Received: 23 July 2018 | Revised: 4 December 2018 | Accepted: 12 December 2018

DOI: 10.1002/jccs.201800287

JOURNAL OF THE CHINESE CHEMICAL SOCIETY

ARTICLE

Ligand-free, copper-catalyzed, one-pot, three-component synthesis of novel 1,2,3-triazole-linked indoles in magnetized water

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Magnetized water (MW) is used as a green and new solvent-promoting medium for the one-pot, three-component synthesis of novel 1,2,3-triazole-linked indoles catalyzed by copper iodide. A broad range of 2-aryl-1-(prop-2-ynyl)-1*H*-indole-3-carbaldehydes were reacted with alkyl halides and sodium azide via copper-catalyzed azide–alkyne cycloaddition reactions in MW in the absence of any ligand. This method offers the advantages of short reaction times, green procedure, low cost, simple work-up, quantitative reaction yields, and no need for any organic solvent.

KEYWORDS

1,2,3-Triazole, Click reaction, Indole, Magnetized water

1 | INTRODUCTION

Indole is an important material used in organic synthesis, and its physiological properties have attracted much scientific attention.[1–3] A variety of 2-phenylindoles have been found to inhibit the growth of human breast cancer cells by dissimilar mechanisms depending upon the type and position of the substituents.[4–7] Recently, 2-phenylindole-3-carboxaldehydes have been proven to exert antimitotic activity in human breast cancer cells by inhibiting tubulin polymerization.[8,9] Moreover, 2-aryl-indole derivatives have displayed diverse biological properties such as anti-estrogen, cytotoxic, and antimitotic[10–12] activity.

1,2,3-Triazoles play essential functions in organic chemistry, medicinal chemistry, agrochemicals, and dyes because of their ease of preparation by "click chemistry."[13,14] For example, some of these compounds display broad pharmacological properties such as antitubercular,[15] antiviral,[16] antibacterial and antifungal,[17] and anticancer[18] activity. On the other hand, when 1,2,3-triazole and indoles are linked by copper-catalyzed click reactions at the specific ring positions of bi- or tri-heterocycle-containing new molecules, interesting physiological proprieties are observed.

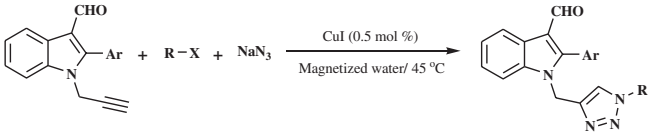
The copper-catalyzed azide–alkyne cycloaddition (CuAAC) reaction, also known as the "click reaction", has become one of the most important reactions used for the preparation of 1,2,3-triazoles.[19] In 2002, Sharpless[20] and Meldal[21] independently claimed that copper catalysts dramatically hasten the reaction and make it totally regioselective toward the 1,4-regioisomer. It is well known that the CuAAC reaction takes place only in the presence of a Cu(I) species but not in the presence of Cu(II) or Cu(0) species. However, Cu(I) salts are not susceptible to redox processes, and thus it is beneficial to protect and stabilize the active copper catalysts during a CuAAC reaction, and this has led to the discovery of various modified methods such as the use of Cu(II)/Cu(0) salts with different additives or ligands.[22–24] Other copper(0) and copper(I) catalysts, such as copper nano-sized powder,[25] copper nanoparticles adsorbed on charcoal,[26] and copper nanoclusters,[27] have also shown good catalytic activity. However, some of these methods suffer from disadvantages

such as expensive reagents, long reaction times, use of large quantities of organic solvents, and harsh reaction conditions. In order to overcome these problems, the development of a milder, cheaper, more general, and highly efficient as well as an environmentally benign method is desirable for the preparation of triazoles.

Among the commonly used solvents in organic synthesis, water is nontoxic, and it is the most economical, most abundant, safest, and most environmentally friendly medium. Sometimes water shows higher reactivity and selectivity compared to the other conventional organic solvents because of its strong hydrogen-bonding ability. These characteristics allow water to act as a solvent, a reactant, or a catalyst, making it different from conventional organic solvents.[28] Furthermore, reactions in water give enhanced yields, require shorter reaction times, and show greater ease of manipulation. Although the majority of CuAAC reactions proceed either in organic solvents or in their mixtures with water, a few reactions have been reported in water itself.[29–32] However, in all these reactions, a suitable ligand is needed to speed up the reaction rate. In addition, in most of these methods, high temperatures are needed for the reaction to proceed.

In 1953, Vermeiren reported that an applied magnetic field can affect the properties of water.[33] The water magnetization technique is an easy one without extra energy consumption when a permanent external magnet is used. A permanent external magnet can be installed on a previously established water tube system, resulting in no additional energy requirement for water magnetization. This green technology is clean and has zero energy consumption. Pure water, as a polar and associative liquid, can modify its intermolecular bonds in an applied magnetic field, changing to a metastable state but keeping that state for some time.[34] Based on Mosin and Ignatov's theory,[35,36] the applied magnetic field directly affects the structure of water because of the polarization of water molecules. These molecules are bound together via low-energy intermolecular Van der Waals forces, dipole–dipole interactions, and hydrogen bonding. The magnetic field can deform the hydrogen bonds and give rise to some partial rupture. In this regard, during the last few years, many researchers have been interested in studying the effect of an applied magnetic field on the properties of water, such as its density, specific heat, refractive index, electric dipole moment, vaporization enthalpy, surface tension, viscosity, and, especially, hydrogen-bond distribution.[37]

In continuation of our interest in the development of organic syntheses in magnetized water (MW) as a new solvent,[38–42] we report here, for the first time, a rapid and mild protocol for the synthesis of novel 1,2,3-triazole-linked indoles via the copper-catalyzed click reactions in MW (Scheme 1).



