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Microwave Heating in Conjunction with UV Irradiation: a Tool for the Oxidation of 1,4-Dihydropyridines to Pyridines

Chad M. Kormos,[A] *Rachel M. Hull,*[A] *and Nicholas E. Leadbeater*[A,B]

[A]Department of Chemistry, University of Connecticut, 55 North Eagleville Road, Storrs, CT 06269-3060, USA.

[B]Corresponding author. Email: nicholas.leadbeater@uconn.edu

Microwave heating is used for the preparation of 1,4-dihydropyridines and then, in conjunction with UV irradiation, is used for the efficient oxidation of the 1,4-dihydropyridines to pyridines. The oxidation reactions are performed in a sealed vessel using oxygen as the oxidant and an electrodeless discharge lamp as the irradiation source.

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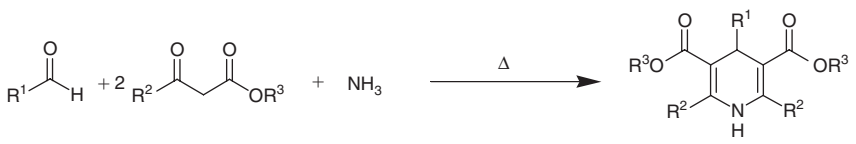
Introduction

The Hantzsch synthesis of 1,4-dihydropyridines (DHPs) has attracted considerable attention due to the biological properties of many of the dihydropyridine products.[1] They serve uses in medicine as calcium channel modulators, vasodilators, and antihypertensive agents as well as NAD(P)H models to probe the mechanism of hydrogen transfer.[2–8] The oxidation of DHPs to the corresponding polysubstituted pyridines has also proved an important reaction.[9] In the present paper, we briefly expand on a route reported by us previously for fast preparation of 1,4-dihydropyridines and then focus attention on a methodology for their oxidation using photogenerated singlet oxygen. Both procedures are performed using microwave heating.

Results and Discussion

The Hantzsch DHP synthesis essentially involves condensation of an aldehyde with a β-dicarbonyl compound and ammonia (Scheme 1).[10] Microwave heating has found use as a tool for performing the reaction.[11] By using microwave irradiation, it is often possible to reduce reaction times significantly as well as improve product yields.[12] In the first report in the area, a series of 4-aryl derivatives were prepared in a domestic microwave with yields ranging from 15 to 52% for a reaction time of 4 min.[13] Other protocols based around these conditions but still using domestic apparatus have been reported.[14–20] More recently, scientific microwave apparatus has been used to prepare a series of dihydropyridines from various aldehydes (1 equiv.), alkyl acetoacetates (6 equiv.), and 25% aqueous ammonium hydroxide (10 equiv.).[21] Reaction times ranged from 10 to 20 min and yields from 53 to 95%.

In our laboratory, we have focussed attention on performing reactions using open-vessel (standard reflux) glassware. This offers operational advantages and opens avenues for scaling up chemistry safely.[22] Using the published sealed-vessel report as our starting point, we have developed an open-vessel protocol.[23] Working on the 5-mmol scale using benzaldehyde (1 equiv.), ethyl acetoacetate (5 equiv.), and 28% aqueous ammonium hydroxide (10 equiv.) as reagents and water (20 mL) as solvent, we found it was possible to obtain the desired dihydropyridine product in 40% yield after a total reaction time of 20 min in an open vessel, this compared with a yield of 72% after 15 min using a sealed tube. Our lower yield was attributed to the fact that the reaction mixture could not be heated above the atmospheric reflux temperature, was biphasic (the organic substrates being insoluble in water), and lost ammonia over time. By adding ethanol as a cosolvent, it was possible to improve the yield considerably to 71%. The maximum temperature reached during the run was 84°C. The quantity of the dicarbonyl used can be reduced from a 3-fold to a 1.6-fold stoichiometric excess without a sacrifice in product yield. Using our optimized conditions, we wanted to prepare a range of 1,4-dihydropyridines as the initial focus of our current work (Fig. 1). Ethyl acetoacetate and 5,5-dimethylcyclohexane-1,3-dione (dimedone) were chosen as the β-dicarbonyl substrates. We screened several aldehydes and found that aromatic and aliphatic substrates can be used. When using paraformaldehyde as a substrate, a poor conversion to the desired product was obtained. This is not unprecedented; other reports have shown similar results. In an alternative approach to prepare 4-unsubstituted dihydropyridines, Vanden Eynde and coworkers have been able to synthesize 4-unsubstituted DHPs



Scheme 1. Hantzsch synthesis of 1,4-dihydropyridines.

