} use of microwave heating,¹³ and selective de-esterification of diesters using acid catalysts.¹⁴ With the exception of the methodology employing microwave heating, reaction times are of the order of 2–40 h and overall yields for the two-step synthesis are significantly lower than quantitative (30–65%). Extractive

work-ups¹⁵ and the need to separate symmetrical diester byproducts from the desired product⁹ serve to increase the usage of volatile organic compounds (VOCs) and decrease efficiency with respect to yield and number of process steps.

Recently, it has been reported that many reactions proceed efficiently, rapidly and with a high degree of selectivity under



Scheme 1

Green Context

4-Aryl-1,4-dihydropyridines are used in the treatment of cardiovascular disease, one of the world's leading causes of disease. Its synthesis is typical of those in organic chemistry that usually involve more than one step, auxiliaries such as reagents and solvents, and low overall atom efficiencies. Here we see how solventless reactions can significantly improve the economic and environmental efficiency of the synthesis of these pyridines. Optimisation of the reaction conditions has been achieved by studying reaction rate and the extent of conversion. The simple but effective synthesis of valuable products is achieved in a single pot, with minimal auxiliaries, easy product recovery and low levels of work.

JHC

[†] 3-Ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulfonate.

[‡] Methyl-2-methylpropyl-1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridinedicarboxylate.

[§] Ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate.

[¶] Dimethyl-1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridinedicarboxylate.

solvent-free conditions.¹⁶ We now report the solvent-free synthesis of 4-aryl-1,4-dihydropyridines and the application of measurement of rate and extent of conversion to the optimisation of such reactions. This methodology provides an exceptionally high-yielding and simple route to some common drug products and is demonstrated to be a significant improvement on the solution phase methodology with respect to energy efficiency, reaction time, extent of conversion and isolated yield. In addition, the hazards associated with the use of volatile organic solvents are obviated and the resultant quantity of waste significantly reduced.

Results and discussion

The solvent-free, two-step synthesis of a number of 4-aryl substituted 1,4-dihydropyridine-3,5-dicarboxylic acid derivatives **5** proceeds rapidly at moderate temperatures to produce pure product in high yield (almost quantitative in most cases) with very small amounts of attendant waste. The results of the synthesis of a number of compounds, with varying aryl, and ester substituents, are presented in Table 1.

In common with the previously published procedures this is a two-step process that initially requires contact between a benzaldehyde derivative **1** and acetoacetate ester **2**, as a solventless reaction, in the presence of a catalytic amount of a 1:1 mixture of piperidine and glacial acetic acid. The resultant benzylidene **3** is then reacted, without further purification, with methyl-3-aminocrotonate **4** and a small additional quantity of glacial acetic acid to generate the corresponding dihydropyridines **5** in quantitative or near-quantitative conversion in almost all cases.

As the reaction may be shown to proceed at reasonable rate even at ambient temperature (25 °C), an analysis of the rate of conversion of **1** and **2** to **3** at different temperatures was undertaken with a view to optimisation of reaction time and temperature.

The system under study is not a closed system (H₂O is allowed to escape) and thus this does not represent a reaction rate but rather an effective rate of conversion to product **3** under the specific circumstances. It should also be noted that a transient intermediate corresponding to the non-dehydrated adduct occurs and the reaction may be represented as **1** + **2** → [alcohol intermediate] → **3** + H₂O. No attempt is made to relate rate and mechanism or 'molecularity' of reaction yet the effective rate measured allows determination of an effective

overall rate constant and therefore analysis of the effect of changing temperature on the rate of conversion.

Measured extents of conversion α , where $\alpha = [\mathbf{3}]/([\mathbf{1}]+[\mathbf{3}])$,¹⁷ at temperatures ranging from 25 to 80 °C are plotted in Fig. 1. An effective first order rate expression $f(\alpha) = kt$ where $f(\alpha) = -\ln(1 - \alpha)$ is found to provide the best fit over the largest range of α values (typically $\alpha = 0-0.9$) and an effective rate constant k is derived from the gradient of the line derived from application of the integrated rate law function at each temperature and used to model continuous rate curves. Values of the effective overall rate constant k derived at each temperature are detailed in Table 2.

