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ORIGINAL PAPER

Synthesis of 4,5-disubstituted-1*H*-1,2,3-triazoles

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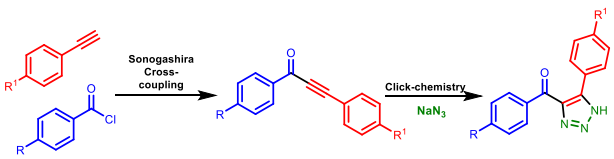
Abstract
Two-step procedure, a palladium catalyzed Sonogashira cross-coupling reaction of aroyl chlorides with aryl acetylenes, and 1,3-dipolar cycloaddition of the 1,3-diarylprop-2-yn-1-ones with sodium azide under catalyst free conditions achieved the synthesis of aryl(4-aryl-1*H*-1,2,3-triazol-5-yl)methanones in moderate-to-good chemical yields (30–90%). The procedures allowed the synthesis of 4,5-disubstituted-1*H*-1,2,3-triazol scaffolds containing electron-neutral, -withdrawing, or -donating groups.

Graphic abstract



Keywords Alkyne · Cycloaddition · NMR spectroscopy · Heterocycles

Introduction

Heterocyclic compounds, more precisely five-membered rings containing heteroatoms of nitrogen, such as triazole, pyrazole, oxazole, imidazole, and thiazole, are structural motifs that often play an important role in biochemical process. Among them 1,2,3-triazole based heterocycles have been well exploited for the generation of many bioactive molecules as well as pharmaceuticals [1–3]. The 1,2,3-triazole moiety does not exist in nature; still, it has gained paramount interest, because this ring is a remarkable pharmacophore. The 1,2,3-triazole heterocycles are well-known privileged medicinal scaffolds because of their significant biological activities such as antifungal [4], antibacterial [5], anti-inflammatory [6], anti-HIV [7], and anti-cancer [8–10] properties. Significant efforts have been made in the last few years towards the design, synthesis, and evaluation of various 1,2,3-triazole based molecules as anti-cancer agents [11]. Among diverse C-4 substituents at 1,2,3-triazole ring, the *p*-substituted phenyl led to increased antiproliferative activity compared to aliphatic branched or unbranched C-4 side chains. Moreover, halophenyl-substituted 1,2,3-triazolyl in bioactive hybrids contributed to strong cytostatic activity in hepatocellular carcinoma cells [12]. The 1,2,3-triazole moieties disubstituted at C-4 and C-5 demonstrated excellent anti-cancer effect against a panel of 60 human cancer [13] and antifungal activities [14]. Some example of the most active compounds is represented in Fig. 1.

The 1,2,3-triazole derivatives are also key synthetic intermediates in many industrial applications such as supramolecular chemistry [15], polymers [16], pigments [17], metal chelators [18], and other areas [19–21]. Triazoles can be used as linker and show bioisosteric effects on peptide linkage, aromatic ring, and double bonds [22]. Some unique

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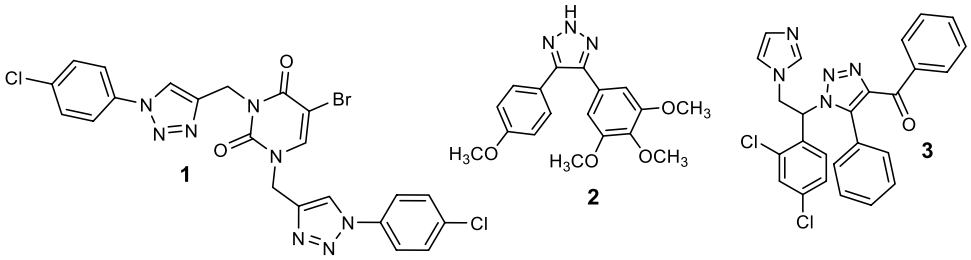


Fig. 1 Example of di- and tri-substituted triazoles with therapeutic effects

features like hydrogen bond formation, dipole–dipole, and π-stacking interactions of triazole compounds have increased their importance in medicinal chemistry as they improved their solubility and their ability to bind with the biological targets [3, 23, 24].

Due to 1,2,3-triazoles versatilities and biological potential above-mentioned, synthetic strategies toward their synthesis had been a subject of intense research. The most common reaction consists in 1,3-dipolar cycloaddition also known as Huisgen cycloaddition, between azides and terminal alkynes [25]. The other common approach is a copper(I)-catalyzed version of azide-alkyne cycloaddition reaction (CuAAC), resulted in the production of many 1,4-disubstituted 1,2,3-triazoles in very high yields [26]. Despite recent advances in synthetic methods toward N-unsubstituted 4,5-disubstituted-1*H*-1,2,3-triazoles [27–32], protocols affording these compounds, especially if the substituents are aromatic or include aromatic rings, are still in demand. Our contribution to the field has been in design, synthesis, and reactivity studies of different substituents (electron-neutral, -withdrawing, or -donating groups) on the aryl rings in the 1,3-dipolar cycloaddition reaction of internal alkynes with sodium azide. A procedure that allows the synthesis of nitro derivatives and that is less expensive was achieved.

Results and discussion

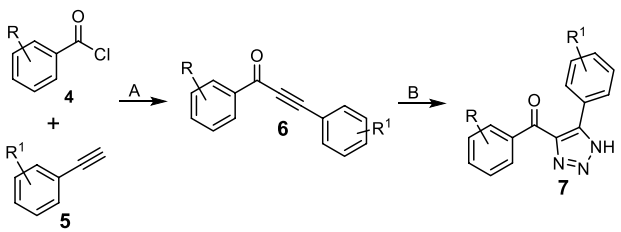
Bearing in mind the above-mentioned facts we envisage the use of Sonogashira cross-coupling reaction to obtain 1,3-diarylprop-2-yn-1-ones **6** [Scheme 1, step (A)], followed by their 1,3-dipolar cycloaddition with sodium azide giving aryl(5-aryl-1*H*-1,2,3-triazol-4-yl)methanones **7** [Scheme 1, step (B)].

