Research and Reviews: Journal of Pharmacy and Pharmaceutical Sciences

Microwave Energy: A Potential and Efficient Source of Energy in Pharmaceutical Chemistry

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Research Article

ABSTRACT

Biphenyl derivatives have been synthesized in very high yields by nucleophilic addition of various substituted boronic acids on iodine substituted methyl ester derivatives, which can be further used as starting material for bio-relevant organic molecules. Here, in this paper we report a novel, fast, eco-friendly synthesis of biphenyl aromatic compound via insertion of phenyl ring in moisture sensitive substrate by using palladium catalyst under microwave irradiation (MWI).

INTRODUCTION

Microwave assisted organic synthesis (MAOS) is fast and revolutionized area in organic synthesis. Microwave irradiation (MWI) is a fast source of energy supply used in various applications such as synthesis of small molecules, materials, and nanomaterial's, biochemical applications and has become popular in both academics and industry [1-4]. In fact, this technique has been rapidly accepted by researcher's using as a valuable tool for accelerating drug discovery and development processes. Microwave energy is a type of electromagnetic energy, that exist at the lower end of the electromagnetic spectrum where it falls in the range of frequency as 300 to 300,000 Megahertza [2,3]. Unlike other forms of electromagnetic energy, microwave energy is non-ionizing, cannot change the molecular structure of the compounds on heating, and it provides only thermal activation. This unique feature of microwave energy can be utilized in microwave assisted chemical transformation, particularly due to dielectric polarization. Dielectric polarization is the mechanism by which electric field component interact with the matrix. In fact, dipole is sensitive to external electric field and energy generated by microwave irradiation is absorbed only by those substances having dipole moment for chemical transformation. There are two types of thermally driven organic transformations such as 1) conventional heating where reactants are slowly activated by a conventional heating and 2) microwave- accelerated heating solvent and substrate abosorve microwave energy by microwave irradtion [2]. In general, microwave energy is wide used in various type of chemical transformation such as: *1)* alkylation, *2)* acylation, *3)* condensation, *4)* cycloaddition, *5)* protection and deprotection, *6)* esterification and desertification and *7)* nucleophilic substution reaction [5-10].

In addition, wide range of chemical transformations, short reaction times of microwave mediated reactions are suited to create large library of bio-relevant organic compounds thus increase its demands in pharmaceutical chemistry. Various compounds such as anthracene-cyclicimides [11], mono- and bis- Schiff's bases [12], amidine and bis-amidine derivatives [13,14], tri- and tetra-cyclic benzoimidazole derivatives [15], N cyclic-substituted imides [16,17], indole and furan derivatives [18] etc. Possessing very good anti-inflammatory and anticancer activities were synthesized in very short time by our research group via adopting solvent free and catalyst free conditions [11-18]. Moisture sensitive reactions need more attentions and precautions under conventional heating and sometime give lower yield. In some extent, these problems have been resolved by using microwave energy as heating source for organic synthesis. By taking advantage of microwave energy as quick and efficient source of energy, we wish to report a fast, efficient and atom-economic synthetic pathway for synthesis of biphenyl derivatives as a precursor for synthesis of organic compounds with pharmacological importance.

CHEMISTRY

Various biphenyl derivatives **3a-c** and **4a-c** mentioned in **Scheme 1** and **6a-c** and **7a-c** in **Scheme 2** were synthesized by following generic synthetic pathway using microwave irradiation as energy source **(Schemes 1 and 2)**. These halogen substituted precursors **1a, 1b (Scheme 1)** and halogen substituted methyl 2-(2-methoxy-2-oxoethoxy) benzoate **5a, 5b (Scheme 2)** were purchased or prepared by O-alkylation of corresponding methyl salicylates. These halogenated (halogen = I) derivatives **1a, 1b, 5a and 5b** were used as starting materials for cross-coupling reactions for synthesis of final products under conditions reported in **Scheme 1 and 2.** These halogen substituted starting materials efficiently underwent to cross-coupling reactions with appropriate substituted arylboronic acids [RB(OH)$_2$; **2a-c**] via following Pd-catalyzed cross-coupling reactions under microwave reaction condition in quantitative yield. By following these aspects, we were able to insert the R- substituent at position 5 and 4 of substrate efficiently to produce corresponding biphenyl derivatives **3a-c, 4a-c, 6a-c and 7a-c** by using palladium acetate and triphenyl phosphine in 1:5 ratio, as catalyst in presence of base K$_2$CO$_3$ in dry toluene under microwave irradiation for 5-7 min.