A plot of $\ln k$ vs. reciprocal temperature, Fig. 2, reveals an interesting phenomenon. At 25, 40 and 60 °C the system exhibits isokinetic behaviour and a straight line may be fitted to yield estimates of E_a and pre-exponential factor A . However $\ln k$ at 80 °C does not fall on this line, in other words the measured k_{eff} is lower, by a factor of 2.4, than would be predicted from an Arrhenius plot ($2.6 \times 10^{-3} \text{ s}^{-1}$ vs. $6.3 \times 10^{-3} \text{ s}^{-1}$). While it is possible that this represents a large experimental error at this rapid rate of conversion, it may be true that a different overall 'mechanism' is implied at this temperature and that elevation of

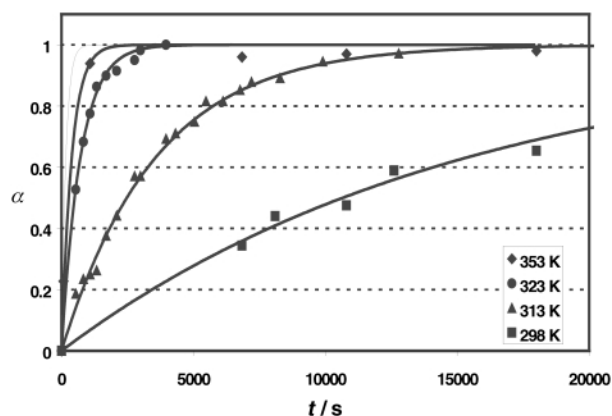


Fig. 1 α vs. time (t) curves for the formation of **3b** from **1b** and ethyl acetoacetate at 25, 40, 60 and 80 °C. Continuous modeled rate curves are derived as follows: the integrated form $f(\alpha)$ of various possible rate law expressions are plotted vs. t and examined for linearity. An effective first order rate expression $f(\alpha) = kt$ where $f(\alpha) = -\ln(1 - \alpha)$ is found to provide the best fit over the widest range of α values (typically $\alpha = 0-0.9$) and k estimated from the gradient of this line is used to generate the solid curves ($\alpha = 1 - e^{-kt}$) depicted here. The fine line represents the curve predicted for conversion at 80 °C from an examination of the Arrhenius plot depicted in Fig. 2.

Table 1 Comparison of yields and duration of reaction for conversion to **3** and **5**

	R ¹	R ²	R ³	3		5		Yield (%)
				Conv. ^a (%)	t/h	Conv. ^a (%)	t/h	
a	H	H	Et	98	0.3	>99	2.4	96
b	NO ₂	H		>99	0.4	61	3.0	— ^c
						73	22 ^b	— ^c
c	H	NO ₂		90	0.2	>99	2	95
d	H	Cl		>99	0.7	>99	1.0	94
e	Cl	Cl		96	1.0	>99	1.8	96
f	H	H	Bu ^t	97	0.3	94	3.0	
						>99	5.0	92
g	NO ₂	H		>99	0.4	5	0.2	— ^c
						27	20	— ^c
h	H	NO ₂		90	1.0	91	1.5	87
i	H	Cl		95	1.0	95	2.0	
						>99	4.0	91
j	H	Cl	PhCH ₂	>99	1.0	>99	1.5	99

^a Compound **3** was not isolated; extent of conversion determined from ¹H NMR analysis. ^b After a further 19 h at ambient temperature the reaction was found to have proceeded, but even lengthy reaction times at elevated temperature did not lead to substantially improved conversion to **5b**. ^c Product not isolated due to poor conversion.

Table 2 Values of k derived from a consideration of the gradient of plots of $f(\alpha) = -\ln(1 - \alpha)$ for the conversion of **2b** and ethylacetoacetate to **3b**

T/K	k/s^{-1}	α Range of fit
298	6.5×10^{-5}	0–0.93
313	2.8×10^{-4}	0–0.97
333	1.4×10^{-3}	0–0.90
353	2.6×10^{-5}	0–0.94

