Facile, Microwave-Assisted Parallel Syntheses of *N*-Substituted 1,4-Dihydropyridines of Biological Interest

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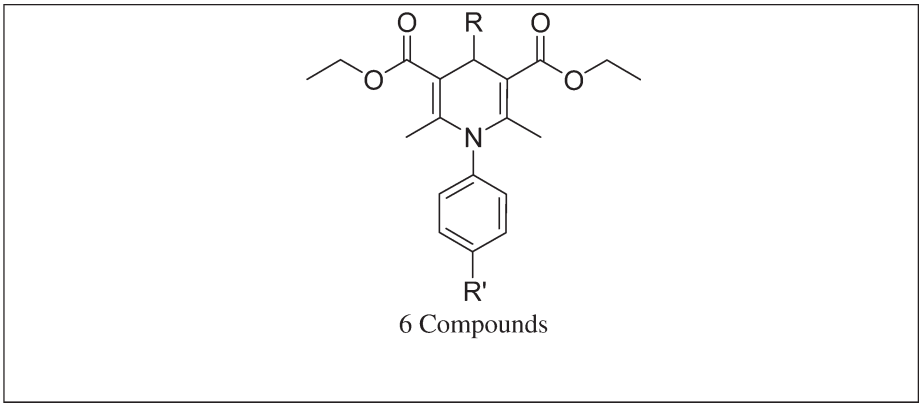

A solventless parallel synthesis of some novel, *N*-substituted dihydropyridines by the application of microwaves is reported. The synthetic methodology adopted to synthesize the titled compounds and their antioxidant activity is described.

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INTRODUCTION

Heterocyclic synthesis plays an important role in medicinal chemistry by virtue of its application in the production of large number of medicinal compounds. Among many utility of heterocyclic syntheses one such important use is in the production of drugs, either currently on the market or those yet to be released.

Dihydropyridine (DHP) chemistry began in 1882, when Hantzsch for the first time published the syntheses of DHPs by multicomponent reaction, which now bears his name [1–3]. 1,4-DHPs such as nifedipine and nitrendipine are used even today as antihypertensive agents [4–6].

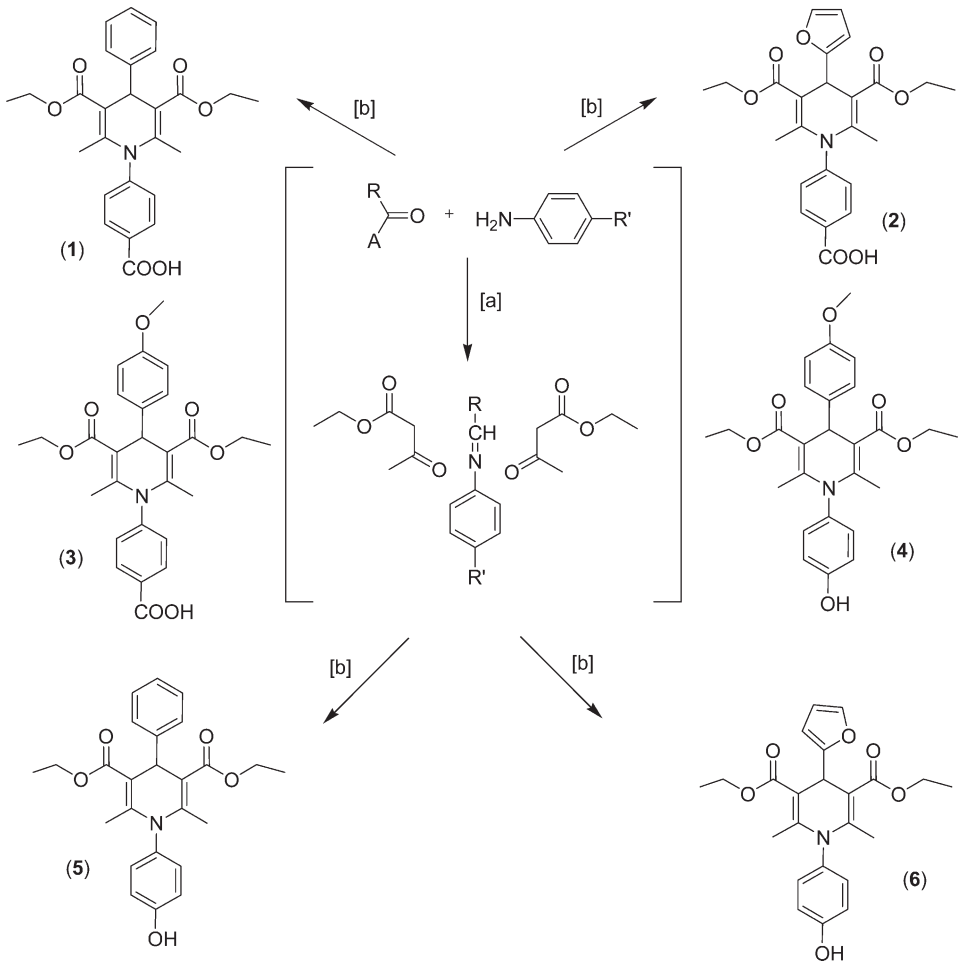
1,4-DHPs are known to possess various biological activities such as multidrug reversal (MDR) in tumor cells [7], potential immunomodulating [8], as well as antitubercular activities [9]. The 3D QSAR results show the minimum structure requirement for DHPs to exhibit antitubercular activity [10]. A further study of *N*-substitution at the labile hydrogen of DHPs skeleton proved to be important for MDR reversal in tumor cells apart from analytical and synthetic interest [11]. These observations provoked us to work on *N*-substituted DHPs for their possible antioxidant activity by incorporating phenolic and carboxyl groups [12].