1a; R^1 = H, R^2 = I
1b; R^1 = I, R^2 = H
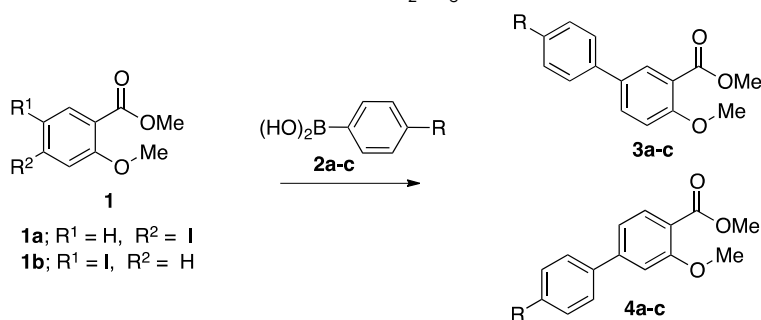
Scheme 1. Synthesis of compound 3a-c and 4a-c.

5a; R^1 = H, R^2 = I
5b; R^1 = I, R^2 = H
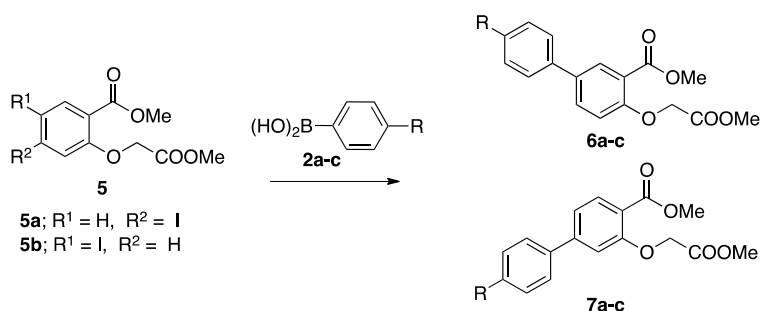
Scheme 2. Synthesis of compound 6a-c and 7a-c.

SYNTHESIS

Chemical Used

Commercially available chemicals such as methyl 2-hydroxy-5-iodobenzoate, methyl 2-hydroxy-4-iodobenzoate, phenylboronic acid, (4-chlorophenyl)boronic acid, (4-methoxyphenyl)boronic acid, K$_2$CO$_3$; solvents such as toluene, methanol, ethyl acetate, hexane, diethyl ether; and catalyst palladium acetate and triphenyl phosphine were purchased from Sigma-Aldrich or Alfa Aesar and used without further purification.

Microwave heating apparatus

For this experiment, all reactions were run in a CEM microwave synthesizer.

Result and Discussion

We have carried out an optimization study for the cross coupling reaction in order to complete with higher efficiency for

synthesis of a variety of biphenyl product. For synthesis of various final products mentioned **(Scheme 1 and 2)**, reaction conditions were systematize by using model reaction in which compound **1a** (methyl 5-iodo-2-methoxybenzoate) and **2a** (phenylboronic acid) were used as starting material to Synthesis of compound **3a-c and 4a-c (Scheme 1).**

Synthesize final product **3a** (methyl 4-methoxy-[1,1'-biphenyl]-3-carboxylate). This model reaction was attempted in both by using conventional heating (Method I) and microwave heating (Method II). After trying various reaction conditions with different substrates for Pd-catalyzed Suzuki coupling reaction, we found that $Pd(CH_3CO_2)_2$ (0.03 eq.), K_2CO_3 (0.03 eq.), PPh_3 (0.15 eq), toluene (5 ml), 110°C under conventional heating and $Pd(CH_3CO_2)_2$ (0.03 eq.), K_2CO_3 (0.03 eq.), PPh3 (0.15 eq), toluene (2 ml), 200 W, 160°C under microwave gave good results. In particular, microwave heating is better reaction conditions than conventional heating source for quantitative yields of these moisture sensitive compounds. By following microwave heating reaction condition, a variety of biphenyl products **(3a-c and 4a-c)** were obtained in quantitative yield (78-80%) **(Table 1).** All these compounds were purified by crystallization and structures assigned to **3a–c and 4a–c** are fully supported by spectral data i.e. 1H NMR.

Table 1. Reactants and Prodcuts.

