Microwave-assisted Synthesis of Phenylenedi(4',4''-tetrahydroquinoline) and di(4',4''-tetrahydropyridine) Derivatives

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The synthesis of bifunctional pyridine and quinolione derivatives were investigated using terephthalic and isophthalic aldehydes as a precursor. The reaction proceeds under microwave irradiation with good yield (70-92%) and short reaction time (7-9 min.). We provide a rapid and efficient method of synthesizing a range of bifunctional monocyclic and bicyclic products related to 1,4-dihydropyridines (1,4-DHPs).

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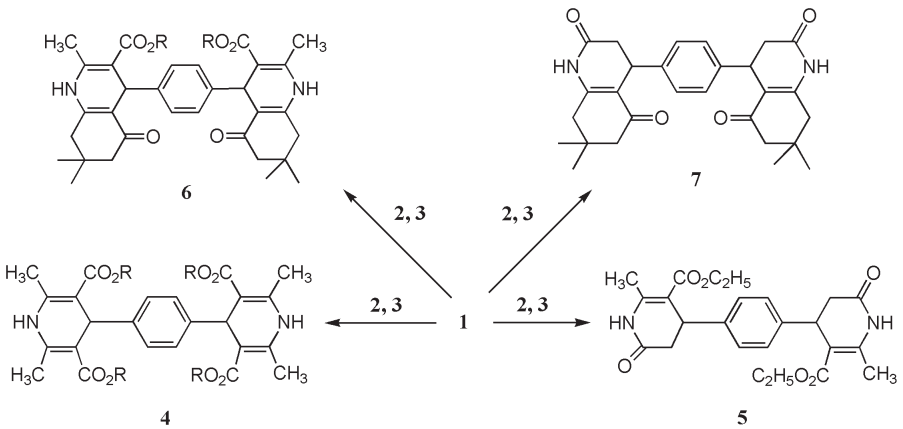
1,4-Dihydropyridines (1,4-DHPs) are well-known compounds because of their attractive pharmacological profile as calcium channel modulators [1]. Extensive efforts have been exerted on developing methodology for the modification of the 1,4-DHP rings [2]. In addition, much attention has been paid to the development of synthesis of monofunctional 1,4-DHPs derivatives and the bifunctional 1,4-DHPs are seldom investigated. Furthermore, introduction of substituents to the pyridine ring often requires a long time to achieve acceptable yields under conventional conditions [3].

Recently, microwave heating was widely used in the synthesis of heterocyclic compounds, for example hexahydroquinolines [4], octahydroquinolines [5] and dihydropyridone [6], pyridopyrimidones [7], as well as decahydroacridines [8], with good yields and short reaction time.

The efficiency of microwave heating in promoting organic synthesis and the success of their application in these heterocyclic syntheses prompted us to extend those procedures to the synthesis of compounds containing two bifunctional compounds containing two 1,4-DHP nuclei.

4-Aryl-2, 6-dimethyl-1,4-dihydropyridine-3, 5-dicarboxylate (1,4-DHP) derivatives are widely used for the treatment of cardiovascular diseases (hypertension, angina pectoris, infarction) [9]. 1,4-DHPs having different ester groups at the 3- and 5-positions possess a stereogenic carbon at the 4-position in the 1,4-DHP nucleus, and their enantiomers often show different biological activities [10]. Quinoline derivatives have also shown amoebicidal, bactericidal, fungicidal and antimalarial activity [11]. Dihyropyridone are potential calcium channel modulators [12]. It is well established that slight structural modification on the DHP ring may bring various pharmacological effect [13]. Compounds which contain monofunctional groups have shown significant biological and pharmacological activities. In this paper we show that microwave irradiation provides a convenient and efficient way to synthesize a range of bifunctional monocyclic and bicyclic products related to 1,4-DHPs with terephthalic and isophthalic aldehydes **1** as a precursor. When a mixture of terephthalic aldehydes or isophthalic aldehydes **1** and active methylene compounds **2** (in proper ratio) was radiated with microwave

