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ARTICLE

Microwave-Assisted C-N Coupling for the Synthesis of 2-(2*H*-1,2,3-Triazol-2-yl)benzoic Acid Scaffold and Novel *N*-Phenyl-2-(2*H*-1,2,3-triazol-2-yl)benzamide Derivatives

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ABSTRACT

We report a novel methodology for the efficient and rapid synthesis of core intermediate 2-(2*H*-1,2,3-triazol-2-yl)benzoic acid using *trans-N,N'*-dimethylcyclohexane-1,2-diamine as a catalyst and copper iodide as co-catalyst under microwave irradiations and a series of novel *N*-phenyl-2-(2*H*-1,2,3-triazol-2-yl)benzamide derivatives *via* acid-amine coupling reaction using DCC as a dehydrating agent and DMAP as a base. In comparison to the conventional heating procedure and performing the reaction using different combinations of catalysts and bases, the time of synthesis and efforts are significantly reduced in the present method, which also gave excellent yield. The scaffold and all novel amides were characterized by spectroscopic techniques.

KEYWORDS

Acid-amine coupling, C-N coupling, Microwave-assisted synthesis, Triazole.

INTRODUCTION

Triazole is a five-membered unsaturated aromatic heterocyclic compound containing three nitrogen atoms, which exists in two isomeric forms *i.e.* 1,2,3-triazole and 1,2,4-triazole. Several derivatives of triazole have been recognized as biologically active molecules. In recent years, 1,2,3-triazole ring system has been the subject of considerable research due to its usefulness in synthetic organic chemistry and also because of the pharmacological properties [1,2]. 1,2,3-Triazoles display biological activities such as anti-HIV activity, antimicrobial activity against Gram-positive bacteria, antiviral and antiproliferative. They are also used as intermediates at the synthesis of antibiotics.

The derivatives of 1,2,3-triazole are applied as insecticides, fungicides and plant growth regulators. 1,2,3-Triazoles have widely used in industrial applications such as dyes, corrosion inhibition (of copper and copper alloys), photostabilizers, photographic materials and agrochemicals. Therefore it is important to synthesize new compounds having 1,2,3-triazole moieties. Although microwave assisted and numerous synthetic approaches have been developed to prepare this family of compounds during the past decades. Triazoles also constitute

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another important class of heterocycles because of their significant anticancer profile in many of the human cell lines. Morever, the triazoles possess properties like moderate dipole character, hydrogen bonding capability, rigidity and stability under *in vivo* conditions [3-5].

Some drugs having 1,2,3-triazole include non-nucleoside reverse transcriptase inhibitor compound **1** *tert*-butyldimethylsilylspiroamino oxathiole dioxide (TSAO), the anticancer compound **2** carboxyamidotriazole (CAI), β-lactum antibiotic compound **3** tazobactum and compound **4** cefatrizine are shown in Fig. 1 [6]. The synthesis of intermediate-1 *i.e.* 2-(2*H*-1,2,3-triazol-2-yl)benzoic acid is reported, but we have synthesized it by microwave assisted method which gave excellent yield in very short time as compare to conventional heating method after carrying out the use of different combinations of catalysts and bases. Moreover, we have synthesized a series of novel N-phenyl-2-(2*H*-1,2,3-triazol-2-yl)benzamide derivatives after carrying out the use of different combinations of different coupling agents and bases.