Serial No.	Reactants and products		
	Entry of 1	Entry of 2	Final products
1	1a (R^1 = H, R^2 = I)	2a (R = H)	3a (R = H)
2	1a (R^1 = H, R^2 = I)	2b (R = OCH_3)	3b (R = OCH_3)
3	1a (R^1 = H, R^2 = I)	2c (R = Cl)	3c (R = Cl)
4	1b (R^1 = I, R^2 = H)	2a (R = H)	4a (R = H)
5	1b (R^1 = I, R^2 = H)	2b (R = OCH_3)	4b (R = OCH_3)
6	1b (R^1 = I, R^2 = H)	2c (R = Cl)	4c (R = Cl)

Similarly, by following above optimized reaction condition {($Pd(CH_3CO_2)_2$ (0.03 eq.), K_2CO_3 (0.03 eq.), PPh_3 (0.15 eq), toluene (2 ml), 200 W, 160°C}, compound **6a-c and 7a-c** were prepared by using corresponding starting materials and phenyl boronic acids under microwave irradiations **(Scheme 2 and Table 2)**. All these compounds were purified by crystallization and structures assigned to **6a–c and 7a–c** are fully supported by spectral data i.e. 1H NMR **(Scheme 2 and Table 2)).**

Table 2. Reactants and prodcuts

Serial No.	Reactants and products		
	Entry of 1	Entry of 2	Final products
1	5a (R^1 = H, R^2 = I)	2a (R = H)	6a (R = H)
2	5a (R^1 = H, R^2 = I)	2b (R = OCH_3)	6b (R = OCH_3)
3	5a (R^1 = H, R^2 = I)	2c (R = Cl)	6c (R = Cl)
4	5b (R^1 = I, R^2 = H)	2a (R = H)	7a (R = H)
5	5b (R^1 = I, R^2 = H)	2b (R = OCH_3)	7b (R = OCH_3)
6	5b (R^1 = I, R^2 = H)	2c (R = Cl)	7c (R = Cl)

EXPERIMENTAL PROTOCOLS

General: Commercially available chemicals were purchased from Sigma-Aldrich or Alfa Aesar and used without further purification. NMR spectra were obtained with Bruker 500 MHz spectrometer. Chemical shifts (δ) are reported in parts per million downfield from tetramethylsilane and referenced from solvent references. Chromatographic separations were performed on silica gel columns chromatography Reactions progress was followed by thin-layer chromatography (TLC) on Merck aluminum silica gel sheets that were visualized under a UV lamp. Evaporation was performed in vacuo (rotating evaporator). Sodium sulfate was always used as the drying agent. Yields refer to isolated and purified products. Microwave assisted reactions were run in a CEM microwave synthesizer. Yields refer to isolated and purified products.

REACTION PROCEDURES

Method I

Methyl 4-methoxy-[1,1'-biphenyl]-3-carboxylate (3a) Palladium acetate (0.017 mmol) was placed into a 2 mL solution of triphenylphosphine (0.085 mmol) in 8 mL dry toluene under nitrogen in two necked round bottom flask. After 10-15 min stirring when yellow precipitate formed, phenylboronic acid (0.74 mmol), potassium carbonate (1.42 mmol) and methyl 5-iodo-2-methoxybenzoate **2a** (0.58 mmol) were added simultaneously to reaction flask. The reaction content were heated under stirring at 110°C under refluxing for overnight. After completion of the reaction, toluene was removed under reduced pressure and reaction mixture was then diluted with water and repeatedly extracted with EtOAc. The organic phase was dried and evaporated to afford a crude residue that was purified by column chromatography (n-hexane/EtOAc 8:2, Rf = 0.34) to give pure **3a** (70% yield).

METHOD II

Methyl 4-methoxy-[1,1'-biphenyl]-3-carboxylate (3a) Palladium acetate (0.017 mmol) was placed into a 2 mL solution of

triphenylphosphine (0.085 mmol) in dry toluene (2 mL) under nitrogen in MW vial. After 10-15 min, phenylboronic acid (0.74 mmol), potassium carbonate (1.42 mmol) and methyl 5-iodo-2-methoxybenzoate **2a** (0.58 mmol) were added simultaneously, to the reaction vial under nitrogen atmosphere. The vial was sealed and heated under continuous stirring at 200 Watt, 160°C in a microwave reactor for 5 min. Reaction completion was checked by thin layer chromatography. After completion of the reaction, toluene was removed under reduced pressure and reaction mixture was then diluted with water and repeatedly extracted with EtOAc. The organic phase was dried and evaporated to afford a crude residue that was purified by column chromatography (n-hexane/EtOAc 8:2, Rf = 0.34) to give pure **3a** (80% yield). Similarly compound **3b, 3c** and **4a-c** were synthesized.

