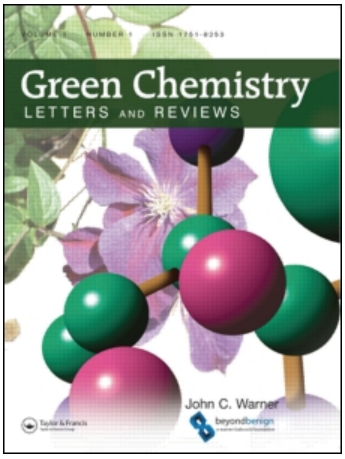


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# Microwave-assisted ammonium formate-mediated synthesis of Hanstzch dihydropyridines under solvent-free conditions - a green protocol

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## ORIGINAL ARTICLE

# Microwave-assisted ammonium formate-mediated synthesis of Hantzsch dihydropyridines under solvent-free conditions – a green protocol

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Microwave-assisted ammonium formate-mediated eco-friendly synthesis of structurally varied Hantzsch dihydropyridines under solvent-free conditions has been successfully accomplished with good yield, minimization of toxic reagents and organic solvents in the process. The elimination of the inorganic support decreased the disposal problem and the extremely small reaction time minimized energy dissipation.

**Keywords:** aldehydes; condensations; cyclizations; dihydropyridines; solvent-free synthesis



4-Substituted 1,4-dihydropyridines are important analogues of NADH coenzymes exhibiting neuroprotectant and platelet anticoagulatory activity and often act as cerebral antischemic agents in the treatment of Alzheimer's disease as well as chemosensitizers in tumor therapy (*1*). Due to their high efficiency as $Ca^{2+}$ channel blockers, Hantzsch dihydropyridines also find immense applications in the treatment of cardiovascular disorders and hypertension (*2*). Moreover, these compounds serve as important synthetic intermediates (*3*) for the preparation of various pyridine derivatives through oxidative aromatization sequences. A number of synthetic protocols (*4*) for the construction of the dihydropyridine skeleton are available in the literature using ammonia (*4a*), *N*-(1-chloroalkyl)-pyridinium chloride (*4b*), refluxing ammonium hydroxide in a closed vessel microwave synthesizer (*4c*), urea–silica gel (*4d*), ammonium acetate in ethanol under microwave irradiation (*4e*), potassium fluoride–alumina (*4f*), ammonium acetate under conventional heating (*4g*), 2,4,6-trichloro-1,3,5-triazine (*4h*), ammonium hydroxide in ethanol (*4i–4k*) or aqueous hydrotope (*4l*) and many others. Many of them use expensive and toxic reagents, have complicated reaction set-up, require long reaction times and form by-products due to various side reactions. Often the reactions are performed in various organic solvents posing a serious threat of fire hazard, especially when they are performed under microwave irradiation. For that purpose several solvent-free protocols (*4d, 4f*) have been developed using supported reagents, but still they require toxic organic solvents during product isolation. Also the disposal of the leftover inorganic supports remains problematic (*4d, 4f*) causing much perturbation in the environment. Therefore, an improved, cost-effective and efficient method for the synthesis of Hantzsch 1,4-dihydropyridine eliminating the inorganic support and minimizing the use of toxic organic solvents becomes a great demand (*5*) from a Green Chemistry standpoint. With these objectives in mind we report herein a solvent-free protocol (Scheme 1) for the efficient synthesis of structurally varied Hantzsch dihydropyridines without any inorganic support, the results of which have been furnished in Table 1.

As shown in Table 1, several structurally varied alkyl, aryl, and heteroaryl aldehydes smoothly underwent a highly rapid multicomponent condensation with ethyl acetoacetate and relatively less toxic ammonium formate under microwave irradiation in the absence of any inorganic support in totally solvent-free condition to accomplish diversely substituted functionally important (*1–4,6*) Hantzsch dihydropyridines in good yield and purity. Aryl aldehydes bearing electron-donating and electron-withdrawing substituents at various locations yielded the corresponding products without affecting the substituents and the substitution patterns (entries 1, 2, 3, 4, 5, and 7). Interestingly, the α,β-unsaturated aryl aldehyde underwent clean transformation (entry 6) without polymerization and other usual side reactions. The long chain aliphatic aldehyde furnished the product in moderate yield (entry 8) yet paraformaldehyde, a solid synthetic equivalent of formaldehyde, produced the 4-unsubstituted dihydropyridine in high yield (entry 9). This compound has

