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Review

Synthesis and Aromatization of Hantzsch 1,4-Dihydropyridines under Microwave Irradiation. An Overview [§]

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Abstract: Domestic microwave ovens as well as laboratory reactors have been successfully employed to prepare dialkyl 1,4-dihydropyridine-3,5-dicarboxylates and to induce the synthesis of the corresponding aromatic derivatives. In that latter particular case, unexpected results have been reported.

Keywords: Aromatization, dihydropyridine, Hantzsch, microwave, oxidation, pyridine

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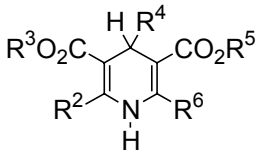
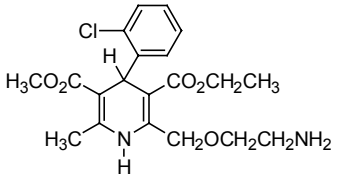
Introduction

Described more than one century ago by Hantzsch [1], dialkyl 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylates (**1**; 1,4-DHP; Figure 1) have now been recognized as vital drugs in the treatment of angina and hypertension. Some of them (Amlodipine **2**, Felodipine **3**, Isradipine **4**, Lacidipine **5**, Nicardipine **6**, Nifedipine **7**, Nimodipine **8**, Nitrendipine **9**) have been commercialized and it has been proven that their therapeutic success is related to their efficacy to bind to calcium channels and consequently to decrease the passage of the transmembrane calcium current, associated in smooth muscle with a long lasting relaxation and in cardiac muscle with a reduction of contractility throughout the heart [2-4].

Figure 1.



Hantzsch1,4-DHP
1



Amlodipine
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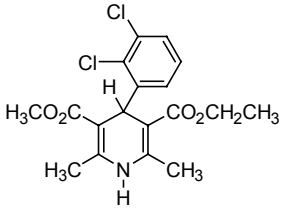

Felodipine
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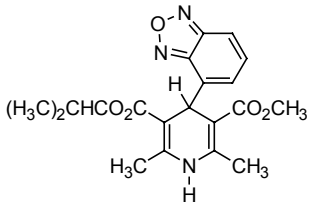
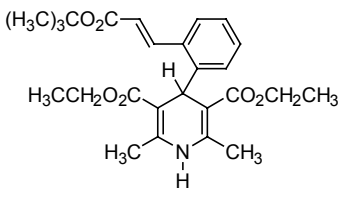


Isradipine
4



Lacidipine
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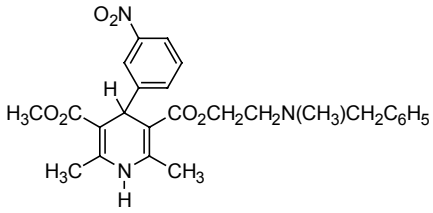

Nicardipine
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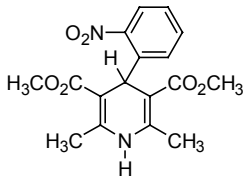

Nifedipine
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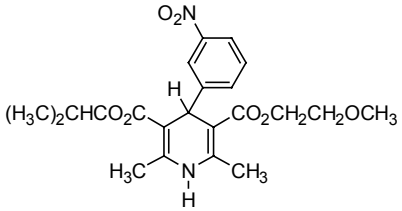
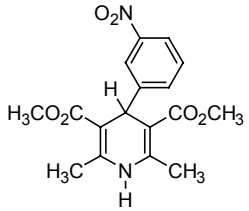