The original Sonogashira reaction requires a copper(I) salt as a co-catalyst in combination with the palladium source. Although essential for the effectiveness, the usage of copper as a co-catalyst in Pd/Cu catalyzed Sonogashira reaction entails several drawbacks including the application of environmentally unfriendly reagents, the formation of undesirable alkyne homocoupling side products, and the necessity of strict oxygen exclusion in the reaction mixture [33]. For these reasons, Cu-free Sonogashira reaction has become an aim of great interest to chemists in the last years [34, 35]. The first step of our transformation involved the Sonogashira reaction in homogenous phase [$(PPh_3)_2PdCl_2$/CuI] and/or heterogenous phase (Pd/C), using a terminal alkyne derivative **5a**–**5c** and aroyl chlorides **4a**–**4c** with different substituents (electron-neutral, -withdrawing, or -donating groups) to obtain the 1,3-diarylprop-2-yn-1-ones **6a**–**6i**) [36–38] (Scheme 2). The 1,3-diarylprop-2-yn-1-one **6a** was obtained in 80% yield by homogenous phase (procedure I) (Table 1, entry 1), while, by procedure II, the yield was half (41%). Having in mind these results, the synthesis of compounds **6b**–**6i** was done using the conditions established in procedure I.

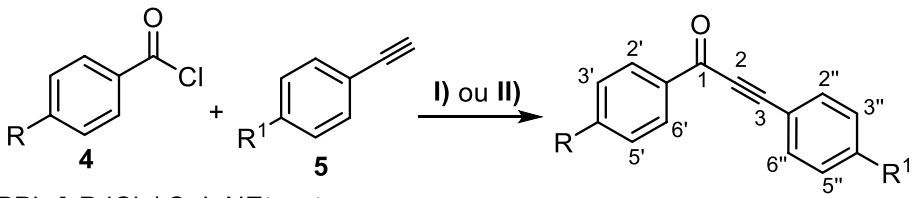
The derivatives **6a**, **6b**, **6d**, and **6e** (Table 1, entries 1, 2, 4, and 5) were obtained in good yields using the procedure I. For the synthesis of compounds having electron-withdrawing group (NO_2) **6c**, **6f**–**6i,** it was necessary some modification in the reaction conditions. In the cases of derivatives **6f** and **6h,** it was only necessary to perform the reaction at 45 °C (Table 1, entries 6 and 9). The synthesis of compound **6i** was done under heterogeneous and homogeneous phase at room temperature and at 45 °C; however, the obtained yields (< 20%) were always lower than the yields obtained under homogeneous phase at room temperature (Table 1, entry 10). For derivatives **6c** and **6g,** the best results were obtained using procedure II (Table 1, entry 3 and entry 8).

Alonso et al. [39] demonstrated that using different sources of palladium as pre-catalyst for the copper-free acylation of terminal alkynes with different carboxylic acid chlorides in toluene in the presence of three equivalents of triethylamine (TEA) as base, giving the corresponding ynones in good yields. They also showed that the coupling reaction of aroyl chlorides such as 4-chlorobenzoyl and

Scheme 1



Scheme 2



I) $[PPh_3]_2PdCl_2$/ CuI; NEt_3, r.t.
II) Pd/C; Et_3N, dry toluene, 110 °C

6a) R= R^1= H
6b) R= H; R^1= OCH_3
6c) R= H; R^1= NO_2
6d) R= OCH_3; R^1= H
6e) R= R^1= OCH_3
6f) R= OCH_3; R^1= NO_2
6g) R= NO_2; R^1= H
6h) R= NO_2; R^1= OCH_3
6i) R= R^1= NO_2

Table 1 Reaction time and yields in the synthesis of 1,3-diarylprop-2-yn-1-ones **6a–6i**

Entry	Compounds	Substituents R	Substituents R^1	Yield/%	Time/h
1	**6a**	H	H	80	3[a]
2	**6b**	H	OCH_3	90	19[a]
3	**6c**	H	NO_2	82	3[b]
4	**6d**	OCH_3	H	60	22[a]
5	**6e**	OCH_3	OCH_3	86	18[a]
6	**6f**	OCH_3	NO_2	80	3[c]
7	**6g**	NO_2	H	20	3[a]
8	**6g**	NO_2	H	50	3[b]
9	**6h**	NO_2	OCH_3	70	8.5[c]
10	**6i**	NO_2	NO_2	40	2.6[a]

[a]Procedure I

[b]Procedure II

[c]Procedure I at 45 °C

4-nitrobenzoyl chlorides with phenylacetylene affording good yields at 110 °C. Chen and Li [40] also reported that toluene could be used as solvent of 4-nitrobenzoyl chloride leading to increase of Sonogashira coupling yield using $(PPh_3)_2PdCl_2$/CuI. Other authors also studied different sources of palladium and conclude that they can influence the yield of nitro derivatives [41]. Therefore, we believe that the reaction conditions, solvent and temperature, and catalyst system are responsible for the best yields obtained in case of derivatives **6c** and **6g**.