Industrial chemistry in this millennium is widely adopting the concept of green chemistry to meet the fundamental scientific challenges of protecting the human health and environment while maintaining commercial viability. The emerging area of green chemistry envisages minimum hazard as the performance criteria while designing new chemical process. One of the thirst areas for achieving this target is to explore alternative reaction conditions and reaction media to accomplish the desired chemical transformations with minimized by-products or waste as well as eliminating the use of conventional organic solvents, if possible. Microwaves (MWs) as an alternative energy source has become an attractive tool in organic synthesis [13,14], resulting in a significant decrease in reaction times, especially for endothermic reactions.

RESULTS AND DISCUSSION

Because of biological interest, we have synthesized *N*-substituted 1,4-DHPs by parallel syntheses using *p*-toluenesulphonic acid (PTSA) as a catalyst under MW irradiation conditions as per Scheme 1. The PTSA was found to be a better catalyst than $AlCl_3$ and HCl in

Scheme 1. Microwave-assisted parallel syntheses of *N*-substituted-1,4-dihydropyridines; (a) Silica gel, MW, 700 W, 8 min; (b) PTSA, MW, 700 W, 12–15 min.

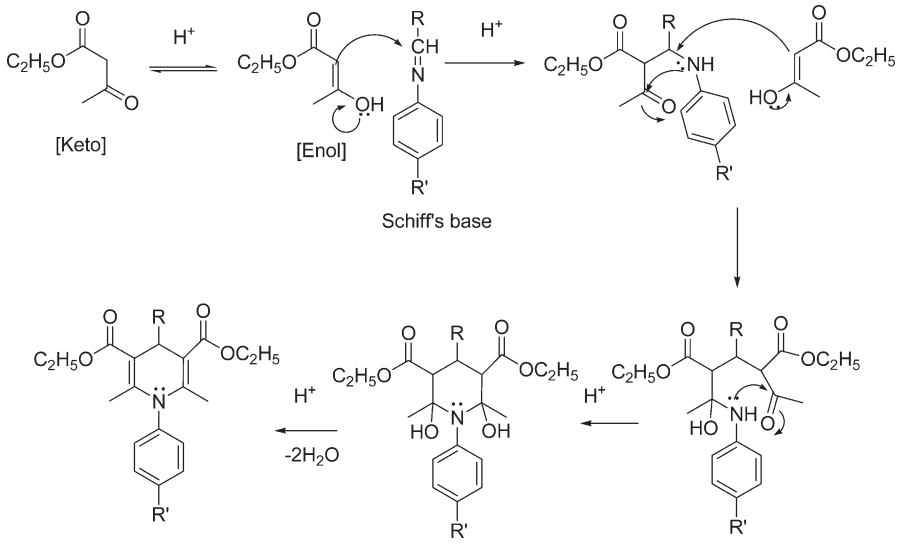


terms of yields. Also, it was convenient to perform the parallel synthesis under solvent free conditions using PTSA as a cyclizing agent and silica gel as adsorbent.