Nimodipine
8



Nitrendipine
9

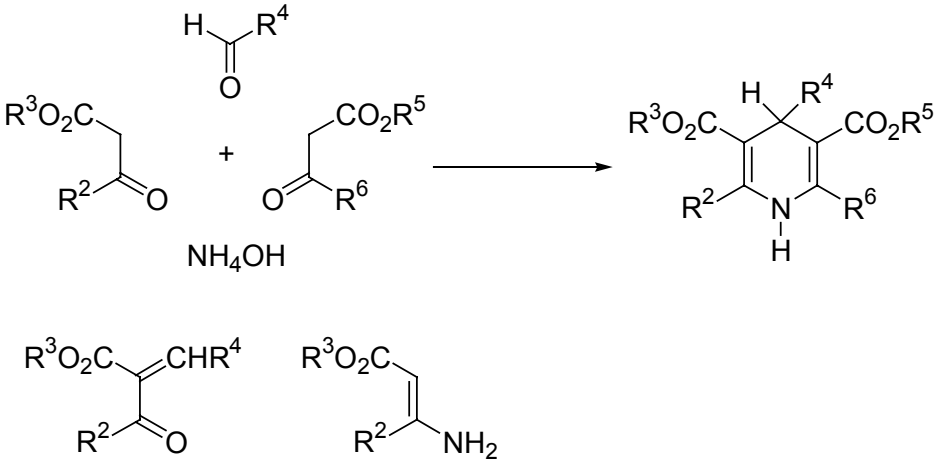
The usefulness of those calcium antagonists has led to the development of novel synthetic strategies to improve classical methods of preparation [5-7] and microwave activation stands among the alternative routes proposed the past decade.

Aromatization of 1,4-DHP has also attracted considerable attention in recent years as Böcker [8] has demonstrated that metabolism of those drugs involves a cytochrome P-450 catalyzed oxidation in the liver. The so-obtained pyridines are devoid of the pharmacological activity of the parent heterocycles and are further transformed by additional chemical modifications. Due to the biological importance of the oxidation step of 1,4-DHP, that reaction has been the subject of a large number of studies and a plethora of reagents has been utilized to mimic the *in vivo* transformation. In that field, surprising results have been collected when the reactions are performed under microwave irradiation.

Hantzsch 1,4-DHP Synthesis

In 1882, Hantzsch [1] reported the first synthesis of dialkyl 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylates from a refluxing mixture of an aldehyde, a β-ketoester, and aqueous ammonium hydroxide in ethanol (Scheme 1). That multicomponent reaction often affords the target compounds in good yields and this experimental method remains the most widely used protocol to access to 1,4-DHP differently substituted in position 4. Some modified procedures have later been proposed and they involve the use of preformed Knoevenagel adducts between the aldehyde and the ketoester or the use of preformed enaminoesters (represented in the *E* form to clarify the scheme).

Scheme 1.



The pioneering report on the use of microwave activation to obtain Hantzsch 1,4-DHP was published by Alajarin *et al.* in 1992 [9]. This group prepared a series of 4-aryl derivatives in a domestic oven by the classical multicomponent method (aldehyde: 15 mmol; alkyl acetoacetate: 43 mmol; ammonia: 30 mmol; ethanol: 3 mL). Yields ranged from 15 to 52 % for a reaction time of 4 minutes. The authors claim that classical protocols for the formation of the same compounds require a