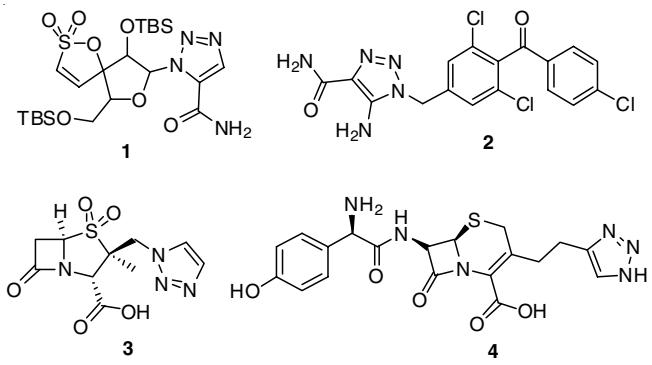


Fig. 1. Structure of some drugs containing 1,2,3-triazole moiety

EXPERIMENTAL

All purchased chemicals were used without further purification. Reactions were monitored by thin layer chromatography (TLC) on silica gel-G plates (G60 F_{254} (Merck)) of 0.5 mm thickness and visualized in ultraviolet light (254 and 365 nm). Melting points were determined using a Buchi B-540 capillary apparatus. NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer (400 MHz for ^{1}H NMR and 101 MHz for ^{13}C NMR) respectively in deuterated solvents like $CDCl_3$ or DMSO-d_6. Their chemical shifts are referenced to the solvent residual signals with respect to tetramethylsilane. Elemental analysis was carried out on Euro EA 3000 elemental analyzer and the results are in agreement with the structures assigned. Microwave experiments were carried out in an Anton-Paar Monowave 300 synthesizer using borosilicate glass G10 vial sealed with PTFE-coated silicone septum. Mass spectra were recorded on a Shimadzu GC-MS-QP-2010 mass spectrometer in ESI (70eV) model using direct inlet probe technique and *m/z* is reported in atomic units per elementary charge. Solvents were evaporated with a Buchi rotary evaporator. Purification was carried out by using column chromatography (normal phase) using silica gel 40-63 μm (200-400 mesh).

General procedure for the synthesis 2-(2*H*-1,2,3-triazol-2-yl)benzoic acid (AMI-INT): 2-Iodobenzoic acid (10 g, 0.04 mol), 2*H*-1,2,3-triazole (4.17 g, 0.06 mol) and cesium carbonate (19.7 g, 0.06 mol) were added in 20 mL DMF in a microwave vial at room temperature. To it copper(I) iodide (760 mg, 0.004 mol) and *trans-N,N'*-dimethylcyclohexane-1,2-diamine (570 mg, 0.004 mol) were added at room temperature. The reaction mixture was stirred at 150 °C for 8 min. After completion of reaction which was monitored by TLC, the reaction mass was diluted with cold water (200 mL) and neutralized with dilute HCl solution. It was extracted with EtOAc (150 mL × 3). Organic layers were combined, dried over Na_2SO_4 and solvents were distilled off under reduced pressure to give crude product, which was purified by silica-gel column chromatography (60-120). The pure fraction was collected in 5 % MDC in MeOH. Solvents were evaporated under vacuum to give Int. 1 as pale brown solid (6 g). Yield: 79 %. m.p.: 114-118 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.56-7.60 (dt, 1H, *J* = 14.8 Hz, (Ph)); 7.67-7.71 (dt, 1H, *J* = 15.6 Hz, ArH (-Ph)); 7.75-7.78 (m, 2H, ArH (-Ph)); 8.08 (s, 2H, ArH (triazole)); ^{13}C NMR (101 MHz, DMSO-d_6): δ 126.74, 128.20, 129.12, 130.52, 130.75, 136.34, 136.54, 165.89; MS: *m/z* [M$^+$] 171.9; Anal. Calcd. for $C_9H_7N_3O_2$: C, 57.14; H, 3.73; N, 22.21; Found: C, 57.10; H, 3.76; N, 22.25 %.