SCHEME 1 Synthesis of 1,2,3-triazole-linked indoles catalyzed by CuI in magnetized water

2 | RESULTS AND DISCUSSION

MW was prepared using a static magnetic system of 0.8T field strength at different exposure times to the magnetic field (Figure 1). Distilled water (5 mL) was taken in a test tube, which was then placed in the magnetic field for 20 min. The tube was subsequently removed from the instrument and used for the reaction.

Then, treatment of 2-aryl-1*H*-indole-3-carbaldehydes (**1**) with propargyl bromide (**2**) in the presence of potassium carbonate in MW at room temperature afforded 2-aryl-1-(prop-2-ynyl)-1*H*-indole-3-carbaldehydes (**3**) in good yields (Table 1). The ^{1}H NMR spectrum of 2-phenyl-1-(prop-2-ynyl)-1*H*-indole-3-carbaldehyde **3a** showed a triplet for the CH proton at δ 3.47, a doublet for the CH2 protons at δ 4.99, a multiplet for the aromatic protons of the indole and phenyl rings at δ 7.35–8.27, and a singlet at δ 9.45 due to the CHO proton.

Preliminary experiments were performed using a ligand-free click reaction of 2-phenyl-1-(prop-2-ynyl)-1*H*-indole-3-carbaldehyde **3a**, benzyl chloride, and sodium azide in the presence of 5 mol% of CuI as a model reaction. In order to find the optimum reaction conditions for the synthesis of compound **5a**, the effects of various solvents and reaction temperatures were studied, and the results are shown in Table 2.

As shown in Table 2, several solvents were screened for the reaction in the presence of a catalytic amount of CuI. The results obtained showed that the efficiency and yield of the reaction in MW at 45°C (Table 2, entry 18) were higher than those obtained in solvents such as CH_2Cl_2, CH_3CN, THF, DMF, ethyl acetate, methanol, ethanol, and distilled water in the absence of any ligand (Table 2, entries 1–18).

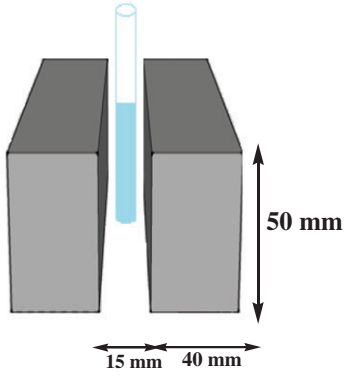
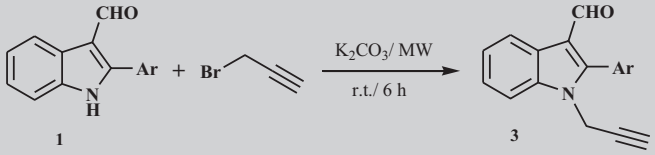


FIGURE 1 Pilot for solvent magnetization apparatus

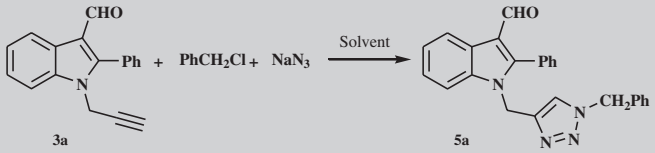
TABLE 1 Synthesis of 2-aryl-1-(prop-2-ynyl)-1*H*-indole-3-carbaldehydes **3**[a]



Entry	Ar	Product	M.p. (°C)	Yield (%)[b]
1	Ph	**3a**	145–147	98
	1a			
2	4-BrC_6H_4-	**3b**	167–169	85
	1b			
3	4-ClC_6H_4-	**3c**	163–165	82
	1c			
4	4-MeC_6H_4-	**3d**	142–144	92
	1d			
5	4-MeOC_6H_4-	**3e**	148–150	90
	1e			

[a] *Reaction condition*: **1** (1 mmol), propargyl bromide (1.2 mmol), K_2CO_3 (2 mmol), MW (5 mL), room temperature, 6 hr.
[b] Isolated yield.

TABLE 2 Synthesis of compound **5a** in different solvents[a]



Entry	Solvent	Temp. (°C)	Yield (%)[b]
1	CH_2Cl_2	rt	—
2	CH_2Cl_2	45	—
3	CH_3CN	rt	10
4	CH_3CN	45	23
5	THF	rt	12
6	THF	45	25
7	DMF	rt	15
8	DMF	45	34
9	Ethyl acetate	rt	—
10	Ethyl acetate	45	—
11	MeOH	rt	17
12	MeOH	45	45
13	EtOH	rt	20
14	EtOH	45	52
15	Distilled water	rt	15
16	Distilled water	45	40
17	Magnetized water (MW)[c]	rt	60
18	Magnetized water (MW)[c]	45	95
19	Magnetized water (MW)[c]	94	60

[a] *Reaction conditions*: **3a** (1.0 mmol), benzyl chloride (1.0 mmol), sodium azide (1.0 mmol), CuI (5 mol%), solvent (5 mL) for 30 min.
[b] Isolated yield.
[c] Magnetization time 20 min.

Also, increasing the temperature did not improve the reaction yield (Table 2, entry 19).

Based on the results obtained (Table 2, entry 18), we tried to optimize the reaction conditions using MW that could help reduce the reaction time and improve the yield of the target product (Table 3). Various parameters including different catalysts, magnetization time, catalyst concentration, reaction time, and volume of MW were studied. From Table 3, it is obvious that the use of CuI results in the best reaction condition (Table 3, entry 4). It seems that the magnetization time of water plays an important role in achieving the product **5a** in high yield (Table 3, entries 4–6). As indicated in Table 3, increasing the water magnetization time to 30 min showed no substantial improvement in the reaction yield (Table 3, entry 5), whereas the yield decreased on decreasing the water magnetization time to 10 min (Table 3, entry 6).