Scheme 1

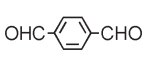
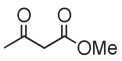
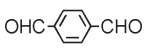
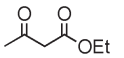
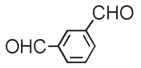
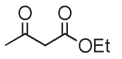
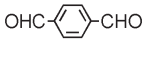
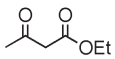
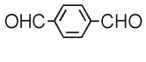
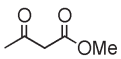
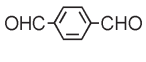
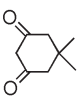
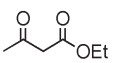
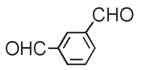
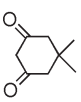
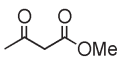
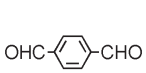
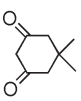


(300 W) using a small amount glycol as energy transfer reagent (Scheme 1), the reactions were almost completed in 7-9 min. Then the reaction mixture was cooled and poured into cold water, filtered and washed with a small volume of ethanol. The crude products were purified by recrystallization from 95% ethanol or acetone to afford products with good yields (70-92%).

All the reactions were followed by TLC. The results for the synthesis of these compounds are indicated in Table 1.

Table 1

Synthesis of Bifunctional 1,4-DHP Derivatives

Entry	Starting material				Ratio	Time (min)	Yield (%)
	1	**2**		**3**			
4a			-	NH_4OAc	1: 4: 3	7	75
4b			-	NH_4OAc	1: 4: 3	8	78
4c			-	NH_4OAc	1: 4: 3	7	70
5				NH_4OAc	1: 2: 2: 3	8	83
6a				NH_4OAc	1: 2: 2: 3	9	92
6b				NH_4OAc	1: 2: 2: 3	8	90
6c				NH_4OAc	1: 2: 2: 3	8	89
7				NH_4OAc	1: 2: 2: 3	8	85

The IR and ^{1}H NMR data of all compounds are consistent with assigned structures. The IR spectra of compound **5** showed the NH group at 3200 and 3100 cm^{-1} region. The ^{1}H NMR spectra of compound **5** showed the NH proton at 9.84 ppm. The two protons on C-3 appeared at 2.39-2.93 ppm and formed a part of an ABX system which was confirmed by a doublet of doublets at 4.01-4.08 ppm corresponding to the proton on C-4 split by coupling with the protons on C-3 ($J_{3,4}$=1.9 and $J_{3',4}$ =7.9 Hz). The ^{1}H NMR spectra of compound **7** showed the NH proton at 10.05 ppm. The two protons on C-3 appeared at 2.18-2.89 ppm and formed a part of an ABX system which was confirmed by a doublet of doublets at 4.06-4.08 ppm corresponding to the proton on C-4 split by coupling with the protons on C-3 ($J_{3,4}$=1.1 and $J_{3',4}$ =8.4 Hz). The two protons on C-6 appeared as an AB system, with a coupling constant ~15.6 Hz indicating that these two protons were nonequivalent. The IR, ^{1}H NMR of compounds **4** and **6** are consistent with the respective structures. And these compounds showed good elemental analysis with their structures. Mechanisms of the formation of **4**, **5**, **6** and **7** were similar to that reported in other sources [3,14].

EXPERIMENTAL

Melting points were determined in a capillary tube and are uncorrected. The ^{1}H NMR spectra were recorded on a DPX 400 MHz spectrometer with TMS as internal standard. The IR spectra were recorded for KBr discs with a SE-1730 instrument. Elemental analyses were determined by using a Perkin-Elmer 240c elemental analysis instrument.

Microwave Assisted Syntheses.

A dry flask (25 mL) was charged with either terephthalic or isophthalic aldehydes (2 mmol), corresponding **2** and **3** in a ratio reported in Table 1, and glycol (2 mL) were refluxed for 7-9 min. in a modifided commercial microwave oven (2450 MHz) set for 650 W. The reaction mixture was then cooled and poured into

cold water then filtered and washed with ethanol (3 mL). The crude products were recrystallized from 95% ethanol or acetone.