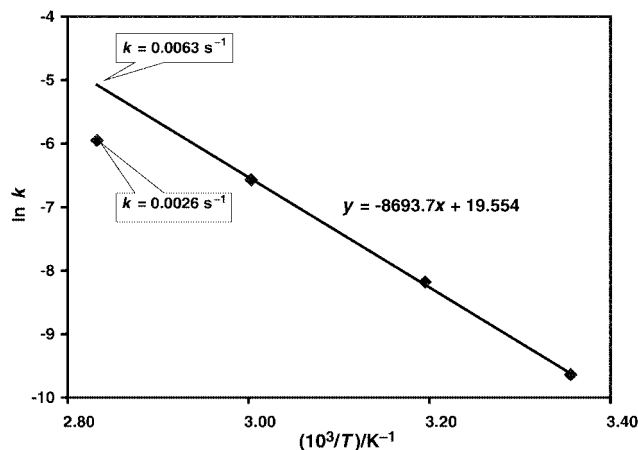


Fig. 2 Arrhenius plot, $\ln k$ vs. t , for k values derived from fit of an F1 rate law. Extrapolation of the line fitted to temperatures ranging from 25 to 60 °C indicates an expected value of k of $6.3 \times 10^{-3} s^{-1}$ while the measured value is found to be only $2.6 \times 10^{-3} s^{-1}$.

temperature does not lead to the expected rate increase. The reaction mixture is an oil which was observed to become steadily more viscous as the reaction proceeds. Thus it is not unreasonable to postulate that diffusion (or mixing) of **1** + **2** becomes the rate limiting factor in the conversion to **3** at elevated temperatures. Above 60 °C diminishing returns are achieved with respect to increase in rate of conversion and an analysis of quantity of product produced vs energy input would be expected to exhibit a maximum at some temperature between 60 and 80 °C. While this optimum temperature may vary for each **3** it is worthy of note that this provides an adequate method for optimisation of temperature to achieve maximum rate of formation of **3**.

The fact that the reaction proceeds at an acceptable rate at room temperature provides an opportunity for reaction in systems containing heat labile species. No large excess of acetoacetate is required to drive the reaction to completion and no disubstituted impurities are detected by NMR analysis.

1H NMR analysis of the benzyldene intermediates **3** reveal a mixture of *E* and *Z* isomers and recrystallisation from ethanol was used to preferentially crystallise the *Z* isomer of **3g** for purposes of identification. In all cases the *Z* isomer predominates. 1H NMR analysis of this crystalline material reveals a single set of signals and the single crystal structure¹⁸ of **3g** confirms the assignment of NMR data. The molecular structure of **3g** is presented in Fig. 3 and analysis of the angles of the planes indicated on the diagram reveal that the aromatic ring is twisted out of the plane of the newly formed double bond system by 53.8(1)°. Similarly the atoms associated with C11 are twisted out of the plane by 70.2(1)° while sp^2 centre C9 and bonded atoms is almost coplanar with the newly formed double bond. The oily nature of unrecrystallised compounds **3** is almost certainly due to the occurrence of a mixture of *E* and *Z* isomers and the presence of small amounts of the catalyst system, as solid *Z* isomer may be isolated quite readily by recrystallisation from solvents such as ethanol. In fact, the oils obtained will often crystallise upon prolonged standing post reaction.

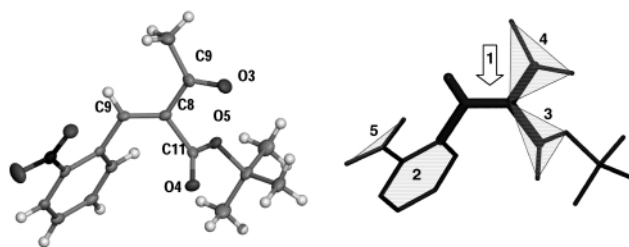


Fig. 3 Molecular diagram of **3g** from single crystal structure data. Ellipsoids are plotted at the 50% probability level. Planes referred to in the text are labelled and all except '1' (the plane of the vinylic bond and substituents) are represented as shaded polygons. The angles (°) between the planes indicated are: 1 and 2, 53.8(1); 5 and 2, 7.4(4); 1 and 4, 14.4(2); 1 and 6, 70.2(1).

The intermediate is not isolated, nor is the catalyst removed prior to reaction with *ca.* 1 mol equivalent of methyl aminocrotonate. A small quantity of glacial acetic acid is added and the reaction **3** + **4** to produce **5** again proceeds with alacrity as evidenced by the extent of conversion vs. time data for the conversion of **3e** to **5e** presented in Fig. 4.