A substantial amount of a heavy-metal catalyst is utilized in the classic copper-catalyzed click reactions. The Cu salts pollute the biologically relevant compounds, they are toxic, and their full removal from the reaction mixture is hard. These problems can be overcome by the use of click reactions in biomedicine. In the recent years, numerous modifications have been reported for reducing the amount of the copper catalyst required for click reactions, such as the use of ligands.[43,44]

One of the roles of such ligands is to increase the solubility of the copper complex in water to deliver higher solution concentrations of the necessary Cu(I) species. Fortunately, since copper iodide is completely soluble in MW, the addition of a ligand to the reaction is not necessary. For environmental and economic reasons, the development of catalytic systems without employing a ligand is an attractive field of research. For this purpose, we decreased the amount of the copper catalyst. Surprisingly, we found that with 0.5 mol% of CuI catalyst, the click reaction proceeded effectively and reached completion to afford the desired product in 98% yield in 20 min (Table 3, entry 13). Furthermore, the volume of MW used had a great effect on the reaction yield (Table 3, entries 15–17). When a small amount of MW (1 mL) was used, the reagents were insoluble in it, and the product was formed in low yield (Table 3, entry 17). Thus the optimal reaction conditions were 0.5 mol% of CuI, at 45°C, in 3 mL of MW (Table 3, entry 15).

It should be noted that the synthesis of 1,2,4-triazoles via CuAAC reactions is generally carried out in the presence of base ligands or heterogeneous catalytic systems with the aid of organic or aqueous solvents.[45–52]

Clearly, these reported methods not only generate a lot of organic or inorganic wastes during the work-up procedure but also result in the complication of carrying away trace amounts of the residual ligand or metal species from the target compound when they are used in pharmaceutical synthesis. Performing the model reaction in MW not only offers a ligand- and base-free click reaction and excellent reaction yield but also avoids the generation of harmful wastes, the use of a great amount organic solvents or catalysts, and a tedious post-treatment. We, therefore, believe that our proposed system is an attractive strategy for the synthesis of the product from the viewpoint of green synthesis.

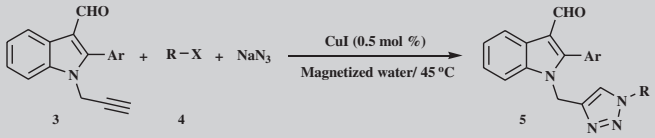
After the optimized conditions were found (Table 3, entry 15), the scope of the reaction was explored with 2-aryl-1-(prop-2-ynyl)-1*H*-indole-3-carbaldehyde (**3**), benzyl or alkyl halides, and sodium azide (Table 4). As shown in

TABLE 3 Synthesis of **5a** in MW under various conditions[a]

Entry	Solvent (mL)	Catalyst (mol%)	Magnetization time (min)	Reaction time (min)	Yield (%)[b]
1	MW (5)	$CuSO_4$ (5)[c]	20	30	70
2	MW (5)	$Cu(OAc)_2$[c]	20	30	88
3	MW (5)	CuCl (5)	20	30	82
4	MW (5)	CuI (5)	20	30	99
5	MW (5)	CuI (5)	30	30	98
6	MW (5)	CuI (5)	10	30	85
7	MW (5)	CuI (3)	20	30	99
8	MW (5)	CuI (2)	20	30	99
9	MW (5)	CuI (1)	20	30	98
10	MW (5)	CuI (0.5)	20	30	98
11	MW (5)	CuI (0.4)	20	30	90
12	MW (5)	CuI (0.2)	20	30	75
13	MW (5)	CuI (0.5)	20	20	98
14	MW (5)	CuI (0.5)	20	10	93
15	MW (3)	CuI (0.5)	20	20	98
16	MW (2)	CuI (0.5)	20	20	72
17	MW (1)	CuI (0.5)	20	20	60

[a] *Reaction conditions*: **3a** (1.0 mmol), benzyl chloride (1.0 mmol), sodium azide (1.0 mmol), CuI, magnetized water, 45°C.
[b] Isolated yield.
[c] Sodium ascorbate (10 mol%).

TABLE 4 Syntheses of novel 1,2,3-triazole-linked indoles **5**[a]



Entry	Substrate	R-X	Product	m.p (°C)	Yield[b] (%)
1	3a	$PhCH_2Cl$ 4a	**5a**	115–117	98
2	3a	4-cl-$C_6H_4CH_2Cl$ 4b	**5b**	75–77	95
3	3a	C_4H_9Br 4c	**5c**	102–104	92
4	3b	4a	**5d**	118–120	93
5	3b	4b	**5e**	70–72	90
6	3b	4c	**5f**	92–94	87
7	3c	4a	**5g**	131–133	90
8	3c	4b	**5h**	88–90	88
9[c]	3c	4c	**5i**	95–97	82
10	3d	4a	**5j**	83–85	96
11	3d	4b	**5k**	75–77	89
12	3e	4c	**5l**	120–122	95
13	3e	4b	**5m**	68–70	86
14[c]	3e	4c	**5n**	88–90	91

[a] *Reaction conditions*: **3** (1.0 mmol), organic halide (1.0 mmol), sodium azide (1.0 mmol), CuI (0.5 mol%), magnetization time (10 min), MW (3 mL), 45°C, reaction time (20 min).
[b] Isolated yield.
[c] Reaction time (120 min).

Table 4, the corresponding 1-([1-alkyl-1*H*-1,2,3-triazol-4-yl] methyl)-2-aryl-1*H*-indole-3-carbaldehyde derivatives (**5**) were isolated as products in high to excellent yields under the present reaction conditions from the reaction of various 2-aryl-1-(prop-2-ynyl)-1*H*-indole-3-carbaldehydes (**3**) and benzyl or alkyl halides with sodium azide.