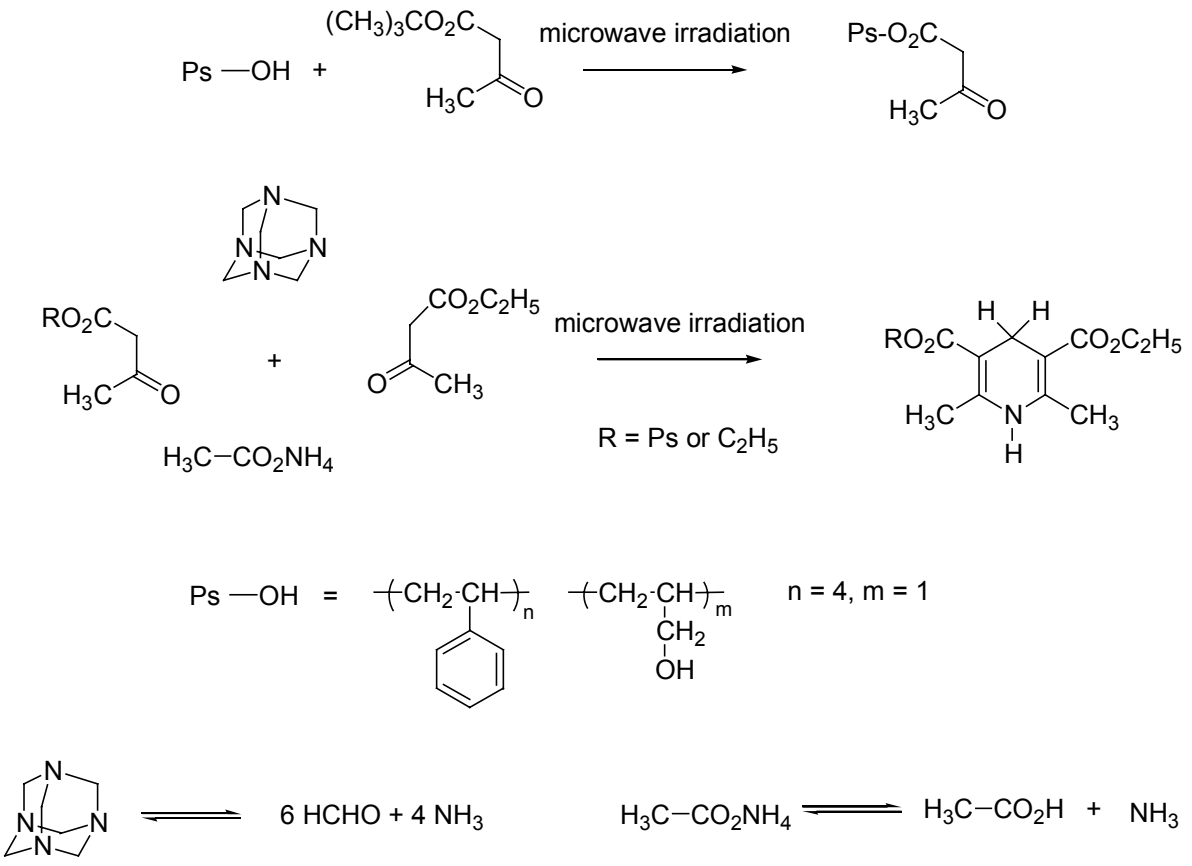
reflux period of 12 hours but they did not notice any yield improvement when microwave irradiation was applied. Three years later the same group extended its work [10] to the preparation of 3,5-unsymmetrically substituted 1,4-DHP starting from arylmethyleneacetoacetate (8 mmol) and 3-aminocrotonate (4 mmol) in ethanol (4.5 mL). This report again emphasizes that the rapidity of the microwave-assisted syntheses does not affect the isolated yields. The same year Zhang [11] obtained four 4-aryl 1,4-DHP from 3-aminocrotonate (20 mmol), methyl acetoacetate (20 mmol) and arylaldehydes (20 mmol) in a domestic oven. For the first time, the preparations were conducted in the absence of solvent. Yields ranging from 59 to 77 % are reported and optimized heating periods do not exceed 10 minutes. To avoid any loss of volatile material, the reaction flasks were fitted with a condenser containing xylene. Also in 1995, Khadilkar [12] used the same building blocks as Zhang but in the presence of a solvent (ethanol, volume not reported; 3-aminocrotonate: 10 mmol; methyl acetoacetate: 14 mmol; arylaldehyde: 10 mmol). The heterocycles were prepared in a domestic oven within 3 to 5 minutes in 32 to 80 % yield.

Interestingly, Khadilkar [13] also described the formation, in a domestic oven, of 1,4-DHP in an aqueous hydrotrope solution (50% butylmonoglycolsulphate : 5 ml). The experiments were performed with 3-aminocrotonate (10 mmol), methyl acetoacetate (14 mmol) and aliphatic or aromatic aldehydes (10 mmol). The final products were obtained within 3 to 6 minutes in 35 to 97 % yield. All reactions described by Khadilkar [12, 13] were carried out by exposing the reactants to microwaves in containers equipped with a condenser charged with precooled carbon tetrachloride. The coupling of microwave heating (in a domestic oven) with the use of a mineral solid support (alumina: 2 g) has later been exploited by Suarez [14] to synthesize, within 6 minutes and with a yield higher than 85 %, an unsymmetrical 1,4-DHP from methyl 3-aminocrotonate (3 mmol), ethyl acetoacetate (3 mmol) and benzaldehyde (3 mmol). A catalytic amount of DMF (0.5 mL), as an energy transfer medium to attain higher temperatures, was added to the reaction mixture.