Close inspection of the early part of the conversion curve reveals an apparently sigmoidal shaped curve. This might well be indicative of an induction period or a change in dominant process leading to two superimposed curves. This induction period is also reflected in preliminary data obtained from calorimetry experiments and is the subject of a significant further investigation. It proved impossible to model this accurately using an F1 expression and instead a deceleratory curve described by the expression $kt = [1 - (1 - \alpha)^{1/3}]^2$ (the so-called D3 rate equation¹⁹) and offset to the coincide with the inflection point, provides the best model. There appears to be a continual increase in the rate of conversion of reagents to products with increased temperature (Table 3, Fig. 5), and it is clear that a minimum temperature exists below which poor conversion of reagents to products is achieved. In fact, at 30 °C

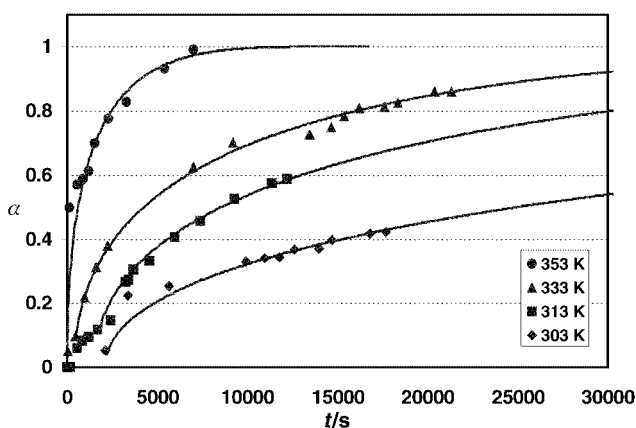


Fig. 4 α vs. t curves for the formation of **5e** from **3e** and ethyl acetoacetate at 30, 40, 60 and 80 °C. Continuous modeled rate curves are generated by the expression $\alpha = 1 - (1 - (kt)^{1/2})^3$ derived from $kt = [1 - (1 - \alpha)^{1/3}]^2$.

Table 3 Values of k derived from a consideration of the gradient of plots of $f(\alpha) = [1 - (1 - \alpha)^{1/3}]^2$ for the conversion of **3e** and methyl aminocrotonate to **5e**

T/K	k/s^{-1}	α Range of fit
303	1.90×10^{-6}	0–0.40 ^a
313	6.00×10^{-6}	0–0.60
333	1.10×10^{-5}	0–0.86
353	7.00×10^{-5}	0–0.93

^a Reaction is arrested at 42% conversion.

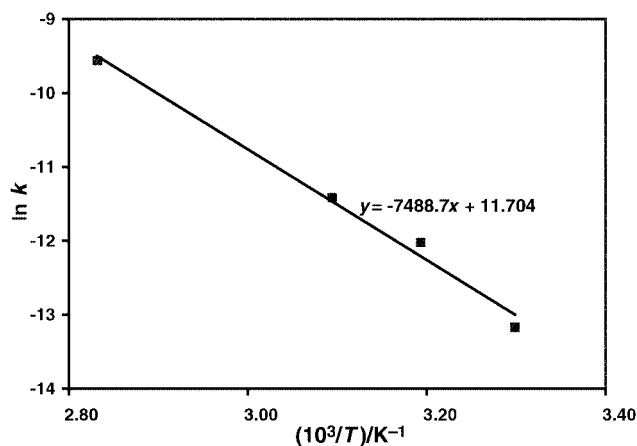


Fig. 5 Arrhenius plot, $\ln k$ vs. $1/T$ for k values derived from fit of a D3 rate law to the overall process of addition and ring closure.

the reaction is arrested at approximately 42% conversion. An increase of only 10 °C to 40 °C is sufficient to drive the reaction substantially to completion under the conditions of the experiment (99% conversion after *ca.* 28 h) and this indicates the wide temperature range over which this conversion may be effected.

Of all the benzylidene derivatives tested only the 2-nitro derivatives **3b** or **3g** proved recalcitrant in conversion to the corresponding dihydropyridines. Conversions remained poor even after lengthy reaction times and the product did not solidify. Analysis of the resultant oils indicated the presence of unreacted starting materials and product. Attempts to improve the extent of conversion by altering the catalyst quantities utilised were ineffective, and an optimum catalyst concentration of 0.2 mol% was identified. Further increase in catalyst quantity reduces the rate of formation of the product and has no effect on the extent of conversion. Similar optimum catalyst concentrations may be identified in each case. The failure of this methodology when applied to *o*-nitro derivatives (although not *p*-nitro) is unfortunate as these constitute an important group of dihydropyridine drugs. This effect has been noted previously and ascribed to a combination of steric and electronic effects.²⁰

In conclusion, an efficient, optimised solvent-free method for the synthesis of 4-aryl-1,4-dihydropyridine compounds has been developed. Efficient conversion to products and resultant reduction in purification, results in minimisation of waste and maximisation of resource use.