Method III

Methyl 4-(2-methoxy-2-oxoethoxy)-[1,1'-biphenyl]-3-carboxylate (6a) Palladium acetate (0.017 mmol) was placed into a 2 mL solution of triphenylphosphine (0.085 mmol) 2 mL in dry toluene under nitrogen in MW vial. After 10-15 min, phenylboronic acid (0.74 mmol), potassium carbonate (1.42 mmol) and methyl 5-iodo-2-(2-methoxy-2-oxoethoxy)benzoate **5a** (0.57 mmol) were added simultaneously to reaction vial under nitrogen atmosphere. The vial was sealed and heated under continuous stirring at 200 Watt, 160°C in a microwave reactor for 5 min. Reaction completion was checked by thin layer chromatography. After completion of the reaction, toluene was removed under reduced pressure and reaction mixture was then diluted with water and repeatedly extracted with EtOAc. The organic phase was dried and evaporated to afford a crude residue that was purified by column chromatography (n-hexane/EtOAc 8:2, Rf = 0.34) to give pure **6a** (78% yield). Similarly **6b, 6c and 7a-c** were synthesized.

Analytical data of compounds 3a-c, 4a-c, 6a-c and 7a-c

(3a) Methyl 4-methoxy-[1,1'-biphenyl]-3-carboxylate: ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 3.88 (s, 3H), 3.96 (s, 3H), 7.02-7.55 (m, 3H), 7.59-7.64 (m, 2H), 7.80 (dd, 1H, J = 2.0, 8.4 Hz), 7.89 (d, 1H, J = 8.8 Hz), 8.04 (d, 1H, J = 2.4 Hz); GCMS m/z 242 (M+ 80%)

(3b) Methyl 4,4'-dimethoxy-[1,1'-biphenyl]-3-carboxylate: Yield: 82%. Rf = 0.20 (n-hexane/EtOAc 9.5:0.5). ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 3.87 (s, 3H), 3.89 (s, 3H), 3.97 (s, 3H), 7.02 (dd, 2H, J = 2.2, 6.8 Hz), 7.57 (dd, 2H, J = 2.2, 6.8 Hz), 7.75 (dd, 1H, J = 1.8, 8.8 Hz) 7.83 (d, 1H, J = 8.8 Hz), 8.03 (d, 1H, J = 2.4 Hz).

(3c) Methyl 4'-chloro-4-methoxy-[1,1'-biphenyl]-3-carboxylate: Yield: 88%. Rf = 0.21 (n-hexane/EtOAc 9.0:0.5). ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 3.88 (s, 3H), 3.96 (s, 3H), 7.07-7.49 (m, 2H), 7.53-7.56 (m, 2H), 7.77 (dd, 1H, J = 2.0, 8.4 Hz), 7.86 (d, 1H, J = 8.8 Hz), 8.04 (d, 1H, J = 2.4 Hz).

(4a) Methyl 3-methoxy-[1,1'-biphenyl]-4-carboxylate: Yield: 88%. Rf = 0.28 (n-hexane/EtOAc 9.5:0.5). ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 3.88 (s, 3H), 3.94 (s, 3H), 7.45-7.56 (m, 3H), 7.58-7.65 (m, 2H), 7.85-7.86 (m, 1H), 8.08 (s, 1H).

(4b) Methyl 3,4'-dimethoxy-[1,1'-biphenyl]-4-carboxylate Yield: 90%. Rf = 0.28 (n-hexane/EtOAc 9.0:1.0). ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 3.86 (s, 3H), 3.88 (s, 3H), 3.92 (s, 3H), 7.02 (d, 2H, J = 8.8 Hz), 7.56 (d, 2H, J = 8.8 Hz), 7.80-7.81 (m, 2H), 8.00 (s, 1H).

(4c) Methyl 4'-chloro-3-methoxy-[1,1'-biphenyl]-4-carboxylate: Yield: 78%. Rf = 0.25 (n-hexane/EtOAc 9.0:1.0). ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 3.88 (s, 3H), 3.94 (s, 3H), 7.46 -7.58 (m, 4H), 7.84 (s, 2H), 8.03 (s, 1H).