General procedure for the synthesis of N-(4-bromophenyl)-2-(2*H*-1,2,3-triazol-2-yl)benzamide (2a) (AMI-1): 2-(2*H*-1,2,3-Triazol-2-yl)benzoic acid (Int. 1) (0.25 g, 1.32 mmol) and substituted aniline (1.32 mmol) were dissolved in 5 mL DCM at room temperature. To it DCC (0.33 g, 1.58 mmol) and DMAP (0.19 g, 1.58 mmol) were added portion wise at room temperature. The reaction mass was allowed to stirr at room temperature for 2-4 h. After completion of reaction, which was monitored by TLC, The reaction mixture was poured in to water (50 mL) and extracted with DCM (50 mL × 2). Organic layers were combined, washed with Aq. HCl solution then aq. $NaHCO_3$ solution respectively, dried over Na_2SO_4 and solvents were distilled off under reduced pressure to give crude product, which was purified by silica-gel column chromatography (60-120). The pure fraction was collected in 30-40 % EtOAc in hexane and solvents were evaporated under vacuum to give **2a** as off-white solid (0.3 g). Yield: 67 %. m.p.: 106-108 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.49-7.51 (dt, 2H, *J* = 7.0 Hz, ArH (-Ph)); 7.57-7.61 (m, 3H, ArH (-Ph)); 7.68-7.72 (d, 2H, *J* = 11.2 Hz, ArH (-Ph)); 7.89-7.91 (d, 1H, *J* = 8.0 Hz, ArH (-Ph)); 8.04 (s, 2H, ArH (triazole)); 10.56 (s, 1H, -CONH); ^{13}C NMR (101 MHz, DMSO-d_6): δ 112.28, 122.79, 126.76, 128.37, 128.82, 130.27, 131.71, 136.42, 137.63, 139.53, 165.81; MS: *m/z* [M$^+$] 341.7 & 343.7; Anal. Calcd. for $C_{15}H_{11}N_4OBr$: C, 52.50; H, 3.23; N, 16.33; Found: C, 52.55; H, 3.45; N, 16.41 %.

N-(4-Chlorophenyl)-2-(2*H*-1,2,3-triazol-2-yl)benzamide (AMI-2) (2b): Off white solid (0.28 g). Yield: 72 %. m.p.: 146-150 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.36-7.38 (d, 2H, *J* = 7.0 Hz, ArH (-Ph)); 7.58-7.61 (m, 1H, ArH (-Ph)); 7.65-7.68 (d, 2H, *J* = 8.4 Hz, ArH (-Ph)); 7.68-7.70 (d, 1H, *J* = 8.0 Hz, ArH (-Ph)); 7.89-7.91 (d, 1H, *J* = 8.0 Hz, ArH (-Ph)); 8.04 (s, 2H, ArH (triazole)); 10.57 (s, 1H, -CONH); ^{13}C NMR (101 MHz, DMSO-d_6): δ 112.35, 122.84, 126.78, 128.41, 128.87, 130.32, 131.73, 136.51, 137.64, 139.59, 165.86; MS: *m/z* [M+] 297.9; Anal. Calcd. for $C_{15}H_{11}ClN_4O$: C, 60.31; H, 3.71; N, 18.76; Found: C, 60.34; H, 3.76; N, 18.71 %.

N-(*p*-Tolyl)-2-(2*H*-1,2,3-triazol-2-yl)-benzamide (AMI-3) (2c): Pale yellow solid (0.29 g). Yield: 80 %. m.p.: 160-162 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.26 (s, 3H, -CH_3); 7.09-7.11 (d, 2H, *J* = 8.4 Hz, ArH (-Ph)); 7.48-7.50 (d, 2H, *J* = 8.4 Hz, ArH (-Ph)); 7.55-7.59 (m, 1H, ArH (-Ph)); 7.65-7.70 (m, 2H, ArH (-Ph)); 7.87-7.89 (d, 1H, *J* = 8.0 Hz, ArH (-Ph)); 8.03 (s, 2H, ArH (triazole)); 10.32 (s, 1H, -CONH); ^{13}C NMR (101 MHz, DMSO-d_6): δ 21.49, 128.35, 129.17, 130.42, 130.65, 131.81, 132.23, 133.47, 134.61, 136.29, 136.74, 165.69; MS: *m/z* [M+] 277.9; Anal. Calcd. for $C_{16}H_{14}N4O$: C, 69.05; H, 5.07; N, 20.13; Found: C, 69.08; H, 5.11; N, 20.12 %.

N-Cyclohexyl-2-(2*H*-1,2,3-triazol-2-yl)-benzamide (AMI-4) (2d): Off white solid (0.28 g). Yield: 80 %. m.p.: 124-126 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.02-1.30 (m, 5H, -Cy); 1.53-1.77 (m, 5H, -Cy); 3.56-3.63 (m, 1H, -Chiral H); 7.47-7.53 (q, 2H, *J* = 7.6 & 15.2 Hz, ArH (-Ph)); 7.57-7.62 (t, 1H, *J* = 8.0 Hz, ArH (-Ph)); 7.75-7.77 (d, 1H, *J* = 8.0 Hz, ArH (-Ph)); 8.04 (s, 2H, ArH (triazole)); 8.14-8.16 (d, 1H, *J* = 8.0 Hz, -CONH); ^{13}C NMR (101 MHz, DMSO-d_6): δ 24.43, 24.62, 25.20, 25.29, 32.01, 33.32, 47.86, 123.36, 128.21, 128.95, 129.93, 132.25, 135.98, 136.61, 165.67; MS: *m/z* [M+] 269.9; Anal. Calcd. for $C_{15}H_{18}N_4O$: C, 66.64; H, 6.71; N, 20.73; Found: C, 66.68; H, 6.73; N, 20.79 %.