What is interesting is that all the solid reagents dissolve in MW, whereas after completion of the reaction, the reaction product is insoluble in MW.

3 | EXPERIMENTAL

3.1 | General

The reagents and solvents used were supplied from Merck, Fluka, or Aldrich. Melting points were determined using an Electrothermal C14500 apparatus. The reaction progress and purity of the compounds were monitored using thin-layer chromatography (TLC) using analytical silica gel plates (Merck 60F250). The ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were obtained using a Bruker Avance DPX-250 FT-NMR spectrometer. The chemical shifts are given as δ values against tetramethylsilane (TMS) as the internal standard, and the *J*-values are given in hertz. Microanalysis was performed on a Perkin-Elmer 240-B microanalyzer.

3.2 | Preparation of MW

In order to prepare the MW sample according to Figure 1, 5 mL distilled water was first taken in a test tube, which was then placed between two neodymium magnets NdFeB (10 cm × 5 cm × 4 cm) with a magnetic field of 0.8 *T*. The test tube was subsequently removed from the magnetic field and used for the reaction.

3.3 | Synthesis of 2-aryl-1-(prop-2-ynyl)-1*H*-indole-3-carbaldehydes 3a–e

A mixture of 2-aryl-1*H*-indole-3-carbaldehyde (**1**) (1 mmol) and K_2CO_3 (2 mmol, 0.27 g) in MW (5 mL) was stirred for 10 min. Then propargyl bromide (1.2 mmol, 0.15 g) was added, and the solution was stirred for 6 hr at room temperature. After completion of the reaction (monitored by TLC), the crude product was washed with water, and the precipitate formed was purified by recrystallization from ethanol to afford the pure title compound.

3.3.1 | 2-Phenyl-1-(prop-2-yn-1-yl)-1*H*-indole-3-carbaldehyde (3a)

IR (KBr): 3,216 (m), 2,320 (m), 1,657 (s), 1,414 (m), 1,372 w), 1,097 (s) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 3.47 (t, 1H, J = 2.4 Hz, C-H), 4.99 (s, 2H, CH_2), 7.35–7.47 (m, 2H, Ar-H), 7.66–7.73 (m, 5H, Ar-H), 7.76 (d, 1H, J = 7.8 Hz, Ar-H), 8.27 (dd, 1H, J = 7.2 Hz, 1.2 Hz, Ar-H), 9.65 (s, 1H, CHO). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 31.1, 34.1, 39.1, 39.4, 39.7, 40.0, 40.2, 40.5, 40.8, 76.4, 78.7, 111.7, 115.5, 121.5, 123.7, 124.5, 125.1, 128.0, 129.3, 130.6, 131.2, 136.4, 150.9, 186.0; MS (*m/z*): 259 $(M)^+$; Anal. calcd for $C_{18}H_{13}NO$: C, 83.37; H, 5.05; N, 5.40%; Found: C, 83.52; H, 5.14; N, 5.53%.

3.3.2 | 2-(4-Bromophenyl)-1-(prop-2-yn-1-yl)-1*H*-indole-3-carbaldehyde (3b)

IR (KBr): 3,210 (m), 2,322 (m), 1,651 (s), 1,420 (m), 1,377 (w), 1,092 (s) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 3.36 (s, 1H, C-H), 5.01 (s, 2H, CH_2), 7.35–7.40 (m, 1H, Ar-H), 7.42–7.48 (m, 1H, Ar-H), 7.66 (d, 2H, J = 8.4 Hz, Ar-H), 7.77 (d, 1H, J = 8.1 Hz, Ar-H), 7.88 (d, 2H, J = 8.4 Hz, Ar-H), 8.28 (D, 1H, J = 7.5 Hz, AR-H), 9.64 (s, 1H, CHO). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 34.1, 76.5, 78.7, 111.7, 115.7, 121.5, 123.8, 124.53, 124.7, 125.0, 127.3, 132.3, 133.3, 136.5, 149.4, 185.9; MS (*m/z*): 337 $(M)^+$; Anal.calcd for $C_{18}H_{12}BrNO$: C, 63.92; H, 3.58; N, 4.14%; Found: C, 63.74; H, 3.50; N, 4.27%.

3.3.3 | 2-(4-Chlorophenyl)-1-(prop-2-yn-1-yl)-1*H*-indole-3-carbaldehyde (3c)

IR (KBr): 3,221 (m), 2,329 (m), 1,655 (s), 1,418 (m), 1,369 (w), 1,089 (s) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 3.47 (t, 1H, J = 2.4 Hz, C-H), 5.02 (d, 2H, J = 2.4 Hz, CH_2), 7.35–7.40 (m, 1H, Ar-H), 7.42–7.47 (m, 1H, Ar-H), 7.74–7.78 (m, 5H, Ar-H), 8.26 (d, 1H, J = 7.5 Hz, Ar-H), 9.65 (s, 1H, CHO). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 34.1, 76.5, 78.7, 111.7, 115.7, 121.5, 123.8, 124.7, 125.0, 126.9, 129.4, 133.0, 135.7, 136.5, 149.4, 185.9; MS (*m/z*): 293 $(M)^+$; Anal. calcd for $C_{18}H_{12}CLNO$: C, 73.60; H, 4.12; N, 4.77%; Found: C, 73.78; H, 4.21; N, 4.63%.