A careful analysis of Table 1 shows that the substituents have a great impact in the reaction conditions and time, for instance the presence of methoxy groups enlarge the reaction time (Table 1, entries 2, 4, and 5), whereas the presence of nitro groups involves mostly the modification of the reaction conditions (Table 1, entries 3, 6, and 8). Moreover, nitro groups tend to lower the yields and, in some cases (Table 1, entry 10), all the attempts to obtain the compounds with better yields failed. It can be inferred that the presence of this withdrawing group in both reagents diminished their reactivity towards the cross-coupling reaction. The 1,3-diarylprop-2-yn-1-ones **6a–6i** characterization by ^{1}H NMR spectra only reveals the signals corresponding to the aromatic protons. On the other hand, the ^{13}C NMR spectra signals are much more elucidative of the compound structure, and at ca. $\delta = 87$ and 93 ppm, the signal characteristics of the triple bond's carbons were assigned to C-2 and C-3, and at ca. 178 ppm, the signal due to the carbonyl carbon.

The next reaction step involves a 1,3-dipolar cycloaddition reaction of the above-mentioned 1,3-diarylprop-2-yn-1-ones **6a–6i** with sodium azide in DMF (Scheme 3). This 1,3-dipolar cycloaddition is one of the most-described methodologies towards the synthesis of 1,2,3-triazoles derivatives [42–46], and nonetheless, we would like to emphasize that, in this case, the products are obtained without the use of any catalyst, which naturally makes the procedure more economical.

First, we tried the synthesis of phenyl(5-phenyl-1*H*-1,2,3-triazol-4-yl)methanone (**7a**) using the conventional heating, and after 17 h of reaction, it was observed a complete disappearance of **6a** by thin-layer chromatography (TLC) and the formation of **7a**. The ^{1}H NMR spectrum confirms the formation of the desired product **7a** in very good yield (78%; Table 2, entry 1).

The same reaction was tried using the microwave irradiation (120 °C for 30 min, at 500 W) as heating source, and again, the desired product **7a** was obtained, but in lower yield (64%). These results led the use of conventional heating to obtain the other derivatives **7b–7i** (Table 2). Under the conventional heating, some nitro derivatives **7c**, **7g**, and **7i** yielded the expected products in lower yields (Table 2, entries 3, 9, 11, and 12), and consequently, the microwave irradiation was tried as an alternative.

Microwave technology has already been applied in many fields and its effect on accelerating chemical reactions was largely studied [47, 48]. The advantages is that the use of

Scheme 3

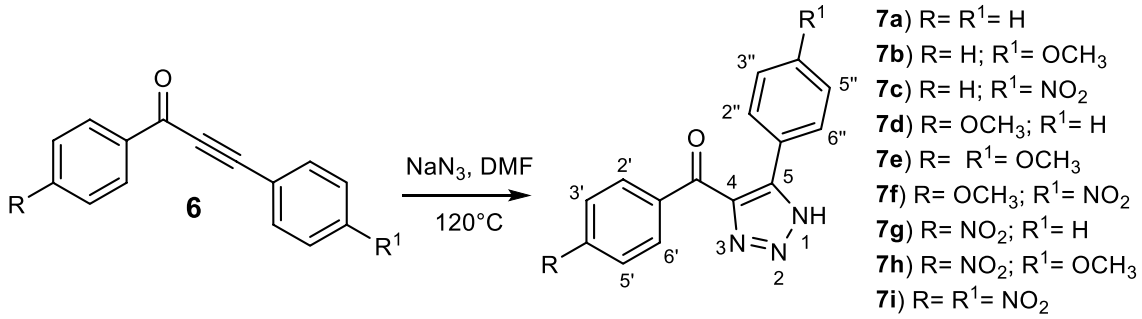


Table 2 Reaction time and yields in the synthesize of 1,2,3-triazole derivatives **7a**–**7i**

Entry	Compounds	Substituents R	Substituents R^1	Yield/%	Time/h
1	**7a**	H	H	78	17
2	**7b**	H	OCH_3	88	22
3	**7c**	H	NO_2	44	21
4	**7c**	H	NO_2	64	0.5[a]
5	**7d**	OCH_3	H	68	15
6	**7e**	OCH_3	OCH_3	90	16
7	**7f**	OCH_3	NO_2	85	16
8	**7g**	NO_2	H	60	5
9	**7g**	NO_2	H	30	16
10	**7g**	NO_2	H	85	0.5[a]
11	**7h**	NO_2	OCH_3	33	17
12	**7h**	NO_2	OCH_3	40	0.75[a]
13	**7i**	NO_2	NO_2	30	25
14	**7i**	NO_2	NO_2	45	1[a]

[a]The product was obtained using microwave irradiation (500 W, 120 °C)

MW in synthetic process such as clean-and-green, environment friendly chemistry, high yield, reduced reaction time, and product selectivity leads the application of this method in 1,3-dipolar cycloaddition [43, 44]. Here in, microwave irradiation was performed to shorten reaction time and increased the reaction yields of the products obtained in low yield under conventional heating.

As can be seen in Table 2 (entries 4, 10, 12, and 14), the change of the heating source from conventional to microwave irradiation was a success in the case of derivatives **7c**, **7g**–**7i**. Under MW irradiation, the heating proceeds directly inside mixture, the rapid orientation, and reorientation of the molecules, which contribute for the stabilization/activation of the benzenic ring and subsequent favor the interaction of the internal alkyne with the azide.