In 2001, a single-mode microwave reactor (SmithSyntheziser from Personal Chemistry, Uppsala, Sweden) was used for the first time to accelerate the preparation of series of 1,4-DHP from various alkyl acetoacetates (12.5 mmol), aldehydes (2.5 mmol) and 25 % aqueous ammonium hydroxide (10.0 mmol) [15]. In comparison with experiments performed in domestic ovens, use of a laboratory synthesizer does not appear to provide improved results. Indeed, for irradiation times varying from 10 to 15 minutes, reported yields fluctuate from “not determined” to 92 % whereas purity, evaluated by LC/MS, ranges from values as modest as 53% to 95%. Among all those reports, let us point out that, independently of the experimental conditions, Nifedipine (**7**) has only been obtained in moderate yields (32 % [12], 34 % [9], 35 % [13], 58 % [10]). On the other hand Nimodepine (**8**) was prepared nearly quantitatively (94 % [10]) whereas Nitrendipine (**9**) was synthesized in 72 % [13] and 98 % [10] yields. Recently, 1,4-DHP anchored to a soluble polymer - poly(styrene-*co*-allyl alcohol) - have been described [16, 17]. Such polymers, as well as the parent 4-unsubstituted 1,4-DHP, can be synthesized (Scheme 2) under solvent-free conditions and microwave irradiation in a monomode oven (Synthewave 402 from Prolabo). The experimental procedure only requires 100 seconds. The original strategy involves ethyl acetoacetate (20 mmol) and hexamethylenetetramine (8 mmol) as the source of

the ammonia-formaldehyde mixture. Ammonium acetate (10 mmol) was added to the reaction medium in order to obtain the stoichiometric balance between ammonia and methanal

Scheme 2.

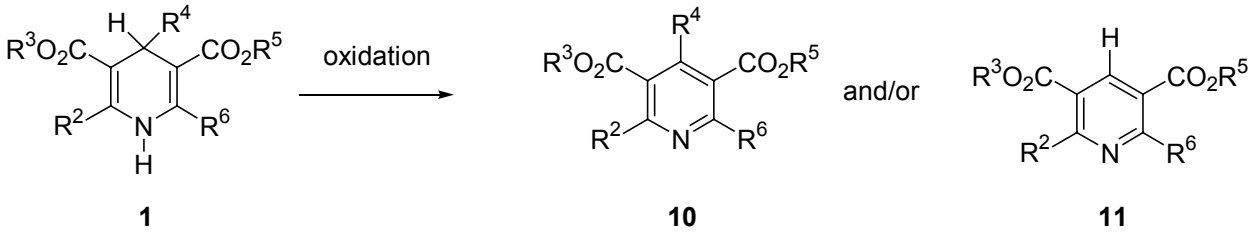


Aromatization of Hantzsch 1,4-DHP

From the numerous results published on the aromatization of Hantzsch 1,4-DHP (excluding the papers dealing with microwave-mediated experiments) the following rules can be established (Scheme 3):

- Heterocycles bearing an aryl (or heteroaryl) group in position 4 always undergo a dehydrogenation process [18];
- Heterocycles bearing a linear alkyl group in position 4 undergo a dehydrogenation process, except *in vivo* where dealkylation occurs and is accompanied by inhibition of cytochrome P-450 [8, 18-20];
- Heterocycles bearing a benzylic or secondary alkyl group in position 4 undergo a dealkylation process except when the oxidizing species is sulfur [21] or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone [22].

Scheme 3.



1 **10** **11**

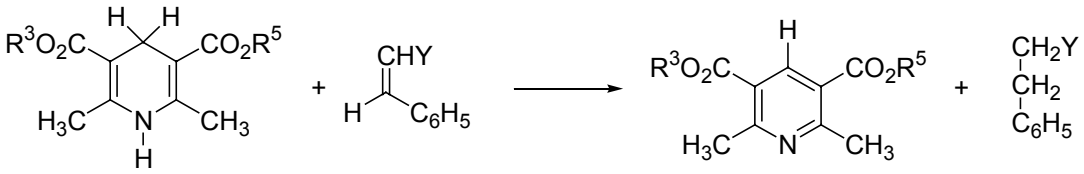
Oxidation of 1,4-DHP under microwave irradiation was reported for the first time in 1991 by Alvarez *et al.* [23, 24]. They oxidized a series of 1,4-DHP (0.5 g) in a domestic oven by treatment on a mixture of manganese dioxide and Mexican bentonite clay (5.0 g, prepared from 1:2 or 1:4 mixtures of potassium permanganate and clay) in the absence of solvent. The procedure is characterized by short reaction times (10 minutes) and fair to quantitative yields (47-100 %). The most noticeable results were observed when starting from 1,4-DHP bearing a methyl, ethyl, or propyl group in position 4. Indeed those reactions afforded, unexpectedly, mixtures of 4-alkylpyridines (**10**) and 4-unsubstituted pyridine (**11**). In contrast, the same group related [25], two years later, that those 4-alkyl 1,4-DHP (0.25 g) do not undergo the dealkylation process when they are treated for 1 minute in a domestic microwave oven in the presence of a HNO_3/Mexican bentonite clay system (2.5 g; prepared from a 1:1 mixture of the components). Aromatization of 1,4-DHP has also been studied by Varma [26]. He observed that solid state oxidation of 1, 4-DHP (1mmol) using elemental sulfur (1.3 mmol) and microwave activation in a domestic oven affords the dehydro derivatives, whichever the 4-substituent is.