N-(2,3-Dimethylphenyl)-2-(2*H*-1,2,3-triazol-2-yl)benzamide (AMI-5) (2e): Pale yellow solid (0.29 g). Yield: 76 %. m.p.: 138-140 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.12 (s, 3H, -CH_3); 2.26 (s, 3H, -CH_3); 7.02-7.10 (m, 2H, ArH (-Ph)); 7.18-7.20 (d, 1H, *J* = 7.2 Hz, ArH (-Ph)); 7.59-7.61 (d, 1H, *J* = 7.6 Hz, ArH (-Ph)); 7.66-7.72 (m, 2H, ArH (-Ph)); 7.85-7.87 (d, 1H, *J* = 8.0 Hz, ArH (-Ph)); 8.07 (s, 2H, ArH (triazole)); 9.92 (s, 1H, -CONH); ^{13}C NMR (101 MHz, DMSO-d_6): δ 13.88, 20.03, 123.20, 124.04, 125.10, 127.23, 128.37, 128.99, 130.45, 131.55, 131.95, 135.72, 136.26, 136.52, 136.93, 165.82; MS: *m/z* [M+] 291.9; Anal. Calcd. for $C_{17}H_{16}N_4O$: C, 69.85; H, 5.52; N, 19.17; Found: C, 69.97; H, 5.47; N, 19.22 %.

N-(2,4-Dimethylphenyl)-2-(2*H*-1,2,3-triazol-2-yl)benzamide (AMI-6) (2f): Off white solid (0.28 g). Yield: 74 %. m.p.: 160-164 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.17 (s, 3H, -CH_3); 2.26 (s, 3H, -CH_3); 6.98-7.00 (d, 1H, *J* = 8.0 Hz, ArH (-Ph)); 7.03 (s, 1H, ArH (-Ph)); 7.28-7.30 (d, 1H, *J* = 8.0 Hz, ArH (-Ph)); 7.59-7.61 (m, 1H, ArH (-Ph)); 7.66-7.72 (m, 2H, ArH (-Ph)); 7.86-7.88 (d, 1H, *J* = 8.0 Hz, ArH (-Ph)); 8.09 (s, 2H, ArH (triazole)); 9.78 (s, 1H, -CONH); ^{13}C NMR (101 MHz, DMSO-d_6): δ 17.64, 20.50, 123.18, 125.69, 126.27, 128.30, 129.07, 130.37, 130.69, 131.64, 132.49, 133.44, 134.56, 136.27, 136.57, 165.60; MS: *m/z* [M+] 291.9; Anal. Calcd. for $C_{17}H_{16}N_4O$: C, 69.85; H, 5.52; N, 19.17; Found: C, 69.98; H, 5.49; N, 19.19 %.

N-(2,5-Dimethylphenyl)-2-(2*H*-1,2,3-triazol-2-yl)-benzamide (AMI-7) (2g): Off white solid (0.3 g). Yield: 79 %. m.p.: 152-154 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.15 (s, 3H, -CH_3); 2.28 (s, 3H, -CH_3); 6.92-6.94 (d, 1H, *J* = 7.6 Hz); 7.08-7.10 (d, 1H, *J* = 7.6 Hz, ArH (-Ph)); 7.26 (s, 1H, ArH (-Ph)); 7.57-7.62 (m, 1H, ArH (-Ph)); 7.66-7.73 (m, 2H, ArH (-Ph)); 7.89-7.87 (d, 1H, *J* = 8.4 Hz, ArH (-Ph)); 8.10 (s, 2H, ArH (triazole)); 9.8 (s, 1H, -CONH); ^{13}C NMR (101 MHz, DMSO-d_6): δ 17.28, 20.59, 123.17, 126.16, 128.30, 129.08, 129.41, 130.00, 130.39, 131.62, 134.74, 135.84, 136.30, 136.55, 165.55; MS: *m/z* [M+] 291.9; Anal. Calcd. for $C_{17}H_{16}N_4O$: C, 69.85; H, 5.52; N, 19.17; Found: C, 69.82; H, 5.55; N, 19.14 %.