(6a) Methyl 4-(2-methoxy-2-oxoethoxy)-[1,1'-biphenyl]-3-carboxylate: Yield: 78%. Rf = 0.34 (n-hexane/EtOAc 8:2), ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 3.81 (s, 3H), 3.92 (s, 3H), 4.76 (s, 2H), 6.99 (d, 1H, J = 8.8 Hz), 7.34-7.48 (m, 3H), 7.54-7.56 (m, 2H), 7.71 (dd, 1H, J = 2.4, 8.8 Hz), 8.08 (d, 1H, J = 2.4 Hz).

(6b) Methyl 4'-methoxy-4-(2-methoxy-2-oxoethoxy)-[1,1'-biphenyl]-3-carboxylate: Yield: 81%. Rf = 0.42 (n-hexane/ethyl acetate 7.5:2.5), ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 3.82 (s, 3H), 3.84 (s, 3H), 3.93 (s, 3H), 4.76 (s, 2H), 6.92-6.99 (m, 3H, Ar), 7.49 (d, 2H, J = 8.9 Hz, Ar), 7.62 (dd, 1H, J=2.0, 8.7 Hz Ar), 8.03 (d, 1H, J=2.2, Ar).

(6c) Methyl 4'-chloro-4-(2-methoxy-2-oxoethoxy)-[1,1'-biphenyl]-3-carboxylate Yield: 80%. Rf = 0.28 (n-hexane/ethyl acetate 7.5:2.5), ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 3.82 (s, 3H), 3.94 (s, 3H), 4.78 (s, 2H), 6.95 (d, 1H, J = 8.6 Hz), 7.37-7.51 (m, 4H), 7.63 (dd, 1H, J = 2.4, 8.6 Hz), 8.04 (d, 1H, J = 2.6 Hz).

(7a) Methyl 3-(2-methoxy-2-oxoethoxy)-[1,1'-biphenyl]-4-carboxylate Yield: 76%. Rf = 0.23 (n-hexane/ethyl acetate 8.0:2.0), ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 3.82 (s, 3H), 3.94 (s, 3H), 4.78 (s, 2H), 6.96 (d, 1H, J = 8.6 Hz), 7.34-7.48 (m, 3H), 7.54-7.57 (m, 2H), 7.67 (dd, 1H, J =2.4, 8.6 Hz), 8.07-8.08 (d, 1H, J = 2.2 Hz).

(7b) Methyl 4'-methoxy-3-(2-methoxy-2-oxoethoxy)-[1,1'-biphenyl]-4-carboxylate Yield: 79%. Rf = 0.21 (n-hexane/ethyl acetate 7.5:2.5). ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 3.83 (s, 3H), 3.89 (s, 3H), 3.95 (s, 3H), 4.79 (s, 2H), 6.97 (d, 2H, J = 8.6 Hz), 7.05 (d, 1H, J =1.6 Hz) 7.22-7.27 (m, 1H), 7.51 (d, 2H, J = 8.6 Hz), 7.93 (d, 1H, J = 7.9 Hz).

(7c) Methyl 4'-chloro-3-(2-methoxy-2-oxoethoxy)-[1,1'-biphenyl]-4-carboxylate Yield: 86%. Rf = 0.28 (n-hexane/ethyl acetate 8.0:2.0), ^{1}H NMR (200 MHz, CDCl$_3$) δ (ppm): 3.81 (s, 3H), 3.95 (s, 3H), 4.79 (s, 2H), 6.96 (d, 1H, J = 8.8 Hz), 7.37-7.52 (m, 4H), 7.65 (dd, 1H, J = 2.6, 8.8 Hz), 8.05 (d, 1H, J = 2.6 Hz).

CONCLUSION

This report demonstrates our efforts in search of new, energy efficient, eco-friendly, atom economic synthetic approach by using microwave energy for development large series of bioactive molecules. Various biphenyl derivatives i.e. **3a–c, 4a–c, 6a–c and 7a-c** were synthesized by coupling reaction of various boronic acids 2a–c with substrate **1a, 1b, 5a and 5c** under microwave irradiation catalyzed by palladium catalyst. On comparing microwave assisted with conventional method, microwave assisted protocol is convenient, less time consuming, atom-economic and environment friendly chemical transformation, can be efficiently utilized for synthesis various precursors for development of drug like molecules.

ACKNOWLEDGEMENT

NOMENCLATURE

MW, Microwave; MWI, Microwave irradiation; MAOS, Microwave assisted organic synthesis; NMR, Nuclear magnetic Resonance Spectroscopy.

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