Our experience in the field of 1,4-DHP chemistry [7, 22, 27] led us to initiate a systematic study of the solvent-free aromatization of Hantzsch 1,4-DHP upon microwave and classical heating in the absence of any external oxidant, except air [28]. In order to compare our results, we determined the temperature increase profile of a bath of alumina under given power settings in a domestic microwave oven and we managed to maintain another bath of alumina at the same final temperature (200 °C) on a hot plate. Then, taking care to use fresh alumina in each experiment, we put a round-bottom flask filled with 10 mmol of the 1,4-DHP in the bath and submitted it either to microwave irradiation or to classical heating for the same given period of time (10 min). The 4-phenyl DHP derivative appeared to be quite stable under microwave and classical conditions. The 4-isopropyl DHP derivative afforded (around 50 % conversion) the 4-unsubstituted pyridine (**11**) under both kinds of heating. Interestingly the 4-propyl DHP derivative yielded a mixture of the (expected) 4-alkylated pyridine (**10**) and the (less expected) 4-unsubstituted pyridine (**11**) under both experimental conditions. We observed that slight modifications of the temperature of the bath were accompanied by dramatic variations of the overall yields: yields increased from 25 % to 80 % when the temperature rose from 180 to 200 °C. However the ratio of concentrations **10**:**11** remains fairly constant and in each case in favor of the dealkylated product (**10**:**11** = 1 : 4). We also noticed that the 4-propylpyridine (**10**) is stable upon heating and therefore formation of the 4-unsubstituted heterocycle (**11**) cannot be explained by a dealkylation of

10. Those preliminary results suggest that specific microwave effects can hardly be claimed to account for the aromatization of 1,4-DHP. On the other hand our observations reveal a particular behavior of Hantzsch 1,4-DHP upon heating and a dramatic influence of the temperature on their susceptibility to be oxidized by air (oxygen) above their melting point. Therefore when considering the aromatization of 1,4-DHP in dry media, the rate of the oxidation process induced by air should not be neglected. That rate being highly temperature-dependent, the presence of an inorganic solid in the reaction mixture emerge as an additional factor that can modify the yields, due to the thermal conductivity properties of that inorganic substance especially under microwave irradiation.

Finally, mention should be made that Barbry [17] utilized the parent 1,4-DHP (6 mmol) in the reduction (Scheme 4) of activated carbon-carbon double bonds (4 mmol) on silica gel (4 g) under microwave irradiation and without solvent. The reactions were performed with comparable success in a domestic multimode oven (8 min) and in the laboratory Synthewave monomode oven (4-6 min). The efficiency of the process appeared to be dependent on steric effects in the DHP as the bulky *tert*-butyl ester derivatives failed to react.