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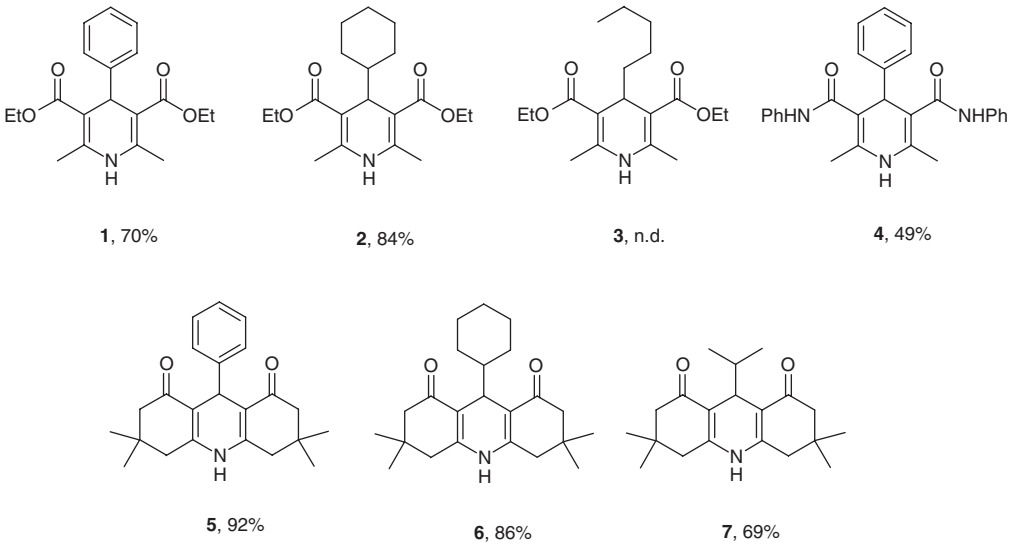


Fig. 1. Hantzsch synthesis of 1,4-dihydropyridines using microwave heating. Product yields shown.

under microwave irradiation by using alkyl acetoacetates in the presence of hexamethylenetetramine as the source of the ammonia–formaldehyde mixture.[24]

A range of oxidants have been used to transform 1,4-DHPs to the corresponding substituted pyridines with varying degrees of success. Examples include potassium permanganate,[25] heteropolyacids,[26] solid-supported pyridinium chlorochromate (PCC),[27] silica-supported ferric nitrate,[28] 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),[29] bismuth nitrate,[11] ceric ammonium nitrate,[30] and *t*-butylhydroperoxide.[31] Problems include low product yield, the use of strong oxidants, long reaction times, and the need for a significant excess of the oxidant. To overcome the issues of long reaction times and low yields, microwave heating has been used as a tool.[32] However, these procedures still often require large excesses of toxic oxidants as reagents.

The cleanest oxidant that could be used for converting 1,4-DHPs to pyridines is molecular oxygen. In the literature, there are numerous physical organic chemistry studies into the interaction of molecular oxygen with 1,4-DHPs, sparked from the desire to understand their biological properties.[33] Alongside these reports, there have been studies into the photochemistry of 1,4-DHPs.[34,35] Bringing these together, the clean oxidation of DHPs involving the use of photogenerated singlet oxygen ($^1O_2$) should be possible. However, this reaction is slow at room temperature and atmospheric pressure.[36–39]