N-(2,4-Difluorophenyl)-2-(2*H*-1,2,3-triazol-2-yl)-benzamide (AMI-8) (2h): Pale yellow solid (0.27 g). Yield: 69 %. m.p.: 104-108 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.08-7.13 (m, 1H, -ArH (-Ph)); 7.29-7.35 (dt, 1H, *J* = 2.8 & 10.6 Hz, ArH (-Ph)); 7.56-7.60 (t, 1H, *J* = 14.8 Hz, ArH (-Ph)); 7.67-7.78 (m, 3H, ArH (-Ph)); 7.89-7.92 (d, 1H, *J* = 8.0 Hz, ArH (-Ph)); 8.08 (s, 2H, ArH (triazole)); 10.25 (s, 1H, -CONH); ^{13}C NMR (101 MHz, DMSO-d_6): δ 103.93, 104.19, 104.43, 110.96, 111.18, 122.87, 126.72, 126.74, 128.20, 129.12, 130.52, 130.75, 136.34, 136.54, 165.89; MS: *m/z* [M+] 299.9; Anal. Calcd. for $C_{15}H_{10}F_2N_4O$: C, 60.00; H, 3.36; N, 18.66; Found: C, 60.07; H, 3.42; N, 18.73 %.

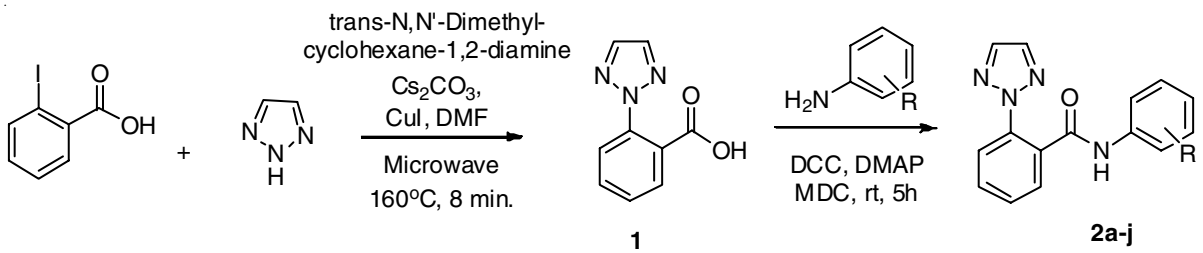
N-(3-Chloro-4-fluorophenyl)-2-(2*H*-1,2,3-triazol-2-yl)-benzamide (AMI-9) (2i): Pale yellow solid (0.33 g). Yield: 80 %. m.p.: 148-150 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.35-7.40 (t, 1H, *J* = 18 Hz, ArH (-Ph)); 7.47-7.51 (m, 1H, ArH (-Ph)); 7.57-7.62 (t, 1H, *J* = 14.8 Hz, ArH (-Ph)); 7.68-7.73 (m, 2H, ArH (-Ph)); 7.91-7.94 (m, 2H, ArH (-Ph)); 8.06 (s, 2H, ArH (triazole)). 10.64 (s, 1H, -CONH); ^{13}C NMR (101 MHz, DMSO-d_6): δ 116.81, 117.02, 118.95, 119.13, 119.71, 119.78, 120.74, 122.98, 128.32, 129.03, 130.60, 130.92, 136.39, 136.46, 165.59; MS: *m/z* [M+] 315.7; Anal. Calcd. for $C_{15}H_{10}ClFN_4O$: C, 56.88; H, 3.18; N, 17.69; Found: C, 56.91; H, 3.22; N, 17.64 %.