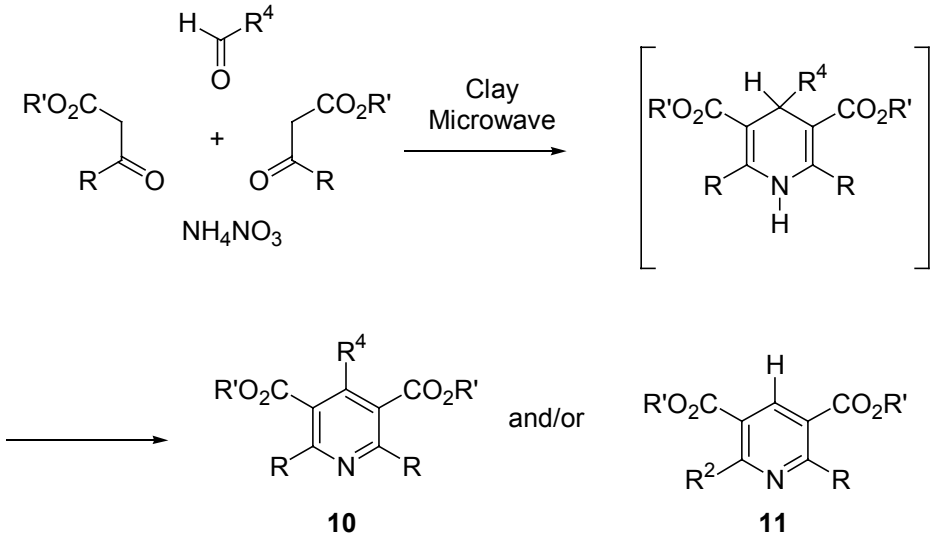
Scheme 4.



Domino Synthesis of Hantzsch Pyridines

To the best of our knowledge, only two papers [29, 30] describe the domino synthesis of Hantzsch pyridines (Scheme 5). Both groups start from a mixture of a bentonite clay, a β-ketoester, and an aldehyde. They used ammonium nitrate as the source of ammonia and oxidizing species. The experiments were carried out in domestic ovens.

Scheme 5.

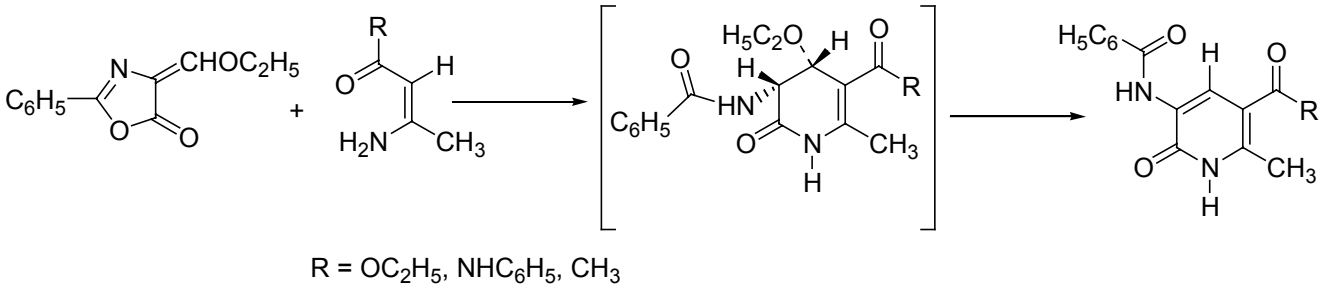


10 **11**

The published results are intriguing as they are somehow contradictory. In the absence of solvent, Penieres [29] isolated from isobutyraldehyde (20 mmol), 40 mmol of the ketoester and 20 mmol of NH_4NO_3 on 5 g of clay the alkylated pyridine (**10**) as the major product. On the other hand he obtained the 4-unsubstituted pyridine (**11**), in substantial yield, when starting from n-butyraldehyde or benzaldehyde. That latter observation also contrasts with the claims of Cotterill [30] who carried out the syntheses in DMF (35 μL) from diverse arylaldehydes (0.1 mmol; 2 eq. of ketoester; 100 mg of a 5:1 w/w mixture of bentonite and NH_4NO_3) in a combinatorial approach and does not mention the presence of the parent pyridine **11** in the final mixtures.

In addition to those two papers, let us also describe the domino preparation of pyridinones structurally related to Hantzsch pyridines (Scheme 6) under microwave irradiation in a domestic oven [31]. The authors found that the pyridinones could readily be obtained from 4-(ethoxymethylene)-2-phenyloxazol-5(*4H*)-one and enaminocarbonyl derivatives in a dry medium, whereas the classical procedure required to heat the reactants in boiling dichlorobenzene for several hours.

Scheme 6.



R = OC_2H_5, NHC_6H_5, CH_3

High-Throughput Synthesis

Due to shorter reaction times associated with experiments performed with the help of microwave irradiation, it is tempting to evoke combinatorial chemistry and to claim preparation of libraries of compounds. Therefore, let us mention in that sense that Cotterill [30] has reported the domino synthesis of Hantzsch pyridines in the 96-well microtiter plate format in a domestic microwave oven and that Ohberg [15] has utilized an automated laboratory reactor for this purpose.