Experimental

Molecular characterisation

All melting points were determined on an Electrochemical digital melting point apparatus and are uncorrected. ¹H NMR spectra were recorded on a Varian Mercury 300 MHz Spectrometer in CDCl₃ solution with TMS as reference. Electrospray mass spectrometry (ESI) was carried out on a Micromass Platform II API QMS Electrospray mass spectrometer with cone voltage at 35 V, using acetone as the mobile phase. Analyses were always conducted in positive (ESI⁺) mode. Single crystal diffraction data were collected on an Enraf-Nonius Kappa CCD at 123 K using graphite monochromated Mo-K α radiation ($\lambda = 0.71073$ Å, $1^\circ \phi$ and ω scans). The structure was solved by direct methods using the program SHELXS-97²¹ and refined by full matrix least-squares refinement on F^2 using the programs SHELXL-97²² and Xseed.²³ Non-hydrogen atoms were refined anisotropically and hydrogen atoms inserted at geometrically calculated positions with

temperature factors constrained to 1.5 times the isotropic equivalents of the parent atoms.

Rates of conversion

Samples were taken from the reaction mixture at measured time intervals, dissolved in CDCl₃ and refrigerated until NMR data could be acquired. (It was ascertained by comparative experiments that dissolution in CDCl₃ followed by refrigeration slowed the rate of reaction to an undetectable level). Estimates of extent of conversion α , where α is the ratio $3/(3+1)$, or $5/(5+3)$ were derived from ¹H NMR integrated peak areas for suitable well resolved signals, and tested against a variety of integrated rate law expressions. The best expression to describe the data was determined from the degree of linearity of the fitted expression over the range $\alpha = 0-0.9$ and the value of k (the effective rate constant) estimated from the gradient of the fitted line.

Synthetic procedures

All reagents were of 98% purity or greater and used as purchased from the supplier unless noted otherwise. Solvent free experiments were performed in round bottom flasks of appropriate capacity, immersed in an oil bath preheated to the desired reaction temperature, with stirring accomplished using a magnetic stirrer. Both were thoroughly cleaned and acetone rinsed prior to use. All catalyst volumes were delivered using a well-calibrated micro-syringe. Extent of conversion for the formation of **3** and **5** were calculated by comparison of integrated values of well-defined product and reagent peaks using suitable ¹H NMR data.

General procedure for the preparation of benzylidene intermediates (3a–e)

In a typical synthesis a 1:1.1 mixture of an appropriate benzaldehyde **1** and an acetoacetate ester **2** were stirred for approximately 1 min at the requisite temperature until the respective reagents had amalgamated to form a homogeneous viscous liquid. 0.018 mol equivalents each of piperidine and glacial acetic acid were added to the stirred mixture and the reaction allowed to proceed until near quantitative conversion was detected by ¹H NMR analysis of samples. The products, which were a mixture of *E* and *Z* isomers, were yellow or orange oils. In some cases the *Z*-isomer could be isolated as a solid by recrystallisation from ethanol, although this was only done for purposes of identification.

3a. Conversion 98% (oil). ESI-MS, m/z 241.0 (calc. 241.1) [M+Na]⁺.

¹H NMR (300 MHz, 298 K, CDCl₃): 2:1 (*Z*:*E*); *Z*-isomer, δ 1.24 (3H, t, $J = 6$ Hz, CH₃), 2.38 (3H, s, CH₃), 4.30 (2H, q, $J = 6$ Hz, OCH₂), 7.34–7.56 (Ar-H), 7.55 (1H, s, vinylic CH). *E*-isomer, δ 1.30 (3H, t, $J = 6$ Hz, CH₃), 2.33 (3H, s, CH₃), 4.27 (2H, q, $J = 6$ Hz, OCH₂), 7.32–7.66 (Ar-H), 7.64 (1H, s, vinylic CH).