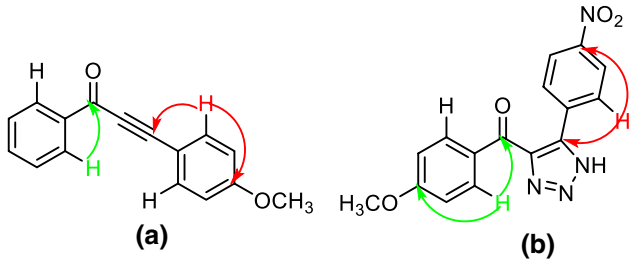


Fig. 2 The most important HMBC signals

The ^{1}H NMR spectra of aryl(5-aryl-1*H*-1,2,3-triazol-4-yl)-methanones **7a**–**7i**[1] only reveal the aromatic protons signals. On the other hand, the ^{13}C NMR spectra signals reveal the presence of signals at ca $\delta = 159$ and 148 ppm, corresponding to carbon C-4 and C-5 resonances of the 1,2,3-triazole ring. The signal at ca 188 ppm confirms the presence of the carbonyl group.

The HMBC correlations observed in the spectrum of 1,3-diarylprop-2-yn-1-one **6b** (Fig. 2a) and aryl(5-aryl-1*H*-1,2,3-triazol-4-yl)methanone **7f** (Fig. 2b) not only confirmed the depicted structures but also allowed the assignment of all protons and carbons resonances. The main correlations in the case of 1,3-diarylprop-2-yn-1-ones are the correlation between the protons H-2′-6′ and carbon C-1 and between protons H-2″, 6″ and carbons C-3 and C-4″ (Fig. 2a). In the case of aryl(5-aryl-1*H*-1,2,3-triazol-4-yl)methanones, the main correlations are between the protons H-2′-6′ and carbons C-1 and C-4′ and between the protons H-2″, 6″ and carbons C-5 and C-4″ (Fig. 2b).

[1] Due to the prototropy of 1,2,3-triazoles, the name of structures **7a**–**7i** can be aryl(5-aryl-1*H*-1,2,3-triazol-4-yl)methanones or aryl(4-aryl-1*H*-1,2,3-triazol-5-yl)methanones. Herein, we used the former one to be coherent with the number system presented in Table 2.

Conclusion

In summary, a simply and efficient protocol for the synthesis of 1,2,3-triazoles with unusually 4,5-disubstituted pattern was described. The protocol herein discussed allowed the synthesis of several derivatives in overall yields above 50%, starting from commercial and readily available reagents. 1,2,3-Triazoles with electron-neutral, -withdrawing, and -donating groups were prepared and can quite useful for the construction of a small focused library. Although the presence of nitro groups lowered the overall yield, it should be emphasized that the use of microwave irradiation as a source of energy allowed the synthesis of the desired products in moderate–good yields (41–85%).

Experimental

All reagents were commercially available and used without further purification. Column chromatography was performed on silica gel 60 Merck 0.032–0.063 mm and 0.063–0.200 mm and preparative thin-layer chromatography (TLC) on silica gel 60 GF254 from Merck. The solvents were commercially available first grade and distillate. Melting points were obtained using a Büchi melting point B-540. Microwave equipment was Ethos MicroSYNTH Labstation (Milestone Inc) using an optic fiber sensor to control the temperature. The NMR spectra were recorded using Avance 300 and 500 spectrometers operating at 300.13 MHz and 500.13 MHz for ^{1}H and 75.47 MHz and 125.76 MHz for ^{13}C, respectively, with tetramethylsilane (TMS) as the internal standard. The chemical shifts are reported as δ values (ppm) and coupling constants (J) in Hz. High-resolution mass spectra were performed at the LTQ Orbitrap XLTM Hybrid Ion Trap-Orbitrap Mass Spectrometer.

Synthesis of 1,3-diarylprop-2-yl-1-ones 6a–6i

Procedure I

8.9 mg Bis[triphenylphosphine]palladium(II) dichloride (2 mol%) and 1.2 mg copper(I) iodide (1 mol%) were added to a mixture of the appropriate alkyne **5a**–**5c** (0.7 mmol) and aroyl chloride **4a**–**4c** (0.84 mmol) in triethylamine (35.9 mmol). The mixture was stirred at room temperature under nitrogen atmosphere. At the end (see Table 1 for reaction time), the mixture was evicted over ice/water (15 cm^3/20 g). Diluted HCl (20%) was added to the reaction mixture and the solid filtrated. The solid was taken in 10 cm^3 ethyl acetate and the water residue was removed over Na_2SO_4. The purification was done by column chromatography using a (9:1) mixture of light petroleum and dichloromethane as eluent.

Procedure II

A mixture of 0.94 mg alkyne **2c** (6.37 mmol), 1.8 cm^3 triethylamine (12.74 mmol), and Pd/C (1 mol %) in 2 cm^3 dry toluene was stirred at room temperature under a nitrogen atmosphere for 30 min. The corresponding acyl chloride **4a** (0.89 cm^3, 7.64 mmol) in dry toluene was added and the solution was heated at 110 °C. The excess of catalyst was removed by filtration and the solution was washed with water (3 × 5 cm^3). The solid was taken in 10 cm^3 ethyl acetate and the water residue was removed over Na_2SO_4. The purification was done by column chromatography using light petroleum as eluent, and then, a 9:1 mixture of light petroleum and ethyl acetate was obtained the 3-(4-nitrophenyl)-1-phenylprop-2-yn-1-one **6c**.