Conclusions

In recent years microwave irradiation has been successfully used to promote reactions yielding Hantzsch 1,4-DHP and the corresponding pyridines. A survey of the literature indicates that construction of 1,4-DHP in a microwave oven has been performed in solution as well as in dry media. Protocols yielding the pyridine derivatives, however, involve solvent-free conditions only and have led to unexpected and somehow contradictory results.

References and Notes

1. Hantzsch, A. Condensationprodukte aus Aldehydammoniak und Ketoniartigen Verbindungen. *Ber.* **1881**, *14*, 1637-1638.
2. Love, B.; Goodman, M.; Snader, K.; Tedeschi, R.; Macko, E. "Hantzsch-type" dihydropyridine hypotensive agents. 3. *J. Med. Chem.* **1974**, *17*, 956-965.
3. Bossert, F.; Meyer, H.; Wehinger, E. 4-Aryldihydropyridines, a new class of highly active calcium antagonists. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 762-769.
4. Katzung, B.G. in *Basic & Clinical Pharmacology* **1998,** Appleton & Lange, Stamford, CT (USA).
5. Gordeev, M.F.; Patel, D.V.; Gordon, E.M. Approaches to combinatorial synthesis of heterocycles: a solid-phase synthesis of 1,4-dihdropyridines. *J. Org. Chem.* **1996**, *61*, 924-928.
6. Breitenbucher, J.G.; Figliozzi, G. Solid-phase synthesis of 4-aryl-1,4-dihydropyridines via the Hantzsch three component condensation. *Tetrahedron Lett.* **2000**, *41*, 4311-4315.
7. Vanden Eynde, J.J.; Mayence, A. New methodologies for the preparation of drugs and their metabolites. Application to 1,4-dihydropyridines structurally related to calcium channel modulators of the Nifedipine-type. *Intl. J. Med. Biol. Environ.* **2000**, *28*, 25-31.
8. Böcker, R.H.; Guengerich, F.P. Oxidation of 4-aryl- and 4-alkyl-substituted 2,6-dimethyl-3,5-bis(alkoxycarbonyl)-1,4-dihydropyridines by human liver microsomes and immunochemical evidence for the involvement of a form of cytochrome P-450. *J. Med. Chem.* **1986**, *29*, 1596-1603.
9. Alajarin, R.; Vaquero, J.J.; Garcia Navio, J.L.; Alvarez-Builla, J. Synthesis of 1,4-dihydropyridines under microwave irradiation. *Synlett* **1992**, 297-298.
10. Alajarin, R.; Jordan, P.; Vaquero, J.J.; Alvarez-Builla, J. Synthesis of unsymmetrically substituted 1,4-dihydropyridines and analogous calcium antagonists by microwave heating. *Synthesis* **1995**, 389-391.
11. Zhang, Y.-W.; Shan, Z.-X.; Pan, B.; Lu, X.-H.; Chen, M.-H. Research on the synthesis of 1,4-dihydropyridines under microwave. *Synth. Commun.* **1995**, *25*, 857-862.
12. Khadilkar, B.M.; Chitnavis, A.A. Rate enhancement in the synthesis of some 4-aryl-1,4-dihydropyridines using methyl 3-aminocrotonate under microwave irradiation. *Ind. J. Chem.* **1995**, *34B*, 652-653.
13. Khadilkar, B.M.; Gaikar, V.G.; Chitnavis, A.A. Aqueous hydrotrope solution as a safer medium for microwave enhanced Hantzsch dihydropyridine ester synthesis. *Tetrahedron Lett.* **1995**, *36*, 8083-8086.
14. Suarez, M.; Loupy, A.; Perez, E. ; Moran, L. ; Gerona, G. ; Morales, A. ; Autié, M. An efficient procedure to obtain hexahydroquinoleines and unsymmetrical 1,4-dihydropyridines using solid inorganic supports and microwave activation. *Heterocycl. Commun.* **1966**, *2*, 275-280.
15. Ohberg, L.; Westman, J. An efficient and fast procedure for the Hantzsch dihydropyridine synthesis under microwave conditions. *Synlett* **2001**, 1296-1298.