3b. Conversion >99% (oil). ESI-MS, m/z 286.0 (calc. 286.1) [M+Na]⁺.

¹H NMR (300 MHz, 298 K, CDCl₃): 2:1 (*Z*:*E*); *Z*-isomer, δ 0.99 (3H, t, $J = 7.2$ Hz, CH₃), 2.49 (3H, s, CH₃), 4.06 (2H, q, $J = 7.2$ Hz, OCH₂), 7.35–8.25 (Ar-H), 8.10 (1H, s, vinylic CH). *E*-isomer, δ 1.36 (3H, t, $J = 6.9$ Hz, CH₃), 2.17 (3H, s, CH₃), 4.34 (2H, q, $J = 6.9$ Hz, OCH₂), 7.35–8.25 (Ar-H), 8.05 (1H, s, vinylic CH).

3c. Conversion 90% (oil). ESI-MS, m/z 286.0 (calc. 286.1) [M + Na]⁺.

¹H NMR (300 MHz, 298 K, CDCl₃): 2:1 (*Z*:*E*); *Z*-isomer, δ 1.30 (3H, t, $J = 7.2$ Hz, CH₃), 2.45 (3H, s, CH₃), 4.33 (2H, q, $J = 7.2$ Hz, OCH₂), 7.56–8.33 (Ar-H), 8.25 (1H, s, vinylic CH). *E*-isomer, δ 1.35 (3H, t, $J = 7.2$ Hz, CH₃), 2.39 (3H, s, CH₃), 4.36 (2H, q, $J = 7.2$ Hz, OCH₂), 7.56–8.33 (Ar-H), 8.33 (1H, s, vinylic CH).

3d. Conversion >99% (oil). ESI-MS, m/z 275.0 (calc. 275.0) [M + Na]⁺.

¹H NMR (300 MHz, 298 K, CDCl₃): 2.5:1 (*Z*:*E*); *Z*-isomer, δ 1.27 (3H, t, $J = 7.2$ Hz, CH₃), 2.41 (3H, s, CH₃), 4.29 (2H, q, $J = 7.2$ Hz, OCH₂), 7.30–7.57 (Ar-H), 7.49 (1H, s, vinylic CH). *E*-isomer, δ 1.32 (3H, t, $J = 7.2$ Hz, CH₃), 2.34 (3H, s, CH₃), 4.32 (2H, q, $J = 7.2$ Hz, OCH₂), 7.30–7.57 (Ar-H), 7.57 (1H, s, vinylic CH).

3e. Conversion 96% (oil). ESI-MS, m/z 309.0 (calc. 309.0) [M + Na]⁺.

¹H NMR (300 MHz, 298 K, CDCl₃) 2:1 (*Z*:*E*); *Z*-isomer, δ 1.15 (3H, t, $J = 7.2$ Hz, CH₃), 2.46 (3H, s, CH₃), 4.21 (2H, q, $J = 7.2$ Hz, OCH₂), 7.30–7.57 (Ar-H), 7.82 (1H, s, vinylic CH). *E*-isomer, δ 1.35 (3H, t, $J = 7.2$ Hz, CH₃), 2.46 (3H, s, CH₃), 4.32 (2H, q, $J = 7.2$ Hz, OCH₂), 7.30–7.57 (Ar-H), 7.89 (1H, s, vinylic CH).

3f. Conversion 97% (oil). ESI-MS, m/z 269.1 (calc. 269.1) [M + Na]⁺.

¹H NMR (300 MHz, 298 K, CDCl₃) 2:1 (*Z*:*E*); *Z*-isomer, δ 1.52 (9H, s, OC(CH₃)₃), 2.41 (3H, s, CH₃) 7.37–7.58 (Ar-H), 7.37 (1H, s, vinylic CH). *E*-isomer, δ 1.53 (9H, s, OC(CH₃)₃), 2.33 (3H, s, CH₃), 7.37–7.58 (Ar-H), 7.48 (1H, s, vinylic CH).

3g. Conversion >99% (oil). ESI-MS, m/z 314.1 (calc. 314.1) [M + Na]⁺.

¹H NMR (300 MHz, 298 K, CDCl₃): 3:1 (*Z*:*E*); *Z*-isomer, δ 1.23 (9H, s, OC(CH₃)₃), 2.46 (3H, s, CH₃) 7.31–8.23 (Ar-H), 7.98 (1H, s, vinylic CH). *E*-isomer, δ 1.55 (9H, s, OC(CH₃)₃), 2.46 (3H, s, CH₃) 7.31–8.23 (Ar-H), 7.92 (1H, s, vinylic CH).