1,3-Diphenylprop-2-yn-1-one (6a) [39, 49, 51, 52] White solid; yield: 115.4 mg (80%); m.p.: 48–51 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 8.23 (dd, J = 1.5, 8.2 Hz, 2H, H-2′, 6′), 7.70 (dd, J = 1.5, 8.2 Hz, 2H, H-2″, 6″), 7.63 (br dd, J = 7.4, 8.2 Hz, 1H, H-4′), 7.54 (brd, J = 7.2 Hz, 2H, H-3′, 5′), 7.48 (m, 1H, H-4″), 7.44 (br d, J = 7.2 Hz, 2H, H-3″, 5″) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 178.0 (C-1), 136.9 (C-1′), 134.1 (C-4′), 133.1 (C-2″, 6″), 130.8 (C-4″), 129.6 (C-2′, 6′), 128.7 (C-3″, 5″), 128.6 (C-3′, 5′), 120.1 (C-1″), 93.1 (C-3), 86.9 (C-2) ppm; MS (ESI$^+$): *m/z* (%) = 207 ([M+H]$^+$, 75), 229 ([M+Na]$^+$, 90).

3-(4-Methoxyphenyl)-1-phenylprop-2-yn-1-one (6b) [50–52] Brown solid; yield: 148.8 mg (90%); m.p.: 70–72 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 8.23 (brd, J = 8.0 Hz, 2H, H-2′, 6′), 7.65 (dd, J = 2.0, 9.0 Hz, 2H, H-2″, 6″), 7.60–7.64 (m, 1H, H-4′), 7.53 (brd, J = 8.0 Hz, 2H, H-3′, 5′), 6.95 (dd, J = 2.0, 9.0 Hz, 2H, H-3″, 5″), 3.87 (s, 3H, 4″-OCH_3) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 178.1 (C-1), 161.7 (C-4″), 137.0 (C-1′), 135.1 (C-2″, 6″), 133.9 (C-4′), 129.5 (C-2′, 6′), 128.5 (C-3′, 5′), 114.4 (C-3″, 5″), 111.9 (C-1″), 94.3 (C-3), 86.9 (C-2), 55.4 (4″-OCH_3) ppm; MS (ESI$^+$): *m/z* (%) = 237 ([M+H]$^+$, 87), 259 ([M+Na]$^+$, 45); FT-MS (ESI): *m/z* calcd for $C_{16}H_{13}O_2$ ([M+H]$^+$) 237.0916, found 237.0900.

3-(4-Nitrophenyl)-1-phenylprop-2-yn-1-one (6c) [39] Brown solid; yield: 131.2 mg (82%); m.p.: 144–145 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 8.30 (dd, J = 2.1, 9.0 Hz, 2H, H-3″, 5″), 8.21 (dd, J = 1.2, 8.3 Hz, 2H, H-3′, 5′), 7.85 (dd, J = 2.1, 9.0 Hz, 2H, H-2″, 6″), 7.65–7.71 (m, 1H, H-4′), 7.55 (brd, J = 8.3 Hz, 2H, H-2′, 6′) ppm; ^{13}C NMR (75.47 MHz,

$CDCl_3$): δ = 177.7 (C-1), 148.6 (C-4″), 136.3 (C-1″), 134.7 (C-4′), 133.7 (C-2′, 6′), 129.7 (C-3″, 5″), 128.8 (C-2″, 6″), 126.8 (C-1′), 123.8 (C-3′, 5′), 95.7 (C-3), 89.2 (C-2) ppm; MS (ESI^+): *m/z* (%) = 252 ($[M+H]^+$, 22); FT-MS (ESI): *m/z* calcd for $C_{15}H_{10}NO_3$ ($[M+H]^+$) 252.0655, found 252.0642.

1-(4-Methoxyphenyl)-3-phenylprop-2-yn-1-one (6d) [39, 52] Brown solid; yield: 99.2 mg (60%); m.p.: 99–100 °C; ^1H NMR (300.13 MHz, $CDCl_3$): δ = 8.21 (dd, *J* = 2.3, 9.3 Hz, 2H, H-2′, 6′), 7.68 (dd, *J* = 1.5, 8.0 Hz, 2H, H-2″, 6″), 7.41–7.47 (m, 3H, H-3″, 4″, 5″), 7.00 (dd, *J* = 2.4, 9.3 Hz, 2H, H-3′, 5′), 3.91 (s, 3H, 4′-OCH_3) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 176.7 (C-1), 164.5 (C-4′), 132.9 (C-2″, 6″), 132.0 (C-2′, 6′), 130.6 (C-4″), 130.3 (C-1′), 128.6 (C-3″, 5″), 120.3 (C-1″), 113.9 (C-3′, 5′), 92.3 (C-3), 86.9 (C-2), 55.6 (4′-O*C*H_3) ppm; MS (ESI^+): *m/z* (%) = 237 ($[M+H]^+$, 87), 259 ($[M+Na]^+$, 45).

1,3-Bis(4-methoxyphenyl)prop-2-yn-1-one (6e) [51] Yellow solid; yield: 160.3 mg (86%); m.p.: 79–80 °C; ^1H NMR (300.13 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 8.9 Hz, 2H, H-2′, 6′), 7.64 (d, *J* = 8.9 Hz, 2H, H-2″, 6″), 6.99 (d, *J* = 8.9 Hz, 2H, H-3′, 5′), 6.94 (d, *J* = 8.9 Hz, 2H, H-3″, 5″), 3.91 (s, 3H, 4″-OCH_3), 3.87 (s, 3H, 4′-OCH_3) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 176.8 (C-1), 164.3 (C-4′), 161.5 (C-4″), 135.0 (C-2″, 6″), 131.8 (C-2′, 6′), 130.4 (C-1″), 114.4 (C-3′, 5′), 113.8 (C-3″, 5″), 112.1 (C-1′), 93.4 (C-3), 86.8 (C-2), 55.6 (4′-O*C*H_3), 55.4 (4″-O*C*H_3) ppm; MS (ESI^+): *m/z* (%) = 267 ($[M+H]^+$, 80), 289 ($[M+Na]^+$, 100).

