# Neat reaction microwave technology for the synthesis of *N*-substituted-1,4-dihydropyridines

**Mazaahir Kidwai and Richa Mohan**

**Abstract:** Hantzsch synthesis of *N*-substituted-1,4-dihydropyridines (1,4-DHP) was carried out using an environmentally benign procedure. Neat reactants were subjected to microwave irradiation (MWI) to give the required products in excellent yield. Appreciable results were not obtained when conventional synthesis using neat reactants was carried out. The good yield and rate enhancement observed in the case of microwave irradiation is attributed to the uniform heating effect of microwaves.

*Key words:* 1,4-dihydropyridines (1,4-DHP), microwave irradiation (MWI), neat reaction, solid support.

**Résumé :** On a réalisé une synthèse de Hantzsch de 1,4-dihydropyridines (1,4-DHP) *N*-substituées en faisant appel à une méthode environnementalement bénigne. On a soumis les réactifs sans solvants à une irradiation par des microondes (IMO) qui a conduit à la formation des produits requis avec d'excellents rendements. On n'a pas obtenu de bons résultats lorsqu'on a effectué la synthèse conventionnelle avec des réactifs sans solvant. On attribue les excellents rendements et l'augmentation de la vitesse de la réaction observée avec une irradiation par des microondes à l'effet de chauffage uniforme des microondes.

*Mots clés :* 1,4-dihydropyridines (1,4-DHP), irradiation par des microondes (IMO), réaction sans solvant, support solide.

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## Introduction

Research on the 1,4-dihydropyridine (1,4-DHP) moiety is of current interest because of its recognition as a core structure in calcium antagonists (1). In the case of structure–activity relationships, the effect of substitution on the 1,4-DHP ring has been thoroughly studied (2). However, most of the studies have been devoted to the Hantzsch synthesis of *N*-unsubstituted dihydropyridines (3, 4), since the classical routes (5), yielding *N*-alkyl or *N*-aryl 1,4-DHP products, suffer from negative results (6) or very poor yields (7). Modified synthetic methodologies (8) for the above compounds reportedly provide improved yields but use expensive reagents and require longer reaction times. The drive for clean technology in the chemical industry requires a level of innovation. Thus, the eco-friendly goal of making organic compounds without using solvents has come several steps closer in recent years (9). With the development of microwave-assisted solid-phase synthesis (10), it has now become easier to perform reactions without solvents, as these high-yield protocols offer the benefits of enhanced reaction rates, greater selectivity, and experimental ease of manipulation (11).

In this communication, synthesis of *N*-substituted-1,4-DHP was carried out under conventional heating by refluxing 1 mol of aldehydes 1a–b, 2 mol of ethylacetoacetate, and 1 mol of amines 2a–d in acetic acid for several hours (Scheme 1). The products were obtained in low yield (Table 1), while the same reaction over acidic alumina[2] using microwave irradiation gave the desired products in good yield within a few minutes. The microwave reaction was also carried out over neutral alumina,[3] wherein appreciable yields were observed within the same reaction time. Although the microwave-assisted solid-support synthesis is a solventless technique, it requires the use of an appreciable amount of solvent at the pre- and post-reaction stages.

In our endeavour to develop an environmentally benign synthesis that eliminates the use of solvent, and in continuation to our earlier work on the neat Hantzsch synthesis (13) of 1,4-DHP, an attempt was made to synthesize *N*-substituted-1,4-DHP under neat reaction conditions. As a test case, 2 mol of ethylacetoacetate and 1 mol each of benzaldehyde and aniline were subjected to microwave irradiation. On completion of reaction, as monitored by TLC, the reaction mixture was cooled at 5 °C for 24 h, and the sticky solid obtained was titurated with a few drops of methanol to give the required product in excellent yield. The positive results obtained in the above case prompted us to synthesize some novel *N*-substituted-1,4-DHP using heterocyclic amines. The products were obtained in less time than with solid support and conventional methodology. A slight improvement in yield was also observed on moving from solid support to

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[2]Aluminium oxide, acidic, Brockmann I (~150 mesh; 58 Å; CAMAG 506-C-1; surface area 155 $m^2$/g).