Initially, we made an attempt to synthesize *N*-aryl-1,4-DHPs through conventional and MW methods. In both the methods there was a formation of Schiff's base, but by the conventional method, we could not prepare *N*-substituted 1,4-DHPs, successfully. We repeated the experiment several times under conventional heating. In each case, the thin layer chromatography (TLC) was unclear and showed multiple spots. PTSA was developed as an efficient catalyst for the formation of final products under MWs when compared with the other reported catalysts such as HCl, $AlCl_3$, *etc*. [2].

We had also made an attempt to prepare the titled compounds by adopting one pot, one step, multicomponent reaction involving equivalent amounts of aryl amine, aryl aldehyde with two equivalent amount of ethyl acetoacetate under similar MW irradiation conditions. However, only 10–20% yields of the final compounds were obtained. In addition, the products were found to be impure with many by-products. One of the major reason why the single step syntheses was not successful was found to be the formation of acetoacetanilide because of a reaction between arylamine and ethyl acetoacetate. This was conformed by subjecting the crude reaction mixture to high-resolution mass spectrometry (HRMS). The syntheses of the titled compounds through the Schiff's base preparation escaped from the formation of acetoacetanilide. Another reason for the success of the reaction was due to the possibility of the correct steric alignment of the Schiff's base with a β-keto ester to react during its reaction mechanism as shown in Scheme 2.

Scheme 2. The possible reaction mechanism for the formation of *N*-substituted1,4-dihydropyridines.



Final compounds were first analyzed by TLC and melting point determination. Then, the synthesized compounds were subjected to spectral analysis such as IR, NMR, and MASS spectrometry to confirm the structures. All the analytical details showed satisfactory results. For all compounds, a characteristic singlet peak for symmetric CH was observed between 5.0 and 5.5 ppm in the ^{1}H NMR spectrum.

The synthesized compounds were tested for *in vitro* antioxidant activity using standard nitric oxide assay method [15]. Among all the synthesized compounds, compounds **4** and **6** exhibited potential antioxidant activity with IC_{50} value at 11 and 28 μg concentrations, respectively. The *in vitro* antioxidant results reveal that there is need for further investigation. Hence, the work in this direction is in progress and it will be reported in our next publication.

In conclusion, a simple protocol for the syntheses of *N*-aryl-1,4-DHPs was developed under environmentally benign, MW irradiation conditions using PTSA as a catalyst. It was found that the MW method is selective and efficient when compared with the conventional method.

EXPERIMENTAL

The IR was recorded on Perkin Elmer Infrared-283 FTIR by KBr pellet technique. NMR was taken on Bruker ACF-300 MHz spectrometer apparatus using TMS as internal standard and $CDCl_3$ or DMSO-d_6 as a solvent. The chemical shifts are expressed in δ ppm and following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. HRMS analysis was done on Perkin-Elmer Sciex API-150-EX by ESI ionization technique. Elemental analysis was carried out for carbon, hydrogen, and nitrogen using an Elementar Vario (EL III Carlo Erba11080). MW irradiation was done using, Whirl Pool domestic MW oven as well as MW Synthesizer (2450 MHz, Catalyst Systems, India). All the reactions were monitored using thin layer chromatogram. TLC was performed using 4% methanol in chloroform as mobile phase on aluminum plates that are precoated with silica gel GF.

General procedure for the preparation of Schiff's bases. Equimolar amounts (0.01*M*) of aromatic amine and aromatic aldehyde were transferred to a clean and dry mortar, triturate to become a uniform mixture. The reaction mixture was then transferred to a 100 mL beaker containing 2 g of activated silica gel. Similarly, all other beakers containing different reaction mixtures were kept inside the MW oven in a circle and then MW irradiation was carried out at 700 W power for about 8 min. Intermittent cooling was done after every 60 s of MW irradiation. During intermittent cooling, the reaction mixtures were thoroughly mixed. The reactions were monitored through TLC. The completed reactions were taken directly for the preparation *N*-substituted DHPs without any work up, immediately.