1-(4-Methoxyphenyl)-3-(4-nitrophenyl)prop-2-yn-1-one (6f, $C_{16}H_{12}NO_4$) Yellow solid; yield: 157.5 mg (80%); m.p.: 158–160 °C; ^1H NMR (300.13 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 9.0 Hz, 2H, H-3″, 5″), 8.18 (d, *J* = 9.0 Hz, 2H, H-2′, 6′), 7.83 (d, *J* = 9.0 Hz, 2H, H-2″, 6″), 7.01 (d, *J* = 9.0 Hz, 2H, H-3′, 5′), 3.92 (s, 3H, 4′-OCH_3) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 174.5 (C-1), 165.0 (C-4′), 148.3 (C-4″), 133.5 (C-2″, 6″), 132.1 (C-2′, 6′), 129.6 (C-1′), 127.0 (C-1″), 123.8 (C-3″, 5″), 114.1 (C-3′, 5′), 95.0 (C-3), 88.3 (C-2) ppm; MS (ESI^+): *m/z* (%) = 282 ($[M+H]^+$, 100), 304 ($[M+Na]^+$, 15); FT-MS (ESI): *m/z* calcd for $C_{16}H_{12}NO_4$ ($[M+H]^+$) 282.0761, found 282.0746.

1-(4-Nitrophenyl)-3-phenylprop-2-yn-1-one (6g) [39, 52] Brown solid; yield: 87.9 mg (50%); m.p.: 162–163 °C; ^1H NMR (300.13 MHz, $CDCl_3$): δ = 8.39 (s, 4H, H-2′, 3′, 5′, 6′), 7.72 (dd, *J* = 1.6, 7.0 Hz, 2H, H-2″, 6″), 7.52 (dd, *J* = 1.6, 7.4 Hz, 1H, H-4″), 7.48 (dd, *J* = 1.6, 7.0 Hz, 2H, H-3″, 5″) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 175.9 (C-1), 150.9 (C-4′), 141.0 (C-1′), 133.3 (C-2″, 6″), 131.4 (C-4″), 130.4 (C-2′, 6′), 128.9 (C-3″, 5″), 123.9 (C-3′, 5′), 119.4 (C-1″), 95.4 (C-3), 86.5 (C-2) ppm; MS (ESI^+): *m/z* (%) = 281 ($[M]^+$, 100), 282 ($[M+H]^+$, 80); FT-MS (ESI): *m/z* calcd for $C_{15}H_{10}NO_3$ ($[M+H]^+$) 252.0655, found 252.0642.

3-(4-Methoxyphenyl)-1-(4-nitrophenyl)prop-2-yn-1-one (6h, $C_{16}H_{12}NO_4$) Brown solid; yield: 137.8 mg (70%); m.p.: 141–142 °C; ^1H NMR (300.13 MHz, $CDCl_3$): δ = 8.37 (brs, 4H, H-2′, 3′, 5′, 6′), 7.68 (d, *J* = 8.9 Hz, 2H, H-2″, 6″), 6.97 (d, *J* = 8.9 Hz, 2H, H-3″, 5″), 3.86 (s, 3H, 4″-OCH_3) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 175.6 (C-1), 162.3 (C-4″), 150.8 (C-4′), 141.3 (C-1′), 135.5 (C-2″, 6″), 130.3 (C-2′, 6′), 123.8 (C-3′, 5′), 114.5 (C-3″, 5″), 111.1 (C-1″), 96.9 (C-3), 86.9 (C-2), 55.5 (4″-O*C*H_3) ppm; MS (ESI^+): *m/z* (%) = 252 ($[M+H]^+$, 35), 274 ($[M+Na]^+$, 15); FT-MS (ESI): *m/z* calcd for $C_{16}H_{12}NO_4$ ($[M+H]^+$) 282.0761, found 282.0746.

1,3-Bis(4-nitrophenyl)prop-2-yn-1-one (6i, $C_{15}H_8N_2O_5$) Brown solid; yield: 82.9 mg (40%); m.p.: 125–127 °C; ^1H NMR (300.13 MHz, $CDCl_3$): δ = 8.39 (d, *J* = 2.5 Hz, 4H, H-3′, 5′, 3″, 5″), 8.33 (dd, *J* = 2.5, 9.0 Hz, 2H, H-2′, 6′), 7.87 (dd, *J* = 2.5, 9.0 Hz, 2H, H-2″, 6″) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 175.4 (C-1), 151.1 (C-4′), 148.8 (C-4″), 140.4 (C-1′), 133.9 (C-2″, 6″), 130.5 (C-2′, 6′), 125.9 (C-1″), 124.1 (C-3″, 5″), 123.5 (C-3′,5′), 91.1 (C-3), 89.0 (C-2) ppm; MS (ESI^+): *m/z* (%) = 296 ($[M]^+$, 100).

Synthesis of aryl(5-aryl-1*H*-1,2,3-triazol-4-yl)-ketones 7a–7i

Sodium azide (0.087 mg, 1.34 mmol) was added a solution of the appropriate 1,3-diarylprop-2-yn-1-one **6a**–**6i** (0.67 mmol) in 7 cm^3 DMF. The mixture was stirred at 120 °C under nitrogen atmosphere until the consumption of the starting material. At the end, the mixture was evicted over ice/water (15 cm^3/20 g). Diluted HCl (20%) was added to the reaction mixture and the solid filtrated. The solid was taken in 10 cm^3 ethyl acetate and the water residue was removed over Na_2SO_4. In case of **7b** and **7e,** the compound was obtained by recrystallization in ethanol and the other derivatives by column chromatography using as eluent light petroleum and ethyl acetate (8:2).