3.3.4 | 1-(Prop-2-yn-1-yl)-2-(*p*-tolyl)-1*H*-indole-3-carbaldehyde (3d)

IR (KBr): 3,211 (m), 2,318 (m), 1,659 (s), 1,416 (m), 1,369 (w), 1,090 (m) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 2.46 (s, 3H, CH_3), 3.47 (s, 1H, C-H), 4.98 (s, 2H, CH_2), 7.34–7.49 (m, 4H, Ar-H), 7.57–7.60 47 (m, 2H, Ar-H), 7.75 (d, 1H, J = 8.1 Hz, Ar-H), 7.76 (d, 1H, J = 7.5 Hz, Ar-H), 9.65 (s, 1H, CHO). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 21.4, 34.1, 76.4, 78.8, 111.7, 115.4, 121.5, 123.7, 124.5, 125.0, 125.1, 129.9, 131.1, 136.4, 140.4, 151.1, 186.0; MS (*m/z*): 273 $(M)^+$; Anal. calcd for $C_{19}H_{15}NO$: C, 83.49; H, 5.53; N, 5.12%; Found: C, 83.66; H, 5.62; N, 5.27%.

3.3.5 | 2-(4-Methoxyphenyl)-1-(prop-2-yn-1-yl)-1*H*-indole-3-carbaldehyde (3e)

IR (KBr): 3,213 (m), 2,327 (m), 1,653 (s), 1,417 (m), 1,370 (w), 1,095 (m) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 3.49 (t, 1H, J = 2.4 Hz, C-H), 4.99 (d, 2H, J = 2.4 Hz, ch2), 7.23 (d, 2H, J = 8.7 Hz, Ar-H), 7.34–7.39 (m, 1H, Ar-H), 7.40–7.45 (m, 1H, Ar-H), 7.64 (d, 2H, J = 8.7 Hz, ar-h), 7.74 (d, 1H, J = 7.8 Hz, Ar-H), 8.25 (d, 1H, J = 7.2 Hz, Ar-H), 9.65 (s, 1H, CHO). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 34.0, 55.8, 76.4, 78.9, 111.6, 114.9, 115.3, 119.9, 121.4, 123.6, 124.4, 125.2, 132.7, 136.4, 151.1, 161.1, 186.1; MS (*m/z*): 289 $(M)^+$; Anal. calcd for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23; N, 4.84%; Found: C, 78.69; H, 5.14; N, 4.99%.

3.4 | General procedure for the synthesis of 1,2,3-triazole-linked indoles 5a–n

To a 10-mL round-bottomed flask equipped with a magnetic stirrer bar and containing MW (3 mL) were added 2-aryl-1-(prop-2-ynyl)-1*H*-indole-3-carbaldehyde (**3**) (1.0 mmol), an organic halide (1.0 mmol), and sodium azide (1.0 mmol, 0.065 g). The reaction mixture was stirred at 45°C, and the reaction progress was monitored by TLC using chloroform as the eluent. After completion of the reaction, the precipitate formed was filtered and purified by recrystallization from ethanol to afford the desired product.

3.4.1 | 1-([1-Benzyl-1*H*-1,2,3-triazol-4-yl]methyl)-2-phenyl-1*H*-indole-3-carbaldehyde (5a)

IR (KBr): 3,072 (w), 2,944 (m), 2,384 (m), 1,651 (s), 1,536 (m), 1,462 (m), 1,420 (w) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 5.42 (s, 2H, CH_2), 5.54 (s, 2H, CH_2), 7.22–7.24 (m, 2H, Ar-H), 7.30–7.40 (m, 5H, Ar-H), 7.58–7.63 (m, 3H, Ar-H), 7.68–7.74 (m, 3H, Ar-h), 8.02 (s, 1H, C-H), 8.22–8.25 (m, 1H, Ar-H), 9.61 (s, 1H, CHO). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 53.2, 111.9, 115.3, 121.4123.3, 124.1, 124.3, 125.2, 128.2, 128.4, 128.5, 129.1, 129.1, 130.4, 131.5, 136.3, 136.7, 143.0, 151.7, 185.9; MS (*m/z*): 392 $(M)^+$; Anal. calcd for $C_{25}H_{20}N_4O$: C, 76.51; H, 5.14; N, 14.28%; Found: C, 76.70; H, 5.23; N, 14.12%.

3.4.2 | 1-((1-[4-Chlorobenzyl]-1*H*-1,2,3-triazol-4-yl)methyl)-2-phenyl-1*H*-indole-3-carbaldehyde (5b)

IR (KBr): 3,070 (w), 2,940 (m), 2,379 (m), 1,650 (s), 1,530 (m), 1,460 (m), 1,422 (w) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 5.43 (s, 2H, CH_2), 5.55 (s, 2H, CH_2), 7.22–7.28 (m, 1H, Ar-H), 7.33–7.35 (m, 2H, Ar-H), 7.43–7.51 (m, 3H, Ar-H), 7.61–7.74 (m, 6H, Ar-H), 8.04 (s, 1H, C-H), 8.25 (d, 1H, J = 6 Hz, Ar-H), 9.62 (s, 1h, CHO). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 52.4, 111.9, 115.5, 121.4, 123.5, 124.3, 124.3, 125.2, 128.4, 129.1, 129.1, 130.2, 130.4, 130.7, 131.5, 133.3, 135.3, 136.7, 143.1, 151.7, 185.9; MS (*m/z*): 426 $(M)^+$; Anal. Calcd for $C_{25}H_{19}ClN_4O$: C, 70.34; H, 4.49; N, 13.12%; Found: C, 70.51; H, 4.39; N, 13.27%.

3.4.3 | 1-([1-Butyl-1*H*-1,2,3-triazol-4-yl]methyl)-2-phenyl-1*H*-indole-3-carbaldehyde (5c)

IR (KBr): 3,077 (w), 2,945 (m), 2,380 (m), 1,652 (s), 1,535 (m), 1,459 (m), 1,420 (w) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 0.77 (t, 3h, j = 7.2 Hz, CH_3), 1.02–1.09 (m, 2H, CH_2), 1.58–1.68 (m, 2H, ch_2), 4.20 (t, 2H, J = 7.2 Hz, CH_2), 5.31 (s, 2H, CH_2), 7.23–7.28 (m, 2H, Ar-H), 7.54–7.61 (m, 4H, Ar-H), 7.66–7.69 (m, 2H, Ar-H), 7.89 (s, 1H, C-H), 8.13–8.16 (m, 1H, Ar-H), 9.53 (s, 1H, CHO). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 13.7, 19.4, 34.1, 49.5, 111.7, 115.5, 121.5, 123.7, 124.6, 125.1, 128.0, 129.1, 129.3, 130.6, 131.2, 131.5, 136.4, 150.9, 186.0; MS (*m*/*z*): 358 $(M)^+$; Anal. calcd for $C_{22}H_{22}N_4O$: C, 73.72; H, 6.19; N, 15.63%; Found: C, 73.90; H, 6.30; N, 15.80%.

