An Efficient and Fast Procedure for the Hantzsch Dihydropyridine Synthesis under Microwave Conditions

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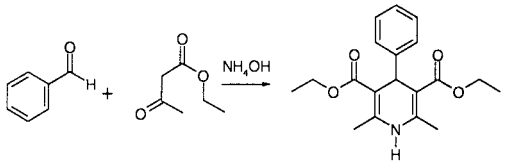
Abstract: A single-mode microwave cavity synthesizer with temperature and pressure control was used to accelerate the Hantzsch synthesis of 4-aryl and 4-alkyl-2,6-dimethyl-1,4-dihydro-3,5-pyridinedicarboxylates. In comparison with both conventional methods and microwave-assisted reactions performed in a domestic microwave oven, shorter reaction times and higher yields were obtained. The improved yields under microwave conditions made it possible to synthesize a small library, with acceptable purity.

Key words: microwave, multicomponent reaction, temperature control, combinatorial synthesis

The preparation of 1,4-dihydropyridines by classical Hantzsch synthesis,[1] a one-pot condensation of an aldehyde with alkyl acetoacetate and ammonia was developed more than one hundred years ago. In the forties the interest for this substance class increased due to their pharmacological activity.[2] 4-Aryl-1,4-dihydropyrdines form an important class of calcium channel antagonists.[3] When sterically hindered aldehydes are employed in classical Hantzsch synthesis, extended reaction times under reflux are needed and still the yields are generally low.[4,5] Improved methods for the Hantzsch synthesis have previously been described by Alajarin *et al* [6] *a*nd Watanabe *et al*.[7] The former authors were able to shorten the reaction times from 12 hours to 4 minutes by using a domestic microwave oven and sealed Teflon bombs. The yields obtained however, were equal or slightly higher compared to those obtained by conventional heating. Watanabe *et al* improved the yields with the use of an autoclave. The drawback was extended reaction times compared to conventional heating. Considerable attention has been received for microwave assisted organic synthesis since 1986, but it is still a bit unclear why many reactions works extremely well with microwave dielectric heating in comparison with conventional methods. It seems however to be accepted that the different temperature range caused by microwave dielectric heating is the main contributing factor to any acceleration observed.[8] It is however important to emphasize that in domestic microwave ovens, the temperature will increase with time when the power is constant, due to lack of temperature control which was well observed by Alajarin *et al* since the Teflon bombs they used were deformed when running at 500 W. Heating at a fixed power of 400 W for 4 min, appeared for them to be the best compromise between efficiency and safety. The temperature increase is also dependent on the volume and the content of the sample, which mean that when changing the amount of substrate or reagents the rate of temperature increase will also change. When optimizing a chemical reaction, one of the parameters that is important to have control of is the temperature. The two reports described above encouraged us to investigate if the yield could be increased and the reaction time decreased, by the use of a microwave cavity with temperature control. We used a Smithsynthesizer™,[9] a single-mode closed vessel microwave synthesizer with both temperature and pressure control.

In the search for optimal reaction conditions different equivalents of benzaldehyde, ethyl aceto-cetate and aqueous ammonium hydroxide were used. Temperature and reaction times were also varied (Table 1). When using the same temperature (110 °C) as described in the paper by Watanabe *et al*, we obtained 55% yield in only 10 min. It should also be noted that the best results were obtained when the reaction temperature was more than 40° C above the normal boiling point, something that could only be achieved in a closed vessel system.[10]

Table 1 Optimization of Reaction Condition for the Synthesis of Diethyl 4-phenyl-2,6-dimethyl-1,4-dihydro-3,5-pyridine dicarboxylate



Entry	Aldehyde Eq.	β-keto ester Eq.	NH_4OH Eq.	Temp(C)/ time(min)	Yield[a]
I	1	2.2	2.4	110°/10	55[b]
II	1	2.2	2.4	120°/20	65[b]
III	1	3.0	4.0	120°/20	70[b]
IV	1	5.0	4.0	120°/20	86[b]
V	1	5.0	4.0	140°/10	85[b]
VI	1	5.0	4.0	160°/10	76[b]
VII	1	5.0	4.0	140°/10	76[c]
VIII	1	5.0	10.0	140°/10	72[d]

[a]Isolated yield > 95% purity, [b]volume 2.6 mL, solvent: 25% NH_4OH (aq), [c]volume 5.0 mL, solvent: 25% NH_4OH (aq), [d] volume 5.0 mL, solvent: ethanol.

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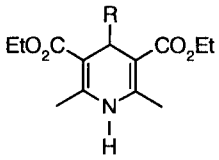
Table 2 Synthesis of Diethyl 4-aryl-2,6-dimethyl-1,4-dihydro-3,5-pyridinedicarboxylates (**1a-1g**) and Diethyl 4-alkyl-2,6-dimethyl-1,4-dihydro-3,5-pyridinedicarboxylates (**2a-2c**)



Compound	R	Temp (C)	Smith Synt.[9,a] Time (min)/ Yield (%)[e]	Domestic microwave[b] Time (min)/ Yield (%)	Reflux Time (h)/ Yield (%)	Autoclave[c] Time(h)/ Yield(%)
1a	Ph	140°	10/84	4/52	12/50	--
1b	2-NO_2-Ph	150°	10/63	4/34	12/50	--
1c	2-OCH_3-Ph	150°	10/68	4/21	12/15	--
1d	2-Cl-Ph	140°	10/81	4/55	12/39	17/92
1e	2-CH_3-Ph	140°	15/66	--	12/72	25/70
1f	2-Br-Ph	140°	10/51	--	--	--
1g	3,4,5-OCH_3-Ph	140°	15/63	--	--	--
2a	cyclohexyl	140°	10/74	--	12/38	--
2b	*i*-propyl	140°	10/92	--	12/61	--
2c	*n*-heptyl	140°	10/74	--	12/26(hexyl)	--

[a]volume 2.6 mL, solvent: 25% NH_4OH (aq), [b] volume 5.0 mL, solvent: 25% NH_4OH (aq), [c]temp: 110°, solvent: ethanol, [e]isolated yield > 95% purity.