Phenyl(5-phenyl-1*H*-1,2,3-triazol-4-yl)methanone (7a) [32] White solid; yield: 78%; m.p.: 94–96 °C; ^1H NMR (300.13 MHz, $CDCl_3$): δ = 8.09 (brd, *J* = 8.3 Hz, 2H, H-2′, 6′), 7.76–7.81 (m, 2H, H-3′, 5′), 7.62 (ddd, *J* = 2.0, 7.0, 8.3 Hz, 1H, H-4′), 7.49 (brd, *J* = 8.0 Hz, 2H, H-2″, 6″), 7.40–7.46 (m, 3H, H-3″, 4″, 5″) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 187.8 (C=O), 159.0 (C-4),148.0 (C-5), 137.0 (C-1′), 133.8 (C-1″), 133.5 (C-4′), 130.4 (C-2′, 6′), 129.6 (C-4″), 128.8 (C-3″, 5″), 128.6 (C-3′, 5′), 128.4 (C-2″, 6″) ppm; MS (ESI^+): *m/z* (%) = 250 ($[M+H]^+$, 13), 272 ($[M+Na]^+$, 100); FT-MS (ESI): *m/z* calcd for $C_{15}H_{12}N_3O$ ($[M+H]^+$) 250.0975, found 250.0964.

[5-(4-Methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]phenylmethanone (7b, $C_{16}H_{13}N_3O_2$) Yellow solid; yield: 164.7 mg (88%); m.p.: 258–260 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): $\delta = 8.10$ (brd, $J = 7.2$ Hz, 2H, H-2′, 6′), 7.77 (dd, $J = 2.5$, 9.3 Hz, 2H, H-2″, 6″), 7.58–7.62 (m, 1H, H-4′), 7.48 (t, $J = 7.5$ Hz, 2H, H-3′, 5′), 6.98 (dd, $J = 2.5$, 9.3 Hz, 2H, H-3″, 5″), 3.85 (s, 3H, 4″-OCH_3) ppm; ^{13}C NMR (75.45 MHz, $CDCl_3$): $\delta = 187.8$ (C=O), 160.7 (C-4″), 146.3 (C-5), 141.0 (C-4), 137.2 (C-1′), 133.3 (C-4′), 130.5 (C-2′, 6′), 130.2 (C-2″, 6″), 128.3 (C-3′, 5′), 120.2 (C-1″), 114.0 (C-3″, 5″), 55.3 (4″-OCH_3) ppm; MS (ESI$^+$): *m/z* (%) = 280 ([M+H]$^+$, 40), 302 ([M+Na]$^+$, 100); FT-MS (ESI): *m/z* calcd for $C_{16}H_{13}N_3O_2$ ([M+H]$^+$) 280.1026, found 280.1018.

[5-(4-Nitrophenyl)-1*H*-1,2,3-triazol-4-yl]phenylmethanone (7c, $C_{15}H_{11}N_4O_3$) Brown solid; yield: 126.2 mg (64%); m.p.: 198–200 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): $\delta = 8.32$ (dd, $J = 2.2$, 9.2 Hz, 2H, H-3″, 5″), 8.03–8.08 (m, 4H, H-2′, 6′, 2″, 6″), 7.71 (t, $J = 7.4$ Hz, 1H, H-4′), 7.57 (t, $J = 7.6$ Hz, 2H, H-3′, 5′) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 187.7$ (C=O), 147.5 (C-4″), 144.9 (C-5), 136.9 (C-1′), 135.9 (C-1″), 133.6 (C-4′), 130.2 (C-2″, 6″), 129.7 (C-2′, 6′), 128.5 (C-3′, 5′), 123.6 (C-3″, 5″) ppm; MS (ESI$^+$): *m/z* (%) = 317 ([M+Na]$^+$, 12); FT-MS (ESI): *m/z* calcd for $C_{15}H_{11}N_4O_3$ ([M+H]$^+$) 295.0826, found 295.0818.

(4-Methoxyphenyl)(5-phenyl-1*H*-1,2,3-triazol-4-yl)methanone (7d, $C_{16}H_{13}N_3O_2$) Brown solid; yield: 127.2 mg (68%); m.p.: 117–118 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): $\delta = 8.12$ (brd, $J = 8.9$ Hz, 2H, H-2′, 6′), 7.76–7.80 (m, 2H, H-2″, 6″), 7.40–7.44 (m, 3H, H-3″, 4″, 5″), 6.95 (brd, $J = 8.9$ Hz, 2H, H-3′, 5′), 3.88 (s, 3H, 4′-OCH_3) ppm; ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 186.5$ (C=O), 163.9 (C-4′), 144.7 (C-5), 141.5 (C-4), 132.9 (C-2′, 6′), 129.8 (C-1′), 129.3 (C-4″), 128.7 (C-3″, 5″), 128.5 (C-2″, 6″), 113.6 (C-3′, 5′), 55.5 (4′-OCH_3) ppm; MS (ESI$^+$): *m/z* (%) = 280 ([M+H]$^+$, 40), 302 ([M+Na]$^+$, 100); FT-MS (ESI): *m/z* calcd for $C_{16}H_{13}N_3O_2$ ([M+H]$^+$) 280.1026, found 280.1020.