3.4.4 | 1-([1-Benzyl-1*H*-1,2,3-triazol-4-yl]methyl)-2-(4-bromophenyl)-1*H*-indole-3-carbaldehyde (5d)

IR (KBr): 3,069 (w), 2,960 (m), 2,382 (m), 1,650 (s), 1,530 (m), 1,460 (m), 1,417 (w) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 5.43 (s, 2H, CH_2), 5.55 (s, 2H, CH_2), 7.23–7.25 (m, 2H, Ar-H), 7.30–7.41 (m, 5H, Ar-H), 7.68–7.74 (m, 3H, Ar-H), 7.78–7.81 (m, 2H, Ar-H), 8.08 (s, 1H, C-H), 8.23–8.26 (m, 1H, Ar-H), 9.62 (s, 1H, CHO). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 53.2, 112.0, 115.6, 121.4, 123.6, 124.1, 124.3, 124.4, 125.1, 127.7, 128.2, 128.5, 129.1, 132.1, 133.5, 136.3, 136.8, 142.9, 150.1, 185.8; MS (*m*/*z*): 470 $(M)^+$; Anal. calcd for $C_{25}H_{19}BrN_4O$: C, 63.70; H, 4.06; N, 11.89%; Found: C, 63.53; H, 4.15; N, 11.74%.

3.4.5 | 2-(4-Bromophenyl)-1-((1-[4-chlorobenzyl]-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-indole-3-carbaldehyde (5e)

IR (KBr): 3,073 (w), 2,951 (m), 2,385 (m), 1,649 (s), 1,525 (m), 1,458 (m), 1,418 (w) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 5.43 (s, 2H, CH_2), 5.55 (s, 2H, CH_2), 7.25–7.28 (m, 2H, Ar-H), 7.32–7.38 (m, 3H, Ar-H), 7.43–7.49 (m, 2H, Ar-H), 7.68–7.73 (m, 3H, Ar-H), 7.78–7.88 (m, 2H, Ar-H), 8.07 (s, 1H, C-H), 8.23–8.25 (m, 1H, Ar-H), 9.62 (s, 1H, CHO). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 52.4, 112.0, 115.7, 121.4, 123.6, 124.1, 124.3, 124.4, 125.1, 127.7, 129.2, 130.2, 132.1, 132.3, 133.3, 133.5, 135.3, 136.8, 143.0, 150.1, 185.8; MS (*m*/*z*): 503 $(M)^+$; Anal. calcd for $C_{25}H_{18}BrClN_4O$: C, 59.37; H, 3.59; N, 11.08%; Found: C, 59.55; H, 3.67; N, 11.25%.

3.4.6 | 2-(4-Bromophenyl)-1-([1-butyl-1*H*-1,2,3-triazol-4-yl]methyl)-1*H*-indole-3-carbaldehyde (5f)

IR(KBr): 3,080 (w), 2,940 (m), 2,371 (m), 1,651 (s), 1,520 (m), 1,460 (m), 1,419 (w) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 0.86 (t, 3H, J = 7.2 Hz, CH_3), 1.11–1.21 (m, 2H, CH_2), 1.67–1.77 (m, 2H, CH_2), 4.29 (t, 2H, J = 7.2 Hz, CH_2), 5.41 (s, 2H, CH_2), 7.30–7.38 (m, 2H, Ar-H), 7.70–7.76 (m, 3H, Ar-H), 7.82–7.85 (m, 2H, Ar-H), 8.02 (s, 1H, C-H), 8.22–8.25 (m, 1H, Ar-H), 9.62 (s, 1H, CHO). ^{13}C NMR (75 MHz, DMSO) δ: 13.7, 19.4, 32.0, 49.5, 112.0, 115.6, 121.4, 123.5, 123.8, 124.3, 124.5, 125.1, 127.7, 132.1, 133.5, 136.8, 142.5, 150.2, 185.8; MS (*m*/*z*): 436 $(M)^+$; Anal. calcd for $C_{22}H_{21}BrN_4O$: C, 60.42; H, 4.84; N, 12.81%; Found: C, 60.60; H, 4.94; N, 12.97%.

3.4.7 | 1-([1-Benzyl-1*H*-1,2,3-triazol-4-yl]methyl)-2-(4-chlorophenyl)-1*H*-indole-3-carbaldehyde (5g)

IR (KBr): 3,078 (w), 2,961 (m), 2,387 (m), 1,655 (s), 1,536 (m), 1,461 (m), 1,410 (w) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 5.43 (s, 2H, CH_2), 5.55 (s, 2H, CH_2), 7.23–7.25 (m, 2H, Ar-H), 7.25–7.38 (m, 5H, Ar-H), 7.66 (d, 2H, J = 8.1 Hz, Ar-H), 7.71–7.74 (m, 1H, Ar-H), 7.77 (d, 2H, J = 8.4 Hz, Ar-H), 8.08 (s, 1H, C-H), 8.23–8.26 (m, 1H, Ar-H), 9.62 (s, 1H, CHO). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 53.2, 112.0, 115.7, 121.4, 123.6, 124.1, 124.4, 125.1, 127.3, 128.5, 129.1, 129.2, 133.3, 135.5, 136.3, 136.8, 142.9150.1, 185.8; MS (*m*/*z*): 426 $(M)^+$; Anal.calcd for $C_{25}H_{19}CLN_4O$: C, 70.34; H, 4.49; N, 13.12%; Found: C, 70.51; H, 4.58; N, 13.27%.