An area that is starting to be explored is the combination of microwave and photochemical irradiation. Although a few reports have appeared in the literature, the synthetic potential of the technique has not been explored in depth. The electrodeless discharge lamps (EDLs) used in these studies have been around since the 1960s, when it was first discovered that a high-frequency electromagnetic field can trigger gas discharge leading to the emission of electromagnetic radiation.[40–42] Using these EDLs, it is possible to place the lamp directly into a microwave vessel and run a reaction under simultaneous UV and microwave irradiation. As a range of filling gases can be placed into EDLs, the emission wavelength can be varied, increasing the scope of the methodology.[43–45] In the field of environmental chemistry, there have been several reports demonstrating increased efficiency by combining microwave irradiation with the photocatalytic degradation of various substrates.[46–49] Similarly, an efficient microwave-assisted photochemical reactor for high-temperature water digestion has been developed,[50] as well as a method for the degradation of bromophenol blue[51] and for the non-catalytic remediation of aqueous solutions in the presence of H_2O_2.[52] Microwave-assisted photocatalysis using TiO_2 nanotubes has been used to degrade atrazine in aqueous solutions.[53] Hajek and coworkers have studied the effects of microwave heating and UV irradiation on 4-*tert*-butylphenol.[54] From a synthetic chemistry perspective, the field is relatively unexplored. Klan and coworkers have pioneered this area, showing the use of photochemistry in conjunction with microwave irradiation for Norrish Type II reactions,[55] aromatic substitution of 4-nitroanisole,[56,57] and the photo-Fries rearrangement of phenyl acetate.[58] This previous work, with one exception, was carried out in a domestic microwave apparatus.[59–61] Nüchter and coworkers studied the photochemical dehydrodimerisation of some hydrocarbons with microwave heating.[62]

We wanted to use this combination of microwave and photochemical technology to oxidize DHPs to pyridines using molecular oxygen as the oxidant. To achieve this, we first needed to design an apparatus that would allow us to load a vessel with a pressure of oxygen. The vessel would also need to be of a capacity large enough to hold an EDL. As a starting point, we used our design for a gas-loading attachment for our monomode microwave apparatus.[63] We developed a similar attachment that would interface with a quartz reaction vessel in a multimode microwave unit (Milestone MicroSynth). The vessel sits in a protective cover that has a small window towards the bottom, through which it is possible to see if the EDL is illuminated and record the vessel temperature via an infrared sensor located in the side of the microwave cavity. The internal temperature can also be monitored using a fibre-optic probe placed inside a ceramic thermal well. The gas is loaded through a fitting located in the vessel screw-cap top. The vessel and its top are shown in Fig. 2a and the apparatus in use is shown in Fig. 2b. We were thus able to load the vessel with gas and monitor the pressure during the course of the reaction.

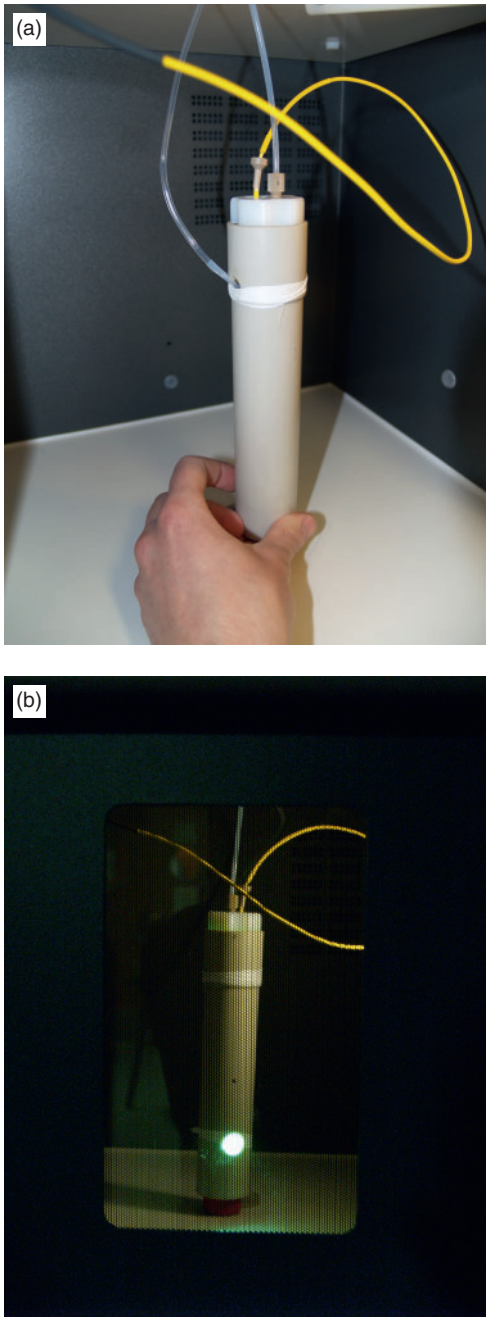
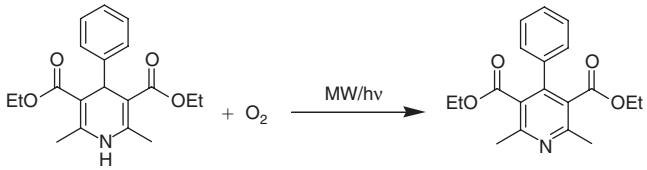