(4-Methoxyphenyl)[5-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]methanone (7e, $C_{17}H_{15}N_3O_3$) Yellow solid; yield: 186.5 mg (90%); m.p.: 170–172 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): $\delta = 7.82$ (dd, $J = 1.9$, 9.0 Hz, 2H, H-2′, 6′), 7.47 (dd, $J = 1.9$, 9.0 Hz, 2H, H-2″, 6″), 6.94 (dd, $J = 1.9$, 9.0 Hz, 2H, H-3″, 5″), 6.91 (dd, $J = 1.9$, 9.0 Hz, 2H, H-3′, 5′), 3.89 (s, 3H, 4′-OCH_3), 3.86 (s, 3H, 4″-OCH_3) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 184.3$ (C=O), 166.1 (C-4′), 162.1 (C-4″), 143.4 (C-5), 135.7 (C-4), 133.5 (C-2′, 6′), 130.5 (C-2″, 6″), 127.0 (C-1′), 115.1 (C-3″, 5″), 115.0 (C-1″), 114.6 (C-3′, 5′), 55.8 (4′-OCH_3), 55.6 (4″-OCH_3) ppm; MS (ESI$^+$): *m/z* (%) = 310 ([M+H]$^+$, 60); FT-MS (ESI): *m/z* calcd for $C_{17}H_{15}N_3NaO_3$ ([M+Na]$^+$) 332.1006, found 332.0990.

(4-Methoxyphenyl)[5-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl]methanone (7f, $C_{16}H_{13}N_4O_4$) Brown solid; yield: 184.6 mg (85%); m.p.: 172–175 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): $\delta = 8.27$ (d, $J = 9.0$ Hz, 2H, H-3″, 5″), 8.11 (d, $J = 9.0$ Hz, 2H, H-2′, 6′), 8.04 (d, $J = 9.0$ Hz, 2H, H-2″, 6″), 6.98 (d, $J = 9.0$ Hz, 2H, H-3′, 5′), 3.90 (s, 3H, 4′-OCH_3) ppm; ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 174.2$ (C=O), 164.3 (C-4′), 148.0 (C-4″), 146.2 (C-5), 138.7 (C-4), 135.9 (C-1′), 132.9 (C-2′, 6′), 129.6 (C-2″, 6″), 129.5 (C-1″), 123.6 (C-3″, 5″), 113.8 (C-3′, 5′), 55.6 (4′-OCH_3) ppm; MS (ESI$^+$): *m/z* (%) = 347 ([M+Na]$^+$, 98); FT-MS (ESI): *m/z* calcd for $C_{16}H_{13}N_4O_4$ ([M+H]$^+$) 325.0931, found 325.0921.

(4-Nitrophenyl)(5-phenyl-1*H*-1,2,3-triazol-4-yl)methanone (7g, $C_{15}H_{11}N_4O_3$) Brown solid; yield: 167.5 mg (85%); m.p.: 136–138 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): $\delta = 8.40$ (m, 4H, H-2′, 3′, 5′, 6′), 7.94 (m, 2H, H-2″, 6″), 7.52 (m, 3H, H-3″, 4″, 5″) ppm; ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 186.9$ (C=O), 151.0 (C-4′), 147.2 (C-5), 143.6 (C-1′), 141.8 (C-4), 132.3 (C-2′, 6′), 130.4 (C-4″), 130.3 (C-1″), 129.8 (C-3″, 5″), 129.2 (C-2″, 6″), 124.0 (C-3′, 5′) ppm; MS (ESI$^+$): *m/z* (%) = 295 ([M+H]$^+$, 12), 317 ([M+Na]$^+$, 45); FT-MS (ESI): *m/z* calcd for $C_{15}H_{11}N_4O_3$ ([M+H]$^+$) 295.0826, found 295.0818.

[5-(4-Methoxyphenyl)-1*H*-1,2,3-triazol-4-yl](4-nitrophenyl)methanone (7h, $C_{16}H_{13}N_4O_4$) Brown solid; yield: 71.7 mg (33%) m.p.: 144–146 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): $\delta = 8.33$ (s, 4H, H-2′, 3′, 5′, 6′), 7.80 (d, $J = 8.8$ Hz, 2H, H-2″, 6″), 7.01 (d, $J = 8.8$ Hz, 2H, H-3″, 5″), 3.87 (s, 3H, 4″-OCH_3) ppm; ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta = 185.7$ (C=O), 161.2 (C-4″), 150.1 (C-4′), 146.3 (C-5), 142.3 (C-1′), 131.4 (C-2′, 6′), 130.4 (C-2″, 6″), 123.3 (C-3′, 5′), 119.4 (C-1″), 114.2 (C-3″, 5″), 55.4 (4″-OCH_3) ppm; MS (ESI$^+$): *m/z* (%) = 347 ([M+Na]$^+$, 98); FT-MS (ESI): *m/z* calcd for $C_{16}H_{13}N_4O_4$ ([M+H]$^+$) 325.0931, found 325.0921.

(4-Nitrophenyl)[5-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl]methanone (7i, $C_{15}H_9N_5O_5$) Brown oil; yield: 68.2 mg (30%); ^{1}H NMR (300.13 MHz, $CDCl_3$): $\delta = 8.37$ (br d, $J = 8.9$ Hz, 2H, H-3′, 5′), 8.34 (brd, $J = 8.9$ Hz, 2H, H-3″, 5″), 8.32 (brd, $J = 8.9$ Hz, 2H, H-2′, 6′), 8.13 (brd, $J = 8.9$ Hz, 2H, H-2″, 6″) ppm; ^{13}C NMR (MHz, $CDCl_3$): $\delta = 185.6$ (C=O), 153.1 (C-5), 150.4 (C-4′), 148.4 (C-4″), 141.7 (C-1′), 141.8 (C-4), 135.2 (C-1″), 131.2 (C-2′, 6′), 130.0 (C-3′, 5′), 123.5 (C-3″, 5″), 123.0 (C-2″, 6″) ppm; MS (ESI$^+$): *m/z* (%) = 340 ([M+H]$^+$, 12).

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