General procedure for the preparation of *N*-substituted-1,4-DHPs (1-6). This reaction was carried out in a parallel synthetic way as shown in Scheme 1. Ethyl acetoacetate (0.02*M*) was transferred in to a dry mortar containing the Schiff's base (∼0.01*M*) obtained in the previous MW procedure. Add a catalytic amount or pinch of PTSA and triturate to become a uniform mixture. The reaction mixture was then transferred to 100 mL beaker. Similarly, all other beakers containing different reaction mixtures were kept inside the MW oven in a circle and then MW irradiation was carried out at 700 W power for about 12–15 min. Intermittent cooling was done after every 60 s of MW irradiation. During intermittent cooling, the reaction mixtures were thoroughly mixed. The reactions were monitored through TLC. The reaction mixtures

were withdrawn from MW oven soon after the reaction is completed based on TLC data at regular intervals. The reaction mixtures were poured in to the beaker containing water and extracted with ethyl acetate. The ethyl acetate layer was dried over sodium sulfate and evaporated under vacuum to get crude products. The obtained crude products were further purified by recrystallization using ethyl acetate-hexane mixture (1:1) or by column chromatography using 5% EtOAc in pet ether as a mobile phase over silica gel.

4-(3,5-Di(ethoxycarbonyl)-2,6-dimethyl-4-phenylpyridin-1(4H)-yl)benzoic acid (1). Pale yellow colored solid, Yield 61%, mp 135–137°C; IR (KBr, cm^{-1}): 3471 (O—H), 3081 (Ar C—H), 2919 (Ali C—H), 1721 (C=O), 1713 (C=O), 1626 (C=C). ^{1}H NMR (δ ppm, $CDCl_3$): 1.19 (t, 6H, $2CH_3$), 2.10 (s, 6H, $2CH_3$), 4.04 (q, 4H, $2CH_2$), 5.31 (s, 1H, CH), 6.94–7.59 (m, 9H, ArH), 12.98 (s, 1H, OH). MS (*m*/*z*): calcd. 449, found 449.21 (M^+). MS: 434, 398, 311, 243, 121. *Anal*. Calcd. for $C_{26}H_{27}NO_6$: C, 69.47; H, 6.05; N, 3.12. Found: C, 69.63; H, 5.94; N, 3.08.

4-(3,5-Di(ethoxycarbonyl)-4-(furan-2-yl)-2,6-dimethylpyridin-1(4H)-yl)benzoic acid (2). Pink-colored solid, Yield 77 %, mp 93–95°C; IR (KBr, cm^{-1}): 3428 (O—H), 3037 (Ar C—H), 2989 (Ali C—H), 1724 (C=O), 1716 (C=O). ^{1}H NMR (δ ppm, $CDCl_3$): 1.22 (t, 6H, $2CH_3$), 1.85 (s, 6H, $2CH_3$), 4.24 (q, 4H, $2CH_2$), 5.34 (s, 1H, CH), 6.01 (d, 1H, CH Fur), 6.23 (t, 1H, CH Fur), 6.88 (d, 2H, ArH), 7.02 (d, 2H, ArH), 7.21 (d, 1H, CH Fur), 12.70 (s, 1H, OH). MS (*m*/*z*): calcd.439, found 439.13 (M^+). MS: 401, 329, 277, 211, 121. *Anal*. Calcd. for $C_{24}H_{25}NO_7$: C, 65.59; H, 5.73; N, 3.19. Found: C, 65.44; H, 5.87; N, 3.57.

4-(3,5-Di(ethoxycarbonyl)-4-(4-methoxyphenyl)-2,6-dimethylpyridin-1(4H)-yl)benzoic acid (3). Pale yellow solid, Yield 75 %, mp 99–101°C; IR (KBr, cm^{-1}): 3446 (O—H), 3053 (Ar C—H), 2939 (Ali C—H), 1717 (C=O), 1709 (C=O), 1623 (C=C). ^{1}H NMR (δ ppm, $CDCl_3$): 1.21 (t, 6H, $2CH_3$), 2.19 (s, 6H, $2CH_3$), 3.71 (s, 3H, OCH_3), 4.07 (q, 4H, $2CH_2$), 5.07 (s, 1H, CH), 6.91–7.53 (m, 8H, ArH), 12.48 (s, 1H, OH). MS (*m*/*z*): calcd. 479, found 479.11 (M^+). MS 464, 387, 301, 142. *Anal*. Calcd. for C_{27} $H_{29}NO_7$: C, 67.63; H, 6.10; N, 2.92. Found: C, 67.78; H, 5.89; N, 2.77.