[3]Aluminium oxide, neutral, Brockmann I (Aldrich Chem. Co., Cat. No., 19997-4; ~150 mesh; 58 Å; surface area 155 $m^2$/g).

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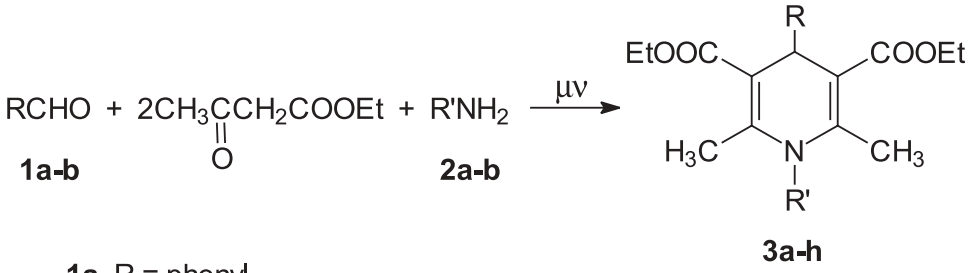
**Scheme 1.**




**1a**, R = phenyl
**1b**, R = 2-furyl
**2a**, R' = phenyl
**2b**, R' = 2-pyridyl
**2c**, R' = 2-furyl
**2d**, R' = 2-methyl-1,3,4-thiadiazolyl

**Table 1.** Comparison of the reaction times and yields for the compounds 3a–h.

| | | | | Solution phase (conventional) | | Solid support (microwave)[a] | | Neat (microwave)[a] | |
|---|---|---|---|---|---|---|---|---|---|
| Compd | R | R′ | mp (°C) | Yield (%) | Time (h) | Yield (%) | Time (min) | Yield (%) | Time (min) |
| **3a** | Phenyl | Phenyl | 159–160[b] | 40 | 12 | 83 | 4.0 | 87 | 3.5 |
| **3b** | Phenyl | 2-Pyridyl | 142–145 | 38 | 16 | 81 | 4.5 | 83 | 4.0 |
| **3c** | Phenyl | 2-Furyl | 137–139 | 32 | 24 | 79 | 5.5 | 80 | 5.5 |
| **3d** | Phenyl | 2-Methyl-1,3,4-thiadiazolyl | 155–157 | 18 | >48 | 73 | 6.5 | 77 | 6.0 |
| **3e** | Furyl | Phenyl | 150–152 | 34 | 14 | 82 | 4.5 | 86 | 4.0 |
| **3f** | Furyl | 2-Pyridyl | 195–198 | 30 | 18 | 80 | 5.0 | 81 | 5.0 |
| **3g** | Furyl | 2-Furyl | 172–175 | 20 | >48 | 75 | 7.0 | 76 | 6.5 |
| **3h** | Furyl | 2-Methyl-1,3,4-thiadiazolyl | 240–242 | 15 | >48 | 71 | 7.0 | 74 | 7.0 |

[a]Microwave heating (800 W, 100–110 °C, 1 min).
[b]Literature (12) value mp 158 °C.

neat reaction methodology (Table 1). The neat reaction was also carried out under conventional heating, keeping similar reaction conditions. Conventional neat synthesis took more time for completion and gave the products in moderate yield and, in certain cases, lead to charring.

Thus, we have developed an easier, practically convenient, and environmentally benign synthesis of bioactive *N*-substituted-1,4-DHP that proceeds under much milder reaction conditions than conventional means. Eliminating organic solvents in chemical synthesis is an important drive towards clean chemical technology. Although solventless reactions are more appropriate for small-scale production, these results may stimulate interest among researchers involved in the industrial scale-up of reactions.

## Experimental section

Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a PerkinElmer FT-IR-1710 spectrophotometer. $^1$H NMR spectra were recorded on an FT-NMR Hitachi R-600 (60 MHz) instrument using TMS as the internal reference. Microwave irradiation was carried out in a Kenstar microwave oven, Model No. OM9925E (2450 MHz, 800 W). Monitoring of the reaction was done through TLC, using silica-gel-coated Al plates (Merck). The reaction temperature was measured using an AZ minigun type non-contact IR thermometer (Model No. 8868).