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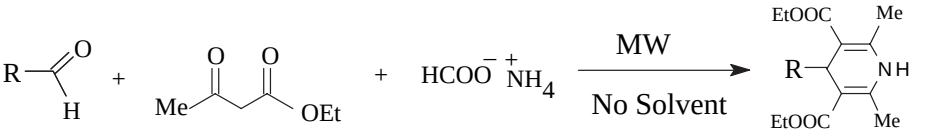


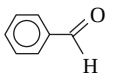
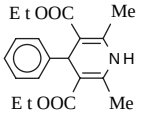
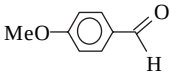
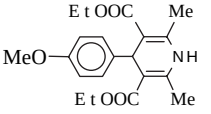
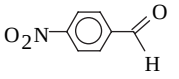
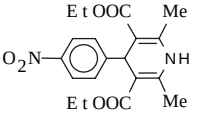
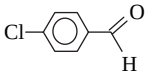
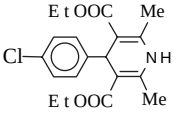
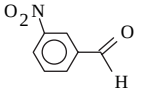
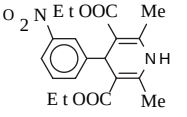
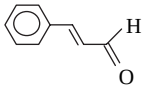
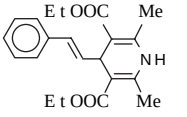
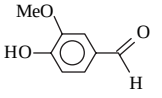
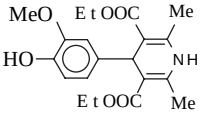
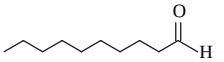
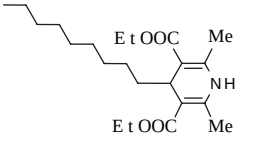
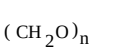
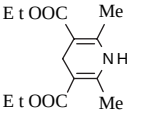
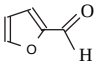
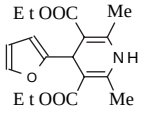

Scheme 1.

found important applications (6) as a component of metal-free transfer hydrogenation reactions. It is noteworthy that the highly vulnerable heteroaryl aldehyde also underwent the multicomponent transformation preferentially over usual thermal polymerization (entry 10). Therefore, the reported method can be utilized for the rapid and efficient synthesis of dihydropyridine skeletons over a wide range of structural diversity. It is important to note that the by-products of this reaction (water and formic acid) are relatively benign compared to many alternative procedures. The aforesaid protocol completely eliminates the inorganic support and the use of toxic and flammable organic solvents as reaction medium and uses an ecologically relatively compatible solvent (namely, ethanol) in small amount during work-up in most of the cases. In this ammonium formate-mediated procedure, the reactions under microwave irradiation are completed more rapidly (1–3 min) compared to the conventional heating (8–10 h). This also maximizes the energy consumption as well as minimizes energy dissipation. So, the present solvent-free protocol under microwave irradiation sets out to minimize energy dissipation and the disposal of unwanted waste products in the environment. From this standpoint, it can be called a green technology. Similar solvent-free synthesis of dihydropyridines using ammonium acetate in place of ammonium formate utilizing conventional heating (*4g*) requires longer reaction time (1–2 h). Various ammonium salts like ammonium acetate, ammonium chloride, and ammonium oxalate under microwave irradiation failed to react at all, even with longer times of exposure. Therefore, the present ammonium formate-mediated microwave-induced solvent-free protocol for the efficient construction of dihydropyridine skeletons having a wide range of substitution patterns is unique of its kind.