3.4.8 | 1-((1-[4-Chlorobenzyl]-1*H*-1,2,3-triazol-4-yl)methyl)-2-(4-chlorophenyl)-1*H*-indole-3-carbaldehyde (5h)

IR (KBr): 3,076 (w), 2,946 (m), 2,383 (m), 1,652 (s), 1,533 (m), 1,460 (m), 1,416 (w) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 5.43 (s, 2H, CH_2), 5.55 (s, 2H, CH_2), 7.25–7.33 (m, 2H, Ar-H), 7.33–7.38 (m, 2H, Ar-H), 7.41–7.53 (m, 2H, Ar-H), 7.64–7.67 (m, 2H, Ar-H), 7.71–7.74 (m, 1H, Ar-H), 7.75–7.78 (m, 2H, Ar-H), 8.06 (s, 1H, C-H), 8.22–8.25 (m, 1H, Ar-H), 9.62 (s, 1H, CHO). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 52.4, 112.0, 115.7, 121.4, 123.5, 124.1, 124.4, 125.1, 127.3, 129.2, 130.2, 130.7, 133.3, 135.3, 135.5, 136.8, 143.0, 150.1, 185.8; MS (*m*/*z*): 460 $(M)^+$; Anal. calcd for $C_{25}H_{18}Cl_2N_4O$: C, 65.09; H, 3.93; N, 12.14%; Found: C, 65.26; H, 3.85; N, 12.29%.

3.4.9 | 1-([1-Butyl-1*H*-1,2,3-triazol-4-yl]methyl)-2-(4-chlorophenyl)-1*H*-indole-3-carbaldehyde (5i)

IR (KBr): 3,073 (w), 1,939 (m), 2,375 (m), 1,657 (s), 1,532 (m), 1,455 (m), 1,428 (w) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 0.86 (t, 3H, J = 7.2 Hz, ch_3), 1.11–1.23 (m, 2H, CH_2), 1.67–1.77 (m, 2H, CH_2), 4.29 (t, 2H, J = 6.9 Hz, CH_2), 5.41 (s, 2H, CH_2), 7.32–7.38 (m, 2H, Ar-H), 7.68–7.72 (m, 2H, Ar-H), 7.72–7.75 (m, 1H, Ar-H), 7.78–7.82 (m, 2H, Ar-H), 8.02 (s, 1H, C-H), 8.22–8.27 (m, 1H, Ar-H), 9.62 (s, 1H, CHO). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 13.7, 19.4, 32.0, 49.5, 112.0, 115.6, 121.4, 121.5, 123.5, 123.8, 124.4, 125.1, 127.3, 129.2, 129.4, 133.1, 133.3, 135.5, 136.8, 142.5, 150.1, 185.8; MS (*m*/*z*): 392 $(M)^+$; Anal. calcd for $C_{22}H_{21}ClN_4O$: C, 67.26; H, 5.39; N, 14.26%; found: C, 67.07; H, 5.29; N, 14.42%.

3.4.10 | 1-([1-Benzyl-1*H*-1,2,3-triazol-4-yl]methyl)-2-(*p*-tolyl)-1*H*-indole-3-carbaldehyde (5j)

IR (KBr): 3,079 (w), 2,937 (m), 2,380 (m), 1,653 (s), 1,531 (m), 1,469 (m), 1,427 (w) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 2.43 (s, 3H, CH_3), 5.41 (s, 2H, CH_2), 5.54 (s,

2H, CH_2), 7.23–7.41 (m, 9H, Ar-H), 7.60–7.69 (m, 3H, Ar-H), 8.03 (s, 1H, C-H), 8.23–8.25 (m, 1H, Ar-H), 9.62 (s, 1H, CHO). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 21.4, 53.2, 111.9, 115.4, 121.4, 123.4, 124.0, 124.2, 125.2, 125.4, 128.2, 128.5, 128.9, 129.1, 129.7, 131.4, 136.4, 136.7, 140.2, 143.1, 151.9, 185.9; MS (*m/z*): 406 $(M)^+$; Anal. calcd for $C_{26}H_{22}N_4O$: C, 76.83; H, 5.46; N, 13.78%; Found: C, 76.65; H, 5.55; N, 13.94%.

3.4.11 | 1-((1-[4-Chlorobenzyl]-1*H*-1,2,3-triazol-4-yl)methyl)-2-(*p*-tolyl)-1*H*-indole-3-carbaldehyde (5k)

IR (KBr): 3,081 (w), 2,940 (m), 2,388 (m), 1,655 (s), 1,540 (m), 1,450 (m), 1,414 (w) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.44 (s, 3H, CH_3), 5.41 (s, 2H, CH_2), 5.55 (s, 2H, CH_2), 7.25–7.29 (m, 2H, Ar-H), 7.31–7.36 (m, 2H, Ar-H), 7.39–7.43 (m, 2H, Ar-H), 7.46–7.48 (m, 2H, Ar-H), 7.60 (d, 2H, J = 7.8 Hz, Ar-H), 7.67–7.70 (m, 1H, Ar-H), 8.00 (s, 1H, C-H), 8.21–8.24 (m, 1H, Ar-H), 9.61 (s, 1H, CHO). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 21.4, 52.4, 111.9, 115.4, 121.3, 123.4, 124.0, 124.2, 125.2, 125.4, 125.1, 129.7, 130.2, 131.3, 133.3, 135.3, 136.7, 140.2, 143.1, 151.9, 185.9; MS (*m/z*): 442 (26), 440 $(M)^+$; Anal. calcd for $C_{26}H_{21}ClN_4O$: C, 70.82; H, 4.80; N, 12.71%; found: C, 70.99; H, 4.89; N, 12.86%.