### General procedure for the synthesis of *N*-substituted diethyl 1,4-dihydro-2,6-dimethyl-4-furyl/phenyl-3,5-pyridinedicarboxylate (3a–h)

#### *Solution phase (conventional)*

A mixture of aldehyde 1a–b (0.01 mol), primary amine 2a–d (0.01 mol), and ethylacetoacetate (0.02 mol) in 30 mL acetic acid was refluxed for a specified time. On completion of the reaction, as monitored by TLC examination, the reaction mixture was cooled for 24 h; the solid obtained was filtered, washed with cold MeOH, dried, and recrystallized from ethanol.

#### *Solid support (microwave)*

To the solution of aldehyde 1a–b (0.01 mol), primary amine 2a–d (0.01 mol), and ethylacetoacetate (0.02 mol) in ethanol (15 mL), solid support (20 g) was added. The reaction mixture was dried in air, kept in an alumina bath, and subjected to MWI for a specified time (Table 1). On completion of the reaction, as examined by TLC (at an interval of 30 s), the product was extracted in ethanol (3 × 15 mL). Re-

covering the solvent under reduced pressure gave the required product, which was recrystallized from ethanol.

***Neat synthesis (microwave)***

A mixture of 0.01 mol of aldehyde 1a–b, 0.01 mol of primary amine 2a–d, and 0.02 mol of ethyl acetoacetate was taken in an Erlenmeyer flask and subjected to MWI. The progress of the reaction was monitored by TLC at an interval of 30 s. On completion of the reaction, the reaction mixture was cooled and titurated with a few drops of methanol, and the product was recrystallized from aqueous methanol.

***Diethyl 1,4-dihydro-2,6-dimethyl-1,4-diphenyl-3,5-pyridinedicarboxylate (3a)***

IR ($cm^{-1}$) $\nu_{max}$: 2989.80, 1728.59, 1628.35, 1091.00. $^1H$ NMR (60 MHz, $CDCl_3$) $\delta_H$: 1.1 (t, 3H, $CH_3$), 2.3 (s, 3H, $CH_3$), 4.2 (q, 2H, $OCH_2$), 5.0 (s, 1H, 4-H), 7.3–7.6 (m, 10H, Ar-H). Anal. calcd. for $C_{25}H_{27}NO_4$: C 74.07, H 6.66, N 3.45; found: C 74.09, H 6.70, N 3.42.

***Diethyl 1,4-dihydro-2,6-dimethyl-4-phenyl-1-(2′-pyridyl)-3,5-pyridinedicarboxylate (3b)***

IR ($cm^{-1}$) $\nu_{max}$: 3115.56, 2965.64, 1689.18, 1635.22, 1042.22. $^1H$ NMR (60 MHz, DMSO-$d_6$) $\delta_H$: 1.2 (t, 3H, $CH_3$), 2.5 (s, 3H, $CH_3$), 4.1 (q, 2H, $OCH_2$), 5.2 (s, 1H, 4-H), 7.2–8.1 (m, 9H, Ar-H & pyridine). Anal. calcd. for $C_{24}H_{26}N_2O_4$: C 70.93, H 6.40, N 6.89; found: C 70.91, H 6.43, N 6.91.

***Diethyl 1,4-dihydro-2,6-dimethyl-1-(1′-furylmethyl)-4-phenyl-3,5-pyridinedicarboxylate (3c)***

IR ($cm^{-1}$) $\nu_{max}$: 3116.53, 2981.36, 1689.60, 1635.95, 1042.53. $^1H$ NMR (60 MHz, DMSO-$d_6$) $\delta_H$: 1.2 (t, 3H, $CH_3$), 2.2 (s, 3H, $CH_3$), 3.1 (s, 2H, $OCH_2$), 4.2 (q, 2H, $CH_2$), 5.2 (s, 1H, 4-H), 6.2–6.4 (m, 3H, furan), 7.2–7.4 (m, 5H, Ar-H). Anal. calcd. for $C_{24}H_{27}NO_5$: C 70.41, H 6.60, N 3.42; found: C 70.43, H 6.62, N 3.45.