## Experimental section

In a typical general procedure, a mixture of 1.0 molar equivalent aldehyde, 1.3 molar equivalent ammonium formate, and 2.2 molar equivalent ethyl acetoacetate in an open vessel fitted with a $CaCl_2$ drying tube was irradiated in a microwave oven (2450 MHz, 300 W, Brand BPL, India) for the stipulated period of time having the installment of 15 s each and intermittent cooling. After completion of the reaction (thin layer chromatography) the reaction mixture was cooled to room temperature and thoroughly mixed with crushed ice (for gummy reaction mixtures, a little amount of ethanol was added prior to addition of ice). The precipitated solid was filtered, washed with water, dried and crystallized from aqueous alcohol, if needed, to get the pure product, characterized by IR, $^1$H-NMR (300 MHz) spectroscopy and comparison of melting point of the pure product with the reported value of the authentic sample (as shown in last two columns of Table 1). All the reaction products have earlier literature precedence (as indicated in the fifth column and the last column of Table 1 as superscripts of the yield and literature melting point data, respectively). In the IR spectra of the products a strong band appeared around 3300–3350 $cm^{-1}$ due to N–H stretching and another band around 1680–1690 $cm^{-1}$ due to C=O stretching of conjugated ester moieties. In the $^1$H-NMR spectra of the reaction products from aryl aldehydes, singlets were observed around $\delta$ 4.90–5.20 due to aryl-CH moiety of the C-4 of the dihydropyridine skeleton. In case of vinylic aldehyde as the substrate (entry 6 in Table 1), this signal appeared at $\delta$ 4.63 as a one-proton doublet with $J = 6.3$ Hz. For aliphatic aldehydes as the substrates (entries 8 and 9 in Table 1), the analogous signals experienced an upfield shift at $\delta$ 3.87 as a one-proton triplet with $J = 5.6$ Hz and at $\delta$ 3.25 as a two-proton singlet, respectively. For heteroaryl aldehyde (entry 10 in Table 1), this signal came at $\delta$ 5.19 as a one-proton singlet. In case of all the products in Table 1, broad singlets appeared around $\delta$ 5.60–5.90 confirming the presence of N–H moiety of the dihydropyridine skeleton. In all the aforesaid cases, six-proton singlets were observed due to olefinic-$CH_3$ around $\delta$ 2.17–2.37 corroborated with the dihydropyridine skeleton. Signals around $\delta$ 4.10–4.30 as well as around 1.20–1.29 with expected splitting pattern were indicative of the presence of ethoxycarbonyl functions. In the $^{13}$C-NMR (75 MHz) spectra, small peak around $\delta$ 167.45–168.15 due to 4°C indicated the presence of conjugated ester moiety, as also evident from the IR spectra.

Table 1. Ammonium formate-mediated solvent-free synthesis of dihydropyridines.

| Entry | Aldehyde | Product (Dihydropyridine) | Time (min) | Yield* (%) | Observed m.p. (°C) | Literature m.p. (°C) |
|---|---|---|---|---|---|---|
| 1 |  |  | 3 | 78 (*4d, 4h*) | 156 | 157 (*4d*) |
| 2 |  |  | 3 | 90 (*4e, 4g*) | 140 | 140 (*4e*) |
| 3 |  |  | 3 | 91 (*4d, 4g*) | 124 | 126 (*4d*) |
| 4 |  |  | 1.25 | 86 (*4d, 4e*) | 145 | 146 (*4d*) |
| 5 |  |  | 3 | 81 (*4d, 4e*) | 161 | 163 (*4d*) |
| 6 |  |  | 3 | 80 (*4d, 4h*) | 146 | 147 (*4d*) |
| 7 |  |  | 1.25 | 79 (*4e*) | 127 | 129 (*4e*) |
| 8 |  |  | 3.5 | 55 (*4d, 4h*) | Viscous liquid | – |
| 9 |  |  | 1.0 | 91 (*3b, 7*) | 182 | 183 (*7*) |
| 10 |  |  | 1.0 | 72 (*4b, 4d*) | 163 | 163 (*4d*) |

*Yields refer to isolated pure products, fully characterized spectroscopically.

## Conclusion

A novel, efficient, economically viable and ecologically compatible synthesis of structurally varied Hantzsch dihydropyridine has been accomplished using easily accessible substrates and reagents. Notable features of the reported green methodology are: (a) good availability of the reagents; (b) ease of set-up and work-up; (c) extremely fast reaction times; (d)

high yield of the product with good purity; (e) complete elimination of the use of toxic reagents, solvents and inorganic support; (f) minimum perturbation in the surroundings in terms of disposal of by-products and other waste products due to their minimum involvement and formation during the reaction; and (g) general applicability accommodating a variety of substitution patterns.

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