3h. Conversion 90% (oil). ESI-MS, m/z 314.1 (calc. 314.1) [M + Na]⁺.

¹H NMR (300 MHz, 298 K, CDCl₃): 3:1 (*Z*:*E*); *Z*-isomer, δ 1.54 (9H, s, OC(CH₃)₃), 2.37 (3H, s, CH₃) 7.28–8.77 (Ar-H), 8.00 (1H, s, vinylic CH). *E*-isomer, δ 1.54 (9H, s, OC(CH₃)₃), 2.37 (3H, s, CH₃), 7.28–8.77 (Ar-H), 7.92 (1H, s, vinylic CH).

3i. Conversion 95% (oil). ESI-MS, m/z 303.0 (calc. 303.1) [M + Na]⁺.

¹H NMR (300 MHz, 298 K, CDCl₃) 2:1 (*Z*:*E*); *Z*-isomer, δ 1.53 (9H, s, OC(CH₃)₃), 2.41 (3H, s, CH₃) 7.30–7.54 (Ar-H), 7.41 (1H, s, vinylic CH). *E*-isomer, δ 1.47 (9H, s, OC(CH₃)₃), 2.33 (3H, s, CH₃), 7.30–7.54 (Ar-H), 7.48 (1H, s, vinylic CH).

3j. Conversion >99% (oil). ESI-MS m/z 337.0 (calc. 337.1) [M + Na]⁺.

¹H NMR (300 MHz, 298 K, CDCl₃): 2:1 (*Z*:*E*); *Z*-isomer, δ 2.39 (3H, s, CH₃), 5.29 (2H, s, OCH₂) 7.18–7.50 (Ar-H), 7.50 (1H, s, vinylic CH). *E*-isomer, δ 2.34 (3H, s, CH₃), 5.28 (2H, s, CH₂), 7.18–7.50 (Ar-H), 7.62 (1H, s, vinylic CH).

General procedure for the preparation of 4-aryl-substituted-1,4-dihydropyridinedicarboxylic esters 5a–j

A 1:1.1 mixture of an appropriate benzylidene intermediate **3** and methyl-3-aminocrotonate **4** were stirred for 1 min at the requisite temperature until the respective reagents had amalgamated to form a homogeneous viscous oil. To this was added 0.15 mol equivalent of glacial acetic acid and the reaction mixture stirred at the elevated temperature under N₂ flow to remove water produced. Quantitative or near quantitative conversions were generally achieved within 1 to 4 h. Where further purification was required, the resultant products **5** were recrystallised from a minimum amount of isopropyl alcohol.

5a. >99%, yield 96% (pale-yellow solid), m.p. 136–137 °C (lit. 135–136 °C²⁴). ESI-MS, m/z 316.2 (calc. 316.2) [M + H]⁺.

¹H NMR (300 MHz, 298 K, CDCl₃): δ 1.22 (3H, t, CH₃), 2.32 (6H, s, CH₃), 3.64 (3H, s, $J = 7.2$ Hz, CH₃), 4.10 (2H, q, $J = 7.2$ Hz, OCH₂), 4.98 (1H, s, CH), 5.68 (1H, br s, NH) 7.09–7.29 (Ar-H).

5b. Conversion 61% (dark orange oil) (the product was not isolated due to the poor conversion measured; no recrystallisation was carried out).

5c. >99%, yield 95% (pale-yellow solid), mp 159 °C (lit. 159 °C¹⁴).

¹H NMR (300 MHz, 298 K, CDCl₃): δ 1.22 (3H, t, $J = 7.2$ Hz, CH₃), 2.36 (6H, s, CH₃), 3.63 (3H, s, CH₃), 4.18 (2H, q, $J = 7.2$ Hz, OCH₂), 5.08 (1H, s, CH), 5.91 (1H, br s, NH), 7.32–8.4 (Ar-H).

5d. Conversion >99%, yield 94% (pale-yellow solid), mp 120–121 °C. ESI-MS, m/z 372.2 (calc. 372.1) [M + Na]⁺.