***Diethyl 1,4-dihydro-2,6-dimethyl-4-phenyl-1-(5′-methyl-1,3,4-thiadiazolyl)-3,5-pyridinedicarboxylate (3d)***

IR ($cm^{-1}$) $\nu_{max}$: 2927.89, 1701.78, 1636.22, 1043.21. $^1H$ NMR (60 MHz, $CDCl_3$) $\delta_H$: 1.3 (t, 3H, $CH_3$), 2.2 (s, 3H, $CH_3$), 2.6 (s, 3H, 5′-$CH_3$), 4.2 (q, 2H, $OCH_2$), 5.1 (s, 1H, 4-H), 7.2–7.4 (m, 5H, Ar-H). Anal. calcd. for $C_{22}H_{25}N_3O_4S$: C 61.82. H 5.85, N 9.83; found: C 61.83, H 5.81, N 9.82.

***Diethyl 1,4-dihydro-2,6-dimethyl-4-furyl-1-phenyl-3,5-pyridinedicarboxylate (3e)***

IR ($cm^{-1}$) $\nu_{max}$: 2983.99, 1669.13, 1628.35, 1066.96. $^1H$ NMR (60 MHz, $CDCl_3$) $\delta_H$: 1.2 (t, 3H, $CH_3$), 2.1 (s, 3H, $CH_3$), 4.2 (q, 2H, $OCH_2$), 5.3 (s, 1H, 4-H), 6.2–6.4 (m, 3H, furan), 7.3–7.7 (m, 5H, Ar-H). Anal. calcd. for $C_{23}H_{25}NO_5$: C 69.87, H 6.32, N 3.54; found: C 69.88, H 6.35, N 3.56.

***Diethyl 1,4-dihydro-2,6-dimethyl-4-furyl-1-(2′-pyridyl)-3,5-pyridinedicarboxylate (3f)***

IR ($cm^{-1}$) $\nu_{max}$: 2989.92, 1692.50, 1635.58, 1035.98. $^1H$ NMR (60 MHz, DMSO-$d_6$) $\delta_H$: 1.2 (t, 3H, $CH_3$), 2.4 (s, 3H, $CH_3$), 4.2 (q, 2H, $OCH_2$), 5.4 (s, 1H, 4-H), 6.2–6.4 (m, 3H, furan), 7.7–8.1 (m, 4H, pyridine). Anal. calcd. for $C_{22}H_{25}N_2O_5$: C 66.66, H 6.06, N 7.07; found: C 66.67, H 6.09, N 7.06.

***Diethyl 1,4-dihydro-2,6-dimethyl-4-furyl-1-(1′-furyl methyl)-3,5-pyridinedicarboxylate (3g)***

IR ($cm^{-1}$) $\nu_{max}$: 3094.54, 1701.78, 1628.50, 1052.36. $^1H$ NMR (60 MHz, DMSO-$d_6$) $\delta_H$: 1.3 (t, 6H, $CH_3$), 2.4 (s, 6H, $CH_3$), 3.2 (s, 2H, $CH_2$), 4.3 (q, 4H, $OCH_2$), 5.3 (s, 1H, 4-H), 6.4–7.0 (m, 6H, furan). Anal. calcd. for $C_{22}H_{25}NO_6$: C 66.16, H 6.26, N 3.50; found: C 66.14, H 6.23, N 3.52.

***Diethyl 1,4-dihydro-2,6-dimethyl-4-furyl-1-(5′-methyl 1′,3′,4′-thiadiazolyl)-3,5-pyridinedicarboxylate (3h)***

IR ($cm^{-1}$) $\nu_{max}$: 3093.76, 1692.50, 1639.52, 1065.98. $^1H$ NMR (60 MHz, $CDCl_3$) $\delta_H$: 1.2 (t, 3H, $CH_3$), 2.3 (s, 3H, $CH_3$), 2.7 (s, 3H, 5′-$CH_3$), 4.1 (q, 2H, $OCH_2$), 5.1 (s, 1H, 4-H), 6.2–6.4 (m, 3H, furan). Anal. calcd. for $C_{20}H_{23}N_3O_5S$: C 57.55, H 5.51, N 10.07; found: C 57.58, H 5.53, N 10.06.

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