N-(3,4-Dichlorophenyl)-2-(2*H*-1,2,3-triazol-2-yl)-benzamide (AMI-10) (2j): Pale yellow solid (0.34 g). Yield: 77 %. m.p.: 180-184 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.34-7.42 (t, 1H, *J* = 18 Hz, ArH (-Ph)); 7.46-7.5 (m, 1H, ArH (-Ph)); 7.59-7.63 (t, 1H, *J* = 14.8 Hz, ArH (-Ph)); 7.7-7.73 (m, 2H, ArH (-Ph)); 7.9-7.95 (m, 2H, ArH (-Ph)); 8.07 (s, 2H, ArH (triazole)). 10.66 (s, 1H, -CONH); ^{13}C NMR (101 MHz, DMSO-d_6): δ 116.88, 117.23, 118.99, 119.19, 119.87, 119.81, 120.64, 122.79, 128.69, 129.13, 130.65, 130.71, 136.47, 136.56, 165.63; MS: *m/z* [M+] 333.2; Anal. Calcd. for $C_{15}H_{10}Cl_2N_4O$: C, 54.07; H, 3.03; N, 16.82; Found: C, 54.02; H, 2.97; N, 16.79 %.

RESULTS AND DISCUSSION

The synthesis of core intermediate 2-(2*H*-1,2,3-triazol-2-yl)benzoic acid was carried out by both conventional heating method and microwave irradiation as shown in **Scheme-I**. Initially, 2-iodobenzoic acid and 2*H*-1,2,3-triazole were reacted *via* normal base catalyzed reaction using weak and strong bases like potassium carbonate, potassium hydroxide, cesium carbonate, *etc*. [4]. But reaction didn't proceed in forward direction. Then different homogeneous catalysts which are generally used in C-C and C-N coupling reactions like palladium(II) acetate, *tris*(dibenzylideneacetone)dipalladium(0), palladium XantPhos, palladium XPhos, *etc*. along with ligands like triphenylphosphine, tricyclohexylphosphine, *etc*. were used with above reaction conditions.

As a positive result, intermediate 1 was formed but was in very poor yield even after refluxing for 16 h. So, above reaction was carried out using catalyst like tetramethylethylenediamine



Scheme-I

(TMEDA), *N,N*-dimethylethylenediamine, *trans-N,N'*-dimethylcyclohexane-1,2-diamine, *etc*. with co-catalyst copper iodide to improve the yield. All the reactions were carried out in both conventional heating as well as microwave irradiations. But the combination of catalyst *trans-N,N'*-dimethylcyclohexane-1,2-diamine and co-catalyst copper(I) iodide in microwave method gave good yield in very short time without using palladium catalysts. In the next step, to synthesize N-phenyl-2-(2*H*-1,2,3-triazol-2-yl)benzamide derivatives, acid-amine coupling using different coupling agents like HATU, HBTU, TBTU, T3P, EDC-HCl with two different bases DIPEA and TEA was carried out but it gave very low yield. Then the acid-amine coupling was performed in $POCl_3$/Pyridne and $SOCl_2$/TEA but they failed to give desired product. Finally, the acid-amine coupling gave good yield using DCC as a dehydrating agent in presence of base DMAP in MDC solvent at room temperature for 2-5 h.

Final crude compounds **2a-j** were purified by normal phase column-chromatography using 60-120 mesh size silica and ethylacetate-hexane solvent system as a eluent. The structures of compounds **2a-j** were characterized by various spectroscopic techniques such as ^{1}H NMR, ^{13}C NMR, mass spectroscopy and Elemental analysis. The reaction time and yield of intermediate-1 using different catalysts and bases by microwave and conventional methods are given in Table-1. The reaction time and yield of final compounds **2a-j** using different coupling agents and bases by conventional heating method are given in Table-2.