The so called superheating effect[11] could only increase the boiling point between 10-20 °C compared to the boiling point at atmospheric pressure. When excluding ethanol, a common solvent in Hantzsch synthesis, from the reaction and using aqueous ammonium hydroxide both as a reagent and a solvent, a slightly higher yield was obtained (see entry VII and VIII, Table 1). Various substituted benzaldehydes with electron withdrawing or electron donating groups and some aliphatic aldehydes were treated with ethyl acetoacetate and aqueous ammonium hydroxide (Table 2) under the conditions found for entry V, Table 1. In our study we found that a reaction time of 10-15 minutes was enough to get 20-40% higher yield compared both to conventional heating and the use of a domestic oven.[7] Compared to the yields obtained by the use of an autoclave our yields are slightly lower. The reaction times are however much shorter, which is in many cases beneficial (Table 2). Due to short reaction times, high yield and easy work-up procedure by recrystallization were possible when following the protocol developed above (entry V, Table 1), a serial synthesis of 24 compounds was performed.

In order to increase the diversity,[12] 6 different aldehydes and 4 different β-keto esters or 1,3- dicarbonyl substrates were used (Table 3). After the reaction the samples were evaporated in a Savant Speed-vac and the residues were recrystallized from ethanol and water. All 24 compounds were formed in moderate to good yield (39%-89%) and with low to excellent purity (53%-99%, determined by LC/MS) (Table 3). Reactions assisted with microwave dielectric heating are described in the literature to give shorter reaction times and often higher yields compared to conventional methods.[13] In conclusion, our results show that microwave assisted synthesis of 1,4-dihydropyridines with temperature control made it possible to increase the yields compared to other methods and still with short reaction times. With the use of the syntheziser, it was also possible to synthesize 24 compounds within a few hours.

We also believe that the reason why microwave heating has not been more accepted in the scientific community during the last 15 years is the lack of controllability and reproducability, and therefore we believe the introduction of instrument with temperature control will change the common attitude towards the technology.

Acknowledgement

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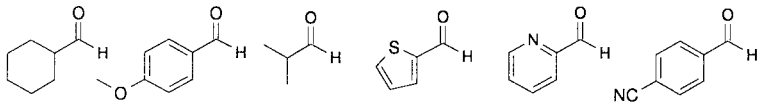
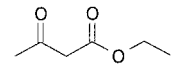
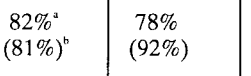
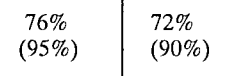
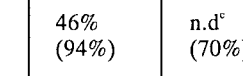
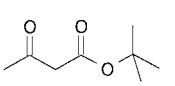
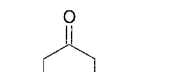
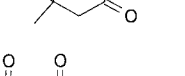
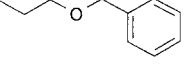
Table 3 Showing the Building Blocks Used in the Library Syntheses.



					
	82%[a] (81%)[b]	78% (92%)	76% (95%)	72% (90%)	46% (94%)	n.d[c] (70%)
	63% (94%)	46% (70%)	54% (72%)	66% (80%)	52% (90%)	68% (88%)
	39% (85%)	80% (86%)	75% (82%)	75% (92%)	80% (94%)	89% (99%)
	n.d[c] (53%)	n.d[c] (60%)	n.d[c] (63%)	n.d[c] (68%)	84% (87%)	n.d[c] (83%)

[a]Isolated yield, [b]purity determined by LC/MS analysis, [c]the product precipitated as an oil together with the starting materials.

References and Notes

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(9) SmithSyntheziser is availible from Personalchemistry.
(10) General procedure: The preparation of Diethyl 4-phenyl-2,6-dimethyl-1,4-dihydro-3,5-pyridinedicarboxylate is representative for all syntheses.
Benzaldehyde (2.5 mmol), ethyl acetoacetate (12.5 mmol) and 25% aqueous ammonium hydroxide (10.0 mmol) were placed in a glass vial, sealed with a teflon septa and then placed in the microwave cavity. The reaction mixture was stirred at 140° C for 10 min. (see Tables 1-3). After completion, crude reaction mixture was evaporated to dryness and purified on a silica gel column (heptane/ethyl acetate 3:1-2:1), which gave pure 2,6-dimethyl-1,4-dihydro-4-phenyl-3,5-pyridinecarboxylate in 84% yield as a white solid. The product was recrystallized from EtOH and water giving a white powder (mp 156-157 °C (lit. Ref[4]. mp 157-159° C)), ^{13}C NMR($CDCl_3$): δ 14.6 (CH_3), 19.8 (CH_3), 40.0 (CH), 60.1 (CH_2O-), 104.4 (C=C), 126.5-128.4 (aromatic C), 144.4 (C=C), 148.2 (aromatic C), 168.1 (carbonyl C); ^{1}H NMR ($CDCl_3$): δ 1.27 (t, 6H, CH_3), 2.35 (s, 6H, CH_3), 4.15 (m, 4H, CH_2O-), 5.04 (s, 1H, CH), 5.88 (s, 1H, NH), 7.10-7.35 (5H, aromatic H).
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