Fig. 2. Photographs of (a) the vessel assembly used for photooxidation chemistry, and (b) the apparatus in use.

We next turned our attention to developing conditions for the oxidation reaction. At the outset, we knew that the key to the success of the procedure was going to be finding a set of conditions under which the EDL would remain illuminated throughout the reaction. We first screened a range of potential solvents for the reaction. Not surprisingly, those that had a high dielectric constant heated very well but, because they absorbed much of the microwave irradiation, did not allow the EDL to illuminate. Low dielectric constant solvents such as hexane, although they heated slowly and the EDL illuminated, were incompatible with the oxidation chemistry because of poor substrate solubility. We decided to focus on moderately microwave-absorbent solvents in which the DHP substrates were soluble. We found that



1 **8a**

Scheme 2. Combination of photochemistry and microwave heating for the oxidation of 1,4-dihydropyridines to the corresponding pyridines.

acetonitrile was a suitable compromise. It was possible to heat this solvent while at the same time keeping the EDL illuminated throughout the entire course of the reaction.

Using diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate **1** as substrate, we started to explore conditions for performing the oxidation reaction (Scheme 2). We loaded the reaction vessel with the DHP and the EDL. It was not possible to stir the reaction mixture owing to the fact that the EDL rested on the bottom of the reaction vessel. Loading the vessel with 1000 kPa of oxygen and heating to 150°C using an initial microwave power of 400 W and holding at this temperature for 30 min led to the formation of a small quantity of the desired pyridine product **8a**. Unfortunately, once the reaction mixture reached temperature, the microwave power dropped substantially, causing the EDL to stop emitting light. To overcome this problem, we made some modifications to the method. The first was to use simultaneous cooling in conjunction with the microwave heating.[64] By removing heat from the reaction vessel, it was possible to increase the microwave energy required to maintain the target temperature, which allowed the EDL to continue emitting light. This was achieved by inserting an air line between the quartz vessel and the protective cover and passing air over the vessel surface during the course of the reaction. We then took a closer look at the microwave heating profile to determine the average microwave power input during the hold time at 150°C. Finding that this was 226 W, we then went back and performed the reaction in a two-stage program. In the first stage, a microwave power of 600 W was used to ramp the reaction mixture to the desired temperature of 150°C and initiate emission from the EDL. In stage 2, we set the maximum microwave power allowed to 250 W for the 30-min duration of the hold time. By doing this, once the reaction mixture had reached 150°C, a fairly constant power was applied to hold it at temperature. The result was that the EDL remained illuminated during the entire course of the reaction. Using this method, we obtained a quantitative conversion of **1** to **8a** (Table 1, entry 1). Shortening the reaction time had a deleterious effect on the product yield, as did performing the reaction at a higher temperature (Table 1, entries 2 and 3). Performing the reaction in an open vessel at reflux with the EDL in place and simply bubbling oxygen through the solution for the duration of the run gave only an 11% yield of the desired pyridine product (Table 1, entry 4). Thus, our optimal conditions were: 1000 kPa O_2, microwave (MW), irradiation with UV light (hν), 150°C, 30 min.