Diethyl-1,4-dihydro-1-(4-hydroxyphenyl)-4-(4-methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (4). Yellowish brown solid, Yield 81 %, mp 88–90°C; IR (KBr, cm^{-1}): 3436 (O—H), 3048 (Ar C—H), 2927 (Ali C—H), 1719 (C=O), 1638 (C=C). ^{1}H NMR (δ ppm, $CDCl_3$): 1.26 (t, 6H, $2CH_3$), 2.22 (s, 6H, $2CH_3$), 3.81 (s, 3H, OCH_3), 4.02 (q, 4H, $2CH_2$), 5.19 (s, 1H, CH), 6.90–7.40 (m, 8H, ArH), 9.41 (s, 1H, OH). MS (*m*/*z*): calcd. 451, found 451.48 (M^+). MS: 436, 398, 312, 151. *Anal*. Calcd. for C_{26} $H_{29}NO_6$: C, 69.16; H, 6.47; N, 3.10. Found: C, 69.35; H, 6.39; N, 2.89.

Diethyl-1,4-dihydro-1-(4-hydroxyphenyl)-2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate(5). Yellow crystals, Yield 78 %, mp 89–91°C; IR (KBr, cm^{-1}): 3448 (O—H), 3078 (Ar C—H), 2912 (Ali C—H), 1719 (C=O), 1712 (C=O), 1611 (C=C). ^{1}H NMR (δ ppm, $CDCl_3$): 1.23 (t, 6H, $2CH_3$), 2.21 (s, 6H, $2CH_3$), 4.10 (q, 4H, $2CH_2$), 5.23 (s, 1H, CH), 6.84–7.47 (m, 9H, ArH), 9.90 (s, 1H, OH). MS (*m*/*z*): calcd. 421, found 421.17 (M^+). MS: 406, 353, 331, 262, 121. *Anal*. Calcd. for C_{25} $H_{27}NO_5$: C, 71.24; H, 6.46; N, 3.32. Found: C, 70.87; H, 6.33; N, 3.41.

Diethyl-4-(furan-2-yl)-1,4-dihydro-1-(4-hydroxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (6). Light brown colored solid, Yield 72%, mp 67–69°C; IR (KBr, cm^{-1}): 3410 (O—H), 3054 (Ar C—H), 2967 (Ali C—H), 1715 (C=O). ^{1}H NMR (δ ppm, $CDCl_3$): 1.20 (t, 6H, $2CH_3$), 1.91 (s, 6H, $2CH_3$), 4.1 (q, 4H, $2CH_2$), 5.25 (s, 1H, CH), 5.9 (d, 1H, CH Fur), 6.1 (t, 1H, CH Fur), 6.8 (d, 2H, ArH), 6.9 (d, 2H, ArH), 7.2 (d, 1H, CH Fur), 9.83 (s, 1H, OH). MS (*m*/*z*): calcd. 411, found 411.32 (M^+). MS: 397, 346, 251, 220, 121. *Anal*. Calcd. for $C_{23}H_{25}NO_6$: C, 67.14; H, 6.12; N, 3.40. Found: C, 67.49; H, 5.85; N, 3.32.

Antioxidant activity screening by nitric oxide radical inhibition assay. The reaction mixture (6 mL) containing sodium nitroprusside (10 m*M*, 4 mL), phosphate buffer saline (1 mL), and compound (1–64 μg/mL) was incubated at 25°C for 150 min. After incubation, 0.5 mL of the reaction mixture was removed, 1 mL of sulfanilic acid reagent (0.33% in 20% glacial acetic acid) was mixed and allowed to stand for 5 min for completion of diazotization reaction, and 1 mL of naphthyl ethylene diamine dihydrochloride was added, mixed, and allowed to stand for 30 min in diffused light. The absorbance was measured at 540 nm against the blank in a 96-well microtitre plate using an ELISA reader.

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