1,4-Bis(2,6-dimethyl-3,5-dimethoxylcarbonyl-1,4-dihydropyridine-4-yl)benzene (**4a**).

This compound was obtained as a yellow solid, 75% yield, mp>300 °C; IR(KBr, *v*, cm^{-1}): 3354(NH), 1692(CO); ^1H NMR (DMSO-d_6) (δ, ppm): 2.24 (6H, s, CH_3), 2.50 (6H, s, CH_3), 3.55 (12H, s, CH_3), 4.46 (2H, s, CH), 6.97 (4H, s, ArH), 8.60 (2H, s, NH).

Anal. Calcd. for $C_{28}H_{32}N_2O_8$: C, 64.11; H, 6.15; N, 5.34. Found C, 64.29; H, 5.88; N, 5.10.

1,4-Bis(2,6-dimethyl-3,5-diethoxylcarbonyl-1,4-dihydropyridine-4-yl)benzene (**4b**).

This compound was obtained as a yellow solid, 78% yield, mp>300 °C; IR(KBr, *v*, cm^{-1}): 3349(NH), 1696(CO); ^1H NMR (DMSO-d_6) (δ, ppm): 1.09 (12H, t, *J*=6.8 Hz, CH_3), 2.23 (12H, s, CH_3), 3.97 (8H, q, *J*=6.8 Hz, OCH_2), 4.77 (2H, s, CH), 6.96 (4H, s, ArH), 8.75 (2H, s, NH).

Anal. Calcd. for $C_{32}H_{40}N_2O_8$: C, 66.19; H, 6.94; N, 4.82; found C, 65.98; H, 6.69; N, 4.63.

1,3-Bis(2,6-dimethyl-3,5-diethoxylcarbonyl-1,4-dihydropyridine-4-yl)benzene (**4c**).

This compound was obtained as a yellow solid, 70% yield, mp>300 °C; IR(KBr, *v*, cm^{-1}): 3341(NH), 1700(CO); ^{1}HNMR (DMSO-d_6) (δ, ppm): 1.11 (12H, t, *J*=6.8 Hz, CH_3), 2.23 (12H, s, CH_3), 3.96 (8H, q, *J*=6.8 Hz, OCH_2), 4.79 (2H, s, CH), 6.86-7.00 (4H, m, ArH), 8.74 (2H, s, NH).

Anal. Calcd. for $C_{32}H_{40}N_2O_8$: C, 66.19; H, 6.94; N, 4.82. Found C, 66.33; H, 6.84; N, 5.01.

1,4-Bis(5-ethoxylcarbonyl-6-methyl-3,4-dihydropyridine-2-one-4-yl)benzene (**5**).

This compound was obtained as a yellow solid, 83% yield, mp 265-266 °C; IR(KBr, *v*, cm^{-1}): 3200(NH), 3100(NH), 1702(CO), 1645(CO-N); ^1H NMR (DMSO-d_6) (δ, ppm): 1.09 (6H, t, *J*=7.0 Hz, CH_3) , 2.29 (6H, s, CH_3), 2.41 (2H, dd, *J*=16.3 Hz, *J*=1.9 Hz, B part of ABX, C_3-H), 2.89 (2H, dd, *J*=16.3 Hz, *J*=7.9 Hz, A part of ABX, $C_{3'}$-H), 3.96 (4H, q, *J*=6.9 Hz, OCH_2), 4.06 (2H, dd, *J*=7.6 Hz, *J*=1.9 Hz, X part of ABX, C_4-H), 7.05 (4H, s, ArH), 9.84 (2H, s, NH).

Anal. Calcd. for $C_{24}H_{28}N_2O_6$: C, 65.44; H, 6.41; N, 6.36. Found C, 65.58; H, 6.62; N, 6.14.

1,4-Bis(3-methoxylcarbonyl-1,4,5,6,7,8-hexahydro-2,7,7-trimethylquinoline-5-one-4-yl)benzene (**6a**).