With a set of conditions in hand, we needed to perform control studies. First, we ran the reaction using **1** as substrate without the EDL in place and obtained a 17% yield of **8a** (Table 1, entry 5). We then performed the reaction with the EDL in the vessel but no overpressure of oxygen, instead using a 1000 kPa-nitrogen loading. In this case, we obtained a 20% conversion to **8a** (Table 1, entry 6). These experiments show that

Table 1. Oxidation of 1 to 8a under various reaction conditions
Reactions were run in a sealed tube, loaded with **1** (100 mg), in acetonitrile (7.5 mL). An initial microwave irradiation power of 600 W was used, the temperature being ramped from room temperature to the desired temperature and held until a total reaction time of 30 min had elapsed

Entry	Conditions	Conversion [%][A]
1	1000 kPa O_2, hν, 150°C, 30 min	100
2	1000 kPa O_2, hν, 150°C, 20 min	68
3	1000 kPa O_2, hν, 180°C, 30 min	46
4	Bubbling O_2, 85°C, 30 min	12
5	1000 kPa O_2, 150°C, 30 min	17
6	1000 kPa N_2, hν, 150°C, 30 min	20

[A]Determined by NMR spectroscopy, weighing the product obtained and using liquid chromatography mass spectrometry.

both oxygen and UV irradiation are key to the success of the reaction. Our findings are contrary to the recent report on the photochemistry of 4-phenyl-1,4-dihydropyridines bearing a substituent on the phenyl ring that suggested that the photooxidation does not require molecular oxygen.[65] We find that the conversion of the DHP to the pyridine is very facile when performed under our reaction conditions and does in fact require molecular oxygen.

We screened a range of DHP substrates under our oxidation conditions in order to probe the scope of the methodology. The results are shown in Table 2. When the group at the 4-position of the DHP ring is an aromatic ring, the only product observed is the 4-substituted pyridine (Table 2, entries 1 and 2). However, when an alkyl group is in the 4-position, we also see formation of the corresponding pyridine product that has been de-alkylated at the 4-position. The ratio of the two products depends on the nature of the alkyl substituent. When it is a methyl group (Table 2, entry 3), we obtain mainly the product with the methyl group intact. Moving to a pentyl group increases the proportion of de-alkylated product (Table 2, entry 4). When the carbon attached to the 4-position of the DHP ring is secondary, more extensive de-alkylation is observed (Table 2, entry 5). When moving from simple DHPs to those derived from dimedone, none of the desired oxidation product is formed (Table 2, entries 7 and 8). Instead, mainly starting material with small quantities of uncharacterized photoproducts are obtained.

Putting our results in context, the oxidative de-alkylation of the 4-position in substituted DHP substrates has been observed previously using standard oxidants[66] and also photochemically,[36,37] particularly in the case of 4-benzyl- and *sec*-alkyl-substituted examples. However, there is often a mixture of both the desalkyl product and that with the alkyl group still intact. Our methodology, particularly in the case of the cyclohexyl-substituted DHP, shows that the formation of the unsubstituted pyridine can be effected almost quantitatively. From a mechanistic perspective, the increased propensity toward photochemical cleavage of an alkyl substituent is not unexpected, a secondary radical being more stable than a primary one. By using cyclohexane carboxaldehyde or the cheaper isobutyraldehyde as a reagent in the preparation of DHPs, it would be possible ultimately to generate pyridines bearing no substituent at the 4-position. This would overcome the issues associated with poor yields when using formaldehyde as a reagent for DHP synthesis. Although the DHP would bear a secondary alkyl group in the 4-position, on photolysis, this would be lost to yield exclusively the desired pyridine unsubstituted in the 4-position. A similar strategy could be applied in the solid-phase synthesis of pyridines. Starting from an immobilized secondary aldehyde, the DHP could be built on the support and then photochemically cleaved in a traceless manner to yield the desired pyridine.