3.4.12 | 1-([1-benzyl-1*H*-1,2,3-triazol-4-yl]methyl)-2-(4-methoxyphenyl)-1*H*-indole-3-carbaldehyde (5l)

IR (KBr): 3,077 (w), 1,953 (m), 2,377 (m), 1,645 (s), 1,530 (m), 1,451 (m), 1,417 (w) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.87 (s, 3H, OCH_3), 5.42 (s, 2H, CH_2), 5.56 (s, 2H, CH_2), 7.15 (d, 3H, J = 8.4 Hz, Ar-H), 7.24–7.26 (m, 2H, Ar-H), 7.31–7.37 (m, 5H, Ar-H), 7.68 (d, 3H, J = 8.1 Hz, Ar-H), 8.06 (s, 1H, C-H), 8.23–8.26 (m, 1H, Ar-H), 9.64 (s, 1H, CHO). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 53.2, 55.8, 111.9, 114.6, 115.4, 120.2, 121.3, 123.4, 124.1, 125.3, 128.2, 128.5, 129.1, 132.9, 136.4, 136.7, 143.1, 151.9, 160.9, 186.0; MS (*m/z*): 422 $(M)^+$; Anal. calcd for $C_{26}H_{22}N_4O_2$: C, 73.92; H, 5.25; N, 13.26%; Found: C, 73.74; H, 5.33; N, 13.41%.

3.4.13 | 1-((1-[4-Chlorobenzyl]-1*H*-1,2,3-triazol-4-yl)methyl)-2-(4-methoxyphenyl)-1*H*-indole-3-carbaldehyde (5m)

IR (KBr): 3,083 (w), 2,936 (m), 2,369 (m), 1,654 (s), 1,533 (m), 1,456 (m), 1,428 (w) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.87 (s, 3H, OCH_3), 5.42 (s, 2H, CH_2), 5.56 (s, 2H, CH_2), 7.65 (d, 2H, J = 8.7 Hz, Ar-H), 7.26–7.29 (m, 2H, Ar-H), 7.31–7.33 (m, 2H, Ar-H), 7.43–7.48 (m, 3H, Ar-H), 7.67 (d, 3H, J = 8.7 Hz, Ar-H), 8.05 (s, 1H, C-H), 8.21–8.24 (m, 1H, Ar-H), 9.62 (s, 1H, CHO). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 52.4, 55.8, 111.8, 114.6, 115.4, 120.2, 121.3, 123.4, 124.1, 124.1, 125.2, 129.1, 130.2, 130.7, 132.9, 133.3, 135.3, 136.7, 143.2, 151.8, 160.9, 186.0; MS (*m/z*): 456 $(M)^+$; Anal. calcd for $C_{26}H_{21}CLN_4O_2$: C, 68.34; H, 4.63; N, 12.26%; Found: C, 68.52; H, 4.55; N, 12.42%.

3.4.14 | 1-([1-Butyl-1*H*-1,2,3-triazol-4-yl]methyl)-2-(4-methoxyphenyl)-1*H*-indole-3-carbaldehyde (5n)

IR (KBr): 3,077 (w), 2,940 (m), 2,376 (m), 1,656 (s), 1,530 (m), 1,440 (m), 1,426 (w) cm^{-1};^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.86 (t, 3H, J = 7.2 Hz, CH_3), 1.11–1.24 (m, 2H, CH_2), 1.68–1.77 (m, 2H, CH_2), 3.88 (s, 3H, OCH_3), 4.29 (t, 2H, J = 7.2 Hz, CH_2), 5.40 (s, 2H, CH_2), 7.17–7.24 (m, 2H, Ar-H), 7.28–7.35 (m, 2H, Ar-H), 7.62–7.67 (m, 1H, Ar-H), 7.69–7.74 (m, 2H, Ar-H), 8.01 (s, 1H, C-H), 8.21–8.26 (m, 1H, Ar-H), 9.65 (s, 1H, CHO). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 13.7, 19.4, 32.0, 49.5, 55.8, 111.9, 114.6, 115.3, 120.3, 121.3, 123.7, 124.1, 125.3, 133.0, 136.7, 142.7, 151.9, 160.9, 186.0; MS (*m/z*): 388 $(M)^+$; Anal.calcd for $C_{23}H_{24}N_4O_2$: C, 71.11; H, 6.23; N, 14.42%; Found: C, 71.29; H, 6.30; N, 14.26%.

4 | CONCLUSIONS

We have developed a highly efficient, inexpensive, green, and one-pot protocol for the synthesis of 1,2,3-triazole-linked indoles using MW as a new solvent. This method not only offers significant improvements in the reaction rates and yields but also avoids (i) the production of harmful wastes, (ii) the use of a large amount of organic solvents or catalysts, and (iii) tedious post-treatment. In addition, the promising points for the presented methodology are its efficiency, generality, short reaction time, mild reaction conditions, easy work-up, excellent yield, low copper catalyst loading, and finally, agreement with green chemistry protocols, making it a useful and attractive process for the synthesis of 1,2,3-triazole-linked indoles. Most importantly, this protocol does not require any additional reducing agent or ligand.

ACKNOWLEDGMENT

This work was supported by the Research Council of the Shahrood University of Technology.

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How to cite this article: Bakherad M, Keivanloo A, Bakherad Z, Toozandejani Z, Mahdavi M. Ligand-free, copper-catalyzed, one-pot, three-component synthesis of novel 1,2,3-triazole-linked indoles in magnetized water. *J Chin Chem Soc*. 2019;1–9. https://doi.org/10.1002/jccs.201800287