16. Vanden Eynde, J.J.; Rutot, D. Microwave-mediated derivatization of poly(styrene-*co*-allyl alcohol), a key step for the soluble polymer-assisted synthesis of heterocycles. *Tetrahedron* **1999**, *55*, 2687-2694.
17. Torchy, S.; Cordonnier, G.; Barbry, D.; Vanden Eynde, J.J. Hydrogen transfer from Hantzsch 1,4-dihydropyridines to carbon-carbon double bonds under microwave irradiation. *Molecules* **2002**, *7*, 528-533.
18. Love, B.; Snader, K. The Hantzsch reaction. I. Oxidation dealkylation of certain dihydropyridines. *J. Org. Chem.* **1965**, *30*, 1914-1916.
19. de Matteis, F.; Hollands, C.; Gibbs, A.H.; de Sa, N.; Rizzardini, M. Inactivation of cytochrome P-450 and production of N-alkylated porphyrins caused in isolated hepatocytes by substituted dihydropyridines. Structural requirements for loss of haem and alkylation of the pyrrole nitrogen atom. *FEBS Lett.* **1982**, *145*, 87-92.
20. Augusto, O.; Beilan, H.S.; Ortiz de Montellano, P.R. The catalytic mechanism of cytochrome P-450. Spin-trapping evidence for one-electron substrate oxidation. *J. Biol. Chem.* **1982**, *257*, 11288-11295.
21. Ayling, E.E. The influences of alkyl groups in carbonyl compounds. *J. Chem. Soc.* **1938**, 1014-1023.
22. Vanden Eynde, J.J.; Delfosse, F.; Mayence, A.; Van Haverbeke, Y. Old reagents, new results: aromatization of Hantzsch 1,4-dihydropyridines with manganese dioxide and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. *Tetrahedron* **1995**, *51*, 6511-6516.
23. Alvarez, C.; Delgado, F.; Garcia, O.; Medina, S.; Marquez, C. MnO_2/bentonite: a new reactive for the oxidation of Hantzsch's dihydropyridines using microwave irradiation in the absence of solvent (I). *Synth. Commun.* **1991**, *21*, 619-624.
24. Delgado, F.; Alvarez, C.; Garcia, O.; Penieres, G.; Marquez, C. Unusual oxidative dealkylation of certain 4-alkyl-1,4-dihydropyridines with MnO_2/bentonite using microwave irradiation in the absence of solvent (II). *Synth. Commun.* **1991**, *21*, 2137-2141.
25. Garcia, O.; Delgado, F.; Cano, A.C.; Alvarez, C. Oxydation d'esters de Hantzsch, par le nouveau système HNO_3/bentonite, et irradiation aux micro-ondes. *Tetrahedron Lett.* **1993**, *34*, 623-625.
26. Varma, R.S.; Kumar, D. Solid state oxidation of 1,4-dihydropyridines to pyridines using phenyliodine (III) bis(trifluoroacetate) or elemental sulfur. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1755-1757.
27. Vanden Eynde, J.J.; Mayence, A.; Maquestiau, A. A novel application of the oxidizing properties of pyridinium chlorochromate: aromatization of Hantzsch 1,4-dihydropyridines. *Tetrahedron* **1992**, *48*, 463-468.
28. Vanden Eynde, J.J. Unpublished results.
29. Penieres, G.; Garcia, O.; Franco, K.; Hernandez, O.; Alvarez, C. A modification to the Hantzsch method to obtain pyridines in a one-pot reaction: use of a bentonitic clay in a dry medium. *Heterocycl. Commun.* **1996**, *2*, 359-360.

30. Cotterill, I.C.; Usyatinsky, A.Y.; Arnold, J.M.; Clark, D.S.; Dordick, J.S.; Michels, P.C.; Khmelnitsky, Y.L. Microwave assisted combinatorial chemistry, synthesis of substituted pyridines. *Tetrahedron Lett.* **1998**, *39*, 1117-1120.
31. Vanden Eynde, J.J.; Labuche, N.; Van Haverbeke, Y. Microwave-mediated domino reaction in dry medium. Preparation of dihydropyridinones and pyridinones structurally related to Hantzsch esters. *Synth. Commun.* **1997**, *27*, 3683-3690.

Sample Availability: Available from MDPI.