Summary

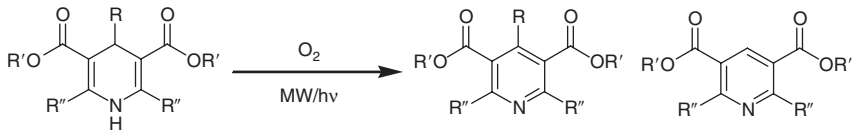
In summary, we have built on our previously reported methodology for the preparation of 1,4-DHPs using microwave heating. We then report for the first time the use of tandem microwave heating and UV irradiation for the efficient oxidation of DHPs to pyridines. The oxidation reactions are performed in a sealed vessel using oxygen as the oxidant and an EDL as the irradiation source. We show that both oxygen and UV irradiation are key to the success of the reaction. The one parameter in the oxidation that we cannot probe unequivocally is the need for heating in conjunction with irradiation. This being said, our methodology is significantly faster than those published previously using photoactivation in the presence of molecular oxygen. The outcome of the oxidation depends on the DHP substrate used. When the substituent at the 4-position of the DHP ring is an aromatic ring, the only product observed is the substituted pyridine. When an alkyl group is in the 4-position, we also see formation of the corresponding pyridine product that has been de-alkylated at the 4-position. The extent to which de-alkylation occurs depends on whether the substituent is primary or secondary. In the case of DHPs generated from dimedone, no oxidation is observed on photolysis under an oxygen atmosphere. Work is under way to probe in more detail the mechanism of the reaction as well as extend the application of tandem microwave heating and UV irradiation to other organic transformations.

Experimental

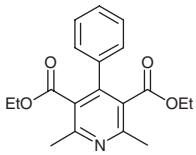
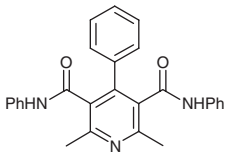
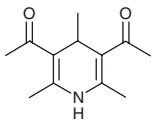
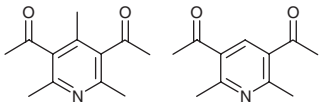
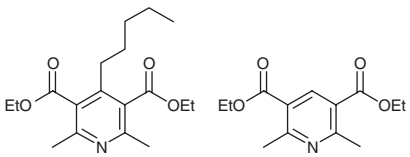
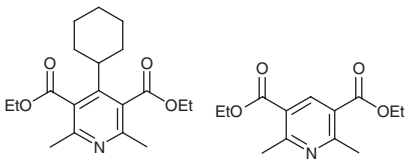
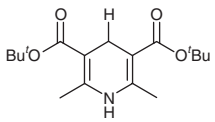
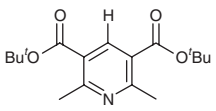
Description of the Apparatus

The apparatus used for preparing the dihydropyridines has been described previously.[23] The oxidation reactions were conducted using a commercially available multimode microwave unit (Milestone MicroSynth). The instrument was equipped with two magnetrons with combined continuous microwave output power from 0 to 1000 W. One quartz reaction vessel (45 mL capacity) was employed. The reagents were placed into the quartz tube, this in turn being placed into a protective sleeve and sealed with a screw-top before being loading into a stand inside the microwave cavity. The sleeve, made of a high-temperature resin material and reinforced with fibreglass, was spring loaded at the bottom such that when the top was screwed down, the spring was compressed, holding the vessel in tight contact with the top. In the screw top there was a thermal well and a hole with a screw thread. Direct temperature monitoring and control was achieved via a fibre-optic probe inserted into the thermal well. The reaction vessel was loaded with gas by attachment of a narrow-gauge Teflon tube to the vessel top by means of the screw thread. The vessel was pressurized from an oxygen cylinder to 1000 kPa linked to a three-way connector. After loading, the gas cylinder was disconnected and the three-way connector turned to be in series with a gauge to allow monitoring of pressure during the course of the reaction. Reaction parameters (temperature, microwave power, and desired time) were programmed into a controller unit. The EDL used was produced by Milestone srl and comprised a high purity quartz vacuum bulb containing mercury vapour.

Table 2. Oxidation of 1,4-dihydropyridines with oxygen gas using microwave irradiation in conjunction with photolysis
Reactions were run in a sealed tube, loaded with 1,4-dihydropyridine (0.3 mmol) in acetonitrile (7.5 mL) and 1000 kPa oxygen. An initial microwave (MW) irradiation power of 600 W was used to heat to 150°C and then a maximum power of 250 W was used to hold the reaction mixture at 150°C for 30 min



a **b**

Entry	Substrate	Products	Conversion [%][A]	Ratio **a**:**b**[B]
1	**1**	 **8a**	100	100:0
2	**4**	 **9a**	99	100:0
3		 **10a** **10b**	95	90:10
4	**3**	 **11a** **11b**	95	28:72
5	**2**	 **12a** **11b**	95	3:97
6		 **13a**	99	n.a.
7	**5**	–	0	n.a.
8	**7**	–	0	n.a.