¹H NMR (300 MHz, 298 K, CDCl₃) δ 1.28 (3H, t, $J = 7.2$ Hz, CH₃), 2.31 (3H, s, CH₃), 2.32 (3H, s, CH₃), 3.61 (3H, s, CH₃), 4.07 (2H, q, $J = 7.2$ Hz, OCH₂), 5.46 (1H, s, CH), 5.62 (1H, br s, NH), 7.04–7.33 (Ar-H).

5e. Conversion >99%, yield 96% (white solid), mp 144–146 °C (lit. 145 °C²⁵). ESI-MS, m/z 384.2 (calc. 384.1) [M + H]⁺.

¹H NMR (300 MHz, 298 K, CDCl₃): δ 1.18 (3H, t, $J = 7.2$ Hz, CH₃), 2.31 (6H, s, CH₃), 3.61 (3H, s, CH₃), 4.06 (2H, q, $J = 7.2$ Hz, OCH₂), 5.45 (1H, s, CH), 5.63 (1H, br s, NH), 7.04–7.33 (Ar-H).

5f. Conversion >99%, yield 92% (pale yellow solid), mp 157–159 °C. ESI-MS, m/z 366.2 (calc. 366.2) [M + Na]⁺.

¹H NMR, (300 MHz, 298 K, CDCl₃): δ 1.35 (9H, s, OC(CH₃)₃), 2.27 (3H, s, CH₃), 2.29 (3H, s, CH₃), 3.56 (3H, s, CH₃), 5.57 (1H, br s, NH), 5.74 (1H, s, CH), 7.21–7.76 (Ar-H).

5g. Conversion 57% (orange oil) (the product was not isolated due to the poor conversion measured; no recrystallisation was carried out).

5h. Conversion 91%, yield 87% (pale yellow solid), mp 112–114 °C.

¹H NMR (300 MHz, 298 K, CDCl₃): δ 1.39 (9H, s, OC(CH₃)₃), 2.33 (3H, s, CH₃), 2.35 (3H, s, CH₃), 3.64 (3H, s, CH₃), 5.03 (1H, s, CH), 5.68 (1H, br s, NH), 7.38–8.18 (Ar-H).

5i. Conversion >99%, yield 91% (pale yellow solid). ESI-MS, m/z 400.2 (calc. 400.1) $[M + Na]^+$.

1H NMR (300 MHz, 298 K, $CDCl_3$): δ 1.40 (9H, s, $OC(CH_3)_3$), 2.31 (3H, s, CH_3), 2.33 (3H, s, CH_3), 3.64 (3H, s, CH_3), 4.96 (1H, s, CH), 5.74 (1H, br s, NH), 7.10–7.25 (Ar-H).

5j. Conversion >99% yield 99% (orange oil). This product was not recrystallised from isopropyl alcohol. Instead, the oil was washed with hexane at slightly elevated temperature (30 °C) for 20 minutes and the hexane decanted. The resultant oil was then washed three times with slightly alkaline Na_2CO_3 solution before drying and weighing. ESI-MS, m/z 412.2 (calc. 412.1) $[M + H]^+$.

1H NMR (300 MHz, 298 K, $CDCl_3$): δ 2.33 (3H, s, CH_3), 2.35 (3H, s, CH_3), 3.64 (3H, s, CH_3), 5.29 (2H, s, OCH_3), 5.64 (1H, br s), 7.10–7.38 (Ar-H).

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- 17 The 'concentration' of components **1** and **3** is, in fact, inferred from inspection of the integrated areas of well resolved signals in the 1H NMR spectra of the reaction mixtures.
- 18 *Crystal data* for **3g**: $C_{15}H_{17}NO_5$, $M_r = 291.30$, orthorhombic, space group $Pna2_1$, $a = 9.1435(2)$, $b = 27.8109(3)$, $c = 5.8488(10)$ Å, $V = 1487.3(3)$ Å³, $Z = 4$, $\mu(Mo-K\alpha) = 0.098$ mm⁻¹. Of 5454 reflections measured, 1978 were unique with 1450 $I > 2\sigma(I)$, R indices [$I > 2\sigma(I)$], $R_1 = 0.0490$, $wR_2 = 0.0869$, GOF on $F^2 = 1.039$ for 194 refined parameters. CCDC reference number 167675. See <http://www.rsc.org/suppdata/gc/b1/b106397a/> for crystallographic data in CIF or other electronic format.
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