TABLE-1
SYNTHESIS OF INTERMEDIATE-1 BY MICROWAVE AND CONVENTIONAL METHOD

Entry	Catalyst	Ligand/Co-Catalyst	Base	Microwave irradiation		Conventional heating	
				Time (min)	Yield (%)	Time (h)	Yield (%)
1	Palladium(II) acetate	PPh_3	K_2CO_3	60	14	16	7
		PCy_3	K_3PO_4	60	19	16	10
		P(*o*-tol)$_3$	Cs_2CO_3	60	23	16	12
2	*Tetrakis*(triphenylphosphine) palladium(0)	PPh_3	K_2CO_3	60	15	16	7
		PCy_3	KO^{t}Bu	60	18	16	12
		P(*o*-tol)$_3$	Cs_2CO_3	60	25	16	8
3	Tris(dibenzylideneacetone) dipalladium(0)	PPh_3	K_2CO_3	60	18	16	12
		PCy_3	KOH	60	23	16	15
		P(*o*-tol)$_3$	Cs_2CO_3	60	28	16	9
4	[1,1'-*Bis*(diphenylphosphino)ferrocene] dichloropalladium(II)	PPh_3	K_2CO_3	60	16	16	11
		PCy_3	21	60	20	16	5
		P(*o*-tol)$_3$	Cs_2CO_3	60	21	16	10
5	*Bis*(triphenylphosphine) palladium(II)diacetate	PPh_3	K_2CO_3	60	17	16	11
		PCy_3	K_3PO_4	60	15	16	13
		P(*o*-tol)$_3$	Cs_2CO_3	60	19	16	9
6	Bis(triphenylphosphine) palladium(II)dichloride	PPh_3	KO^{t}Bu	60	21	16	15
		PCy_3	KOH	60	18	16	14
		P(*o*-tol)$_3$	Cs_2CO_3	60	27	16	14
7	[1,1'-Bis(diphenylphosphino)ferrocene] dichloropalladium(II)	Xantphos	K_2CO_3	60	12	16	20
		Xphos	K_3PO_4	60	10	16	11
		BINAP	Cs_2CO_3	60	15	16	13
8	Tris(dibenzylideneacetone) dipalladium(0)	Xantphos	K_2CO_3	60	9	16	13
		Xphos	KO^{t}Bu	60	11	16	17
		BINAP	Cs_2CO_3	60	12	16	21
9	*N,N*-Dimethylethylenediamine	CuI	K_2CO_3	8	33	16	31
		CuI	KOH	8	26	16	25
		CuI	Cs_2CO_3	8	39	16	35
10	Tetramethylethylenediamine (TMEDA)	CuI	KO^{t}Bu	8	30	16	28
		CuI	KOH	8	27	16	28
		CuI	Cs_2CO_3	8	36	16	34
11	*trans-N,N'*-Dimethylcyclohexane-1,2-diamine	CuI	K_2CO_3	8	63	16	57
		CuI	K_3PO_4	8	45	16	42
		CuI	Cs_2CO_3	8	79	16	70

TABLE-2
SYNTHESIS OF COMPOUND **2a** BY CONVENTIONAL HEATING METHOD

Entry	Coupling reagent	Base	Conventional heating	
			Time (h)	Yield (%)
1	HATU	DIPEA	16	17
		TEA	16	19
2	HBTU	DIPEA	16	5
		TEA	16	5
3	TBTU	DIPEA	16	3
		TEA	16	5
4	T3P	DIPEA	16	11
		TEA	16	8
5	EDC-HCl	DIPEA	16	7
		TEA	16	8
6	$POCl_3$	Pyridine	16	13
7	$SOCl_2$	TEA	16	6
8	DCC	DMAP	2-5	67-80

Conclusion

We have synthesized 2-(2*H*-1,2,3-triazol-2-yl)benzoic acid scaffold (intermediate-1) by both conventional heating method and microwave irradiations. We have also used different combinations of palladium catalysts and ligands as far as the C-N coupling is concerned. We found that the combination of catalyst *trans-N,N'*-Dimethylcyclohexane-1,2-diamine and co-catalyst copper iodide in microwave irradiations method gave the best results regarding the time, yield and cost according to the results shown in Table-1.

Moreover, we have also synthesized a series of novel *N*-phenyl-2-(2*H*-1,2,3-triazol-2-yl)benzamide derivatives. The route of its synthesis *i.e*. acid-amine coupling is also novel. It was carried out by using different combinations of coupling agents and bases in conventional heating method. The combination of DCC and DMAP gave good yield and was completed in short time as compare to other reagents according to the results shown in Table-2. The scaffold and the final compounds were characterized by different spectroscopy like ^{1}H NMR, ^{13}C NMR, Mass and elemental analysis.

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