[A]Determined by NMR spectroscopy, weighing the product obtained and using liquid chromatography mass spectrometry (LC-MS).
[B]Determined by LC-MS.

*General Experimental Procedure for the Preparation of 1,4-Dihydropyridines: Preparation of **1***

Benzaldehyde (0.51 mL, 5 mmol), ethyl acetoacetate (2.15 mL, 17 mmol), concentrated aqueous ammonium hydroxide (2.8 mL, 4.1 mmol), water (5 mL), and ethanol (5 mL) were combined in a 100-mL round-bottom long-neck flask equipped with a stir bar. The flask was placed into the microwave cavity and a reflux condenser attached to the flask. The solution was heated to reflux (84°C) and then held at this temperature for a further 25 min. The contents of the vessel were allowed to cool to 60°C, and then poured onto ice (30 g). The crude product was filtered, washed with water, dissolved in ethyl acetate (50 mL), and washed with water. The organic phase was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate **1** (1.18 g, 72% yield) as a light yellow solid. δ_H ($CDCl_3$, 500 MHz) 1.23–1.26 (6H, m), 2.34 (6H, s), 4.08–4.15 (4H, m), 5.01 (1H, s), 5.75 (bs), 7.14 (1H, t, *J* 6.7), 7.23 (2H, t, *J* 7.5), 7.30 (2H, d, *J* 8.0). δ_C ($CDCl_3$, 126 MHz) 14.3, 19.6, 39.6, 59.7, 104.2, 126.1, 127.8, 128.0, 143.9, 147.8, 167.7.

NMR Data for Other 1,4-Dihydropyridines Prepared in the Present Study

2: δ_H ($CDCl_3$, 500 MHz) 0.93–1.30 (6H, m), 1.32 (6H, t, *J* 7.1), 1.56–1.80 (5H, m), 2.32 (6H, s), 3.95 (1H, d, *J* 5.7), 4.13–4.27 (4H, m), 5.61 (1H, bs). δ_C ($CDCl_3$, 126 MHz) 14.4, 19.5, 26.6, 26.7, 28.8, 38.4, 45.8, 59.6, 102.0, 144.4, 168.7.

3: δ_H ($CDCl_3$, 300 MHz) 0.86 (3H, t, *J* 7.0), 1.15–1.35 (14H, m), 2.30 (6H, s), 3.94 (1H, t, *J* 5.8), 4.04–4.29 (4H, m), 5.53 (1H, bs).

4: δ_H ([D_6]DMSO, 400 MHz) 2.09 (6H, s), 5.10 (1H, s), 6.96 (2H, t, *J* 7.3), 7.08 (1H, t, *J* 6.8), 7.18–7.24 (8H, m), 7.54 (4H, d, *J* 7.9), 8.05 (s, 1H), 9.28 (2H, s). δ_C ([D_6]DMSO, 100 MHz) 17.3, 42.0, 105.7, 119.4, 122.6, 125.9, 127.1, 128.0, 128.4, 137.8, 139.5, 167.4.

5: δ_H ($CDCl_3$, 400 MHz) 1.10 (6H, s), 1.24 (6H, s), 2.29–2.49 (8H, m), 5.54 (1H, s), 7.09 (2H, d, *J* 7.8), 7.17 (1H, t, *J* 7.1), 7.26 (2H, m), 11.90 (1H, bs). δ_C ($CDCl_3$, 100 MHz) 27.4, 29.7, 31.4, 32.8, 46.5, 47.1, 115.6, 125.8, 126.8, 128.2, 138.1, 190.4.