This compound was obtained as a yellow solid, 92% yield, mp>300 °C; IR(KBr, *v*, cm^{-1}): 3291(NH), 1698(CO); ^1H NMR (DMSO-d_6) (δ, ppm): 0.79(6H, s, CH_3), 0.97(6H, s, CH_3), 1.94-2.49 (8H, m, CH_2), 2.25 (6H, s, CH_3), 3.50 (6H, s, CH_3), 4.77 (2H, s, CH), 6.90 (4H, s, ArH), 9.00 (2H, s, NH).

Anal. Calcd for $C_{34}H_{40}N_2O_6$: C, 71.31; H, 7.04; N, 4.89. Found C, 71.05; H, 6.79; N, 4.62.

1,4-Bis(3-ethoxylcarbonyl-1,4,5,6,7,8-hexahydro-2,7,7-trimethylquinoline-5-one-4-yl)benzene (**6b**).

This compound was obtained as a yellow solid, 90% yield, mp>300 °C; IR (KBr, *v*, cm^{-1}): 3291(NH), 1698(CO); ^{1}HNMR (DMSO-d_6) (δ, ppm): 0.86 (6H, s, CH_3), 1.04 (6H, s, CH_3), 1.08 (6H, t, *J*=6.8 Hz, CH_3), 1.91-2.41 (8H, m, CH_2), 2.23 (6H, s, CH_3), 3.50(4H, q, *J*=6.8 Hz, OCH_2), 4.76(2H, s, CH), 6.83-6.94 (4H, m, ArH), 9.00 (2H, s, NH).

Anal. Calcd. for $C_{36}H_{44}N_2O_6$: C, 71.97; H, 7.38; N, 4.66. Found C, 71.78; H, 7.15; N, 4.37.

1,3-bis(3-methoxylcarbonyl-1,4,5,6,7,8-hexahydro -2,7,7-trimethylquinoline-5-one-4-yl)benzene (**6c**).

This compound was obtained as a yellow solid, 89% yield, mp>300 °C; IR(KBr, *v*, cm^{-1}): 3293(NH), 1701(CO); ^1H NMR (DMSO-d_6) (δ, ppm): 0.82 (6H, s, CH_3), 0.99 (6H, s, CH_3), 1.90-2.43 (8H, m, CH_2), 2.23 (6H, s, CH_3), 3.50 (6H, s, OCH_3), 4.76 (2H, s, CH), 6.83-6.94 (4H, m, ArH), 9.00 (2H, s, NH).

Anal. Calcd. for $C_{34}H_{40}N_2O_6$: C, 71.31; H, 7.04; N, 4.89. Found C, 71.09; H, 6.75; N, 4.68.

1,4-Bis(7,7-dimethyl-1,2,3,4,5,6,7,8-octahydroquinoline-2,5-dione-4-yl)benzene (**7**).

This compound was obtained as a yellow solid, 85% yield, mp>300 °C; IR(KBr, *v*, cm^{-1}): 3379(NH), 1713(CO), 1645(CO-N); ^1H NMR (DMSO-d_6) (δ, ppm): 0.98(6H, s, CH_3), 1.04 (6H, s, CH_3), 2.31 (2H, dd, *J*=15.6 Hz, C_6-H), 2.24 (2H, dd, J=15.6 Hz, $C_{6'}$-H), 2.31(2H, dd, *J*=15.2 Hz, *J*=1.1 Hz, B part of ABX, C_3-H), 2.88 (2H, dd, *J*=8.4 Hz, *J*=15.2 Hz, A part of ABX, $C_{3'}$-H), 4.07 (2H, dd, *J*=8.4 Hz, *J*=1.1 Hz, X part of ABX, C_4-H), 7.00 (4H, s, ArH), 10.05 (2H, s, NH).

Anal. Calcd. for $C_{28}H_{32}N_2O_4$: C, 73.02; H, 7.00; N, 6.08. Found C, 72.93; H, 6.77; N, 5.87.

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