6: δ_H ($CDCl_3$, 300 MHz) 0.76 (2H, q, *J* 10.9), 1.07 (6H, s), 1.09 (6H, s), 1.16–1.35 (3H, m), 1.58–1.75 (5H, m), 2.20–2.40 (8H, m), 2.49–2.68 (1H, m), 3.60 (1H, d, *J* 11.1), 11.5 (1H, bs).

7: δ_H ($CDCl_3$, 300 MHz) 0.85 (6H, d, *J* 6.8), 1.07 (6H, s), 1.10 (6H, s), 2.24–2.38 (8H, m), 2.93–2.98 (1H, m), 3.48 (1H, d, *J* 11.1), 11.5 (1H, bs).

*General Experimental Procedure for the Oxidation of 1,4-Dihydropyridines: Preparation of **8a***

To a quartz reaction vessel was added **1** (104.2 mg, 0.316 mmol), acetonitrile (7.5 mL), and the EDL. The vessel was sealed with the screw-top with ports for gas-addition and fibre optic temperature measurement. A pressure of 1000 kPa oxygen was introduced, then vented to the atmosphere. This process was repeated three times. A final charge of 1000 kPa oxygen was introduced. The vessel was then sealed, the temperature probe inserted, and the vessel placed in the microwave cavity. The reaction was heated to 150°C with a 600 W maximum for the first minute of heating, then the maximum was decreased to 250 W. An external pressurized air line was fitted into the vessel jacket so that the vessel could be cooled enough to require more than 100 W to maintain the desired temperature of 150°C. After 20 min at 150°C, the reaction was cooled to 50°C; then the remaining pressure was carefully vented. The solvent was removed under vacuum. ^1H and ^{13}C NMR in $CDCl_3$ indicated >95% conversion to **8a**. Liquid chromatography mass spectrometry was used to verify the product and determine the proportion of de-alkylation, if any. δ_H ($CDCl_3$, 500 MHz) 0.91 (6H, t, *J* 7.1), 2.62 (6H, s), 4.01 (4H, q, *J* 7.2), 7.24–7.38 (5H, m). δ_C ($CDCl_3$, 126 MHz) 14.3, 19.6, 39.6, 59.7, 104.2, 126.1, 127.8, 128.0, 143.9, 147.8, 167.7.

NMR Data for Other Pyridines Prepared in the Present Study

9a: δ_H ($CDCl_3$, 500 MHz) 0.93–1.30 (6H, m), 1.32 (6H, t, *J* 7.1), 1.56–1.80 (5H, m), 2.32 (6H, s), 3.95 (1H, d, *J* 5.7), 4.13–4.27 (4H, m), 5.61 (1H, bs). δ_C ($CDCl_3$, 126 MHz) 14.4, 19.5, 26.6, 26.7, 28.8, 38.4, 45.8, 59.6, 102.0, 144.4, 168.7.

10a: δ_H ($CDCl_3$, 400 MHz) 2.06 (3H, s), 2.43 (6H, s), 2.48 (6H, s). δ_C ($CDCl_3$, 100 MHz) 16.1, 21.8, 32.2, 135.9, 151.7, 175.6, 205.5.

11a: δ_H ($CDCl_3$, 300 MHz) 0.86 (3H, m), 1.40 (3H, t, *J* 7.1), 1.10–1.40 (6H, m), 2.83 (6H, s), 3.98 (2H, t, *J* 6.6), 4.38 (4H, q, *J* 7.1). δ_C ($CDCl_3$, 75 MHz) 13.9, 14.2, 22.2, 22.4, 24.5, 27.3, 28.0, 61.5, 123.2, 141.1, 162.1, 165.8.

11b: δ_H ($CDCl_3$, 500 MHz) 1.41 (6H, t, *J* 7.1), 2.85 (6H, s), 4.40 (4H, q, *J* 7.2), 8.69 (1H, s). δ_C ($CDCl_3$, 126 MHz) 14.3, 24.4, 61.5, 123.4, 141.2, 162.1, 165.8.

13a: δ_H ($CDCl_3$, 300 MHz) 1.57 (18H, s), 2.78 (6H, s), 8.52 (1H, s). δ_C ($CDCl_3$, 75 MHz) 24.5, 28.2, 82.3, 124.9, 141.0, 161.0, 165.2.

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