Tetrahedron Letters xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Preparation of 4,5 disubstituted-2*H*-1,2,3-triazoles from (*Z*)-2, 3-diaryl substituted acrylonitriles

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ARTICLE INFO

Article history:
Received 18 April 2014
Revised 6 May 2014
Accepted 7 May 2014
Available online xxxx

Keywords:
Sodium azide
Triazole synthesis
Acrylonitrile
Huisgen cycloaddition

ABSTRACT

2*H*-1,2,3-Triazoles (**2**) were synthesized by [3+2] cycloaddition of (*Z*)-2,3-diaryl substituted acrylonitriles (**1**) with sodium azide and ammonium chloride in DMF/water. This method represents a facile and efficient reaction procedure for the synthesis of 4,5-diaryl-2*H*-1,2,3-triazoles in modest to good yields.

1,2,3-Triazoles are an important class of heterocycles which have a wide range of applications in agricultural,[1] industrial,[2] and pharmaceutical industries.[3] This ring system is present in a number of drugs with biological properties, such as anti-cancer,[4] anti-fungal,[5] anti-viral,[6] anti-consulvant,[7] and anti-HIV agents.[8] Industrial applications include dyes,[9] photostabilizers, photographic materials,[9] and anti-corrosives.[2] Our laboratory is currently focusing on the development of anticancer agents structurally related to combretastatin A4 (CA4) and *trans*-cyano-combretastatin A4 (cyano-CA4) (Fig. 1e).[10,11] CA4 and cyano-CA4 suffer from chemical instability in solution, due to *cis-trans* isomerism.[12] We are currently involved in identifying chemically stable *cis*-cyano-CA4 analogs. One approach we are exploring is the replacement of the acrylonitrile moiety in these active anticancer agents with a triazole moiety to afford geometrically stable triazole analogs of cyano-CA4 (Figs. 1 and 2e).

The conventional route for preparing 1,2,3-triazoles is via Huisgen 1,3-dipolar cycloaddition of azides with alkynes. However, the disadvantages of this synthetic approach are poor regioselectivity and long reaction times. A variety of triazoles can also be synthesized by the click chemistry methodologies developed by Sharpless et al. between azides and alkynes, to yield 1,5-disubstituted 1,2,3-triazoles.[13] However, inorganic azides (NaN_3) are not good substrates for this reaction, and these methods cannot be applied to the synthesis of internal alkynes. Recently, Majireck et al.[14] and Tsai et al.[15] have reported the synthesis of 4,5-disubstituted 2*H*-1,2,3-triazoles by cycloaddition of internal alkynes with alkyl azides or metal azides, but the disadvantage is the low yielding synthesis of the alkyne reactant, especially when an electron donating group is attached to the alkyne terminus.

A less explored route for the synthesis of 2*H*-1,2,3-triazoles is the cycloaddition of azides with alkenes bearing a good leaving group. Zard et al.[16] reported the synthesis of 4,5-disubstituted-1*H*-1,2,3-triazoles from nitroalkenes, but did not report any formation of 4,5-disubstituted 2*H*-1,2,3-triazoles via this approach. Sengupta et al.[17] have reported the synthesis of 4,5-disubstituted 2*H*-1,2,3-triazoles from nitroalkenes; however, the presence of a vinyl group was necessary for the reaction to proceed.

Herein, we report a novel synthetic procedure for the synthesis of 4,5-disubstituted 2*H*-1,2,3-triazoles from (*Z*)-2,3-diaryl-substituted acrylonitriles by treatment with NaN_3/NH_4Cl in aqueous DMF (Scheme 1). The advantage of this methodological approach is that cyano-CA4 analogs bearing a broad range of aromatic functionalities can be easily converted to their corresponding 2*H*-1,2,3-triazole derivatives in one step.

Utilizing (*Z*)-3-(3,4-dichlorophenyl)-2-(3,4-dimethoxyphenyl) acrylonitrile as a model reactant, it was observed that using a combination of 10:1 volumes of DMF/H_2O as solvent significantly improved the yield of 4-(3,4-dichlorophenyl)-5-(3,4-dimethoxyphenyl)-2*H*-1,2,3-triazole compared to using DMF alone (Scheme 2). The reaction did not proceed in anhydrous THF. The rate of the reaction was found to be dependent on the molar amount of NaN_3/NH_4Cl used (Table 1). The optimum conditions for this reaction are: heating the reactant under reflux with 3 molar equivalents of NH_4Cl and 3 molar equivalents of NaN_3 in

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http://dx.doi.org/10.1016/j.tetlet.2014.05.045
0040-4039/

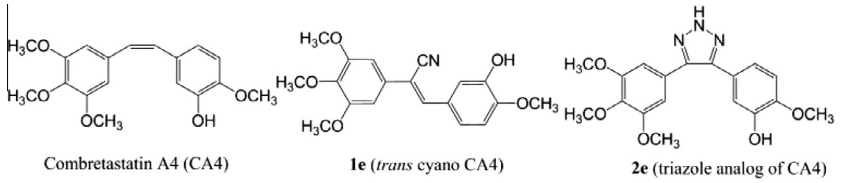


Figure 1. Structures of combretastatin A-4 (CA4), *trans*-cyano CA4 (**1e**) and the 2*H*-1,2,3-triazole analog of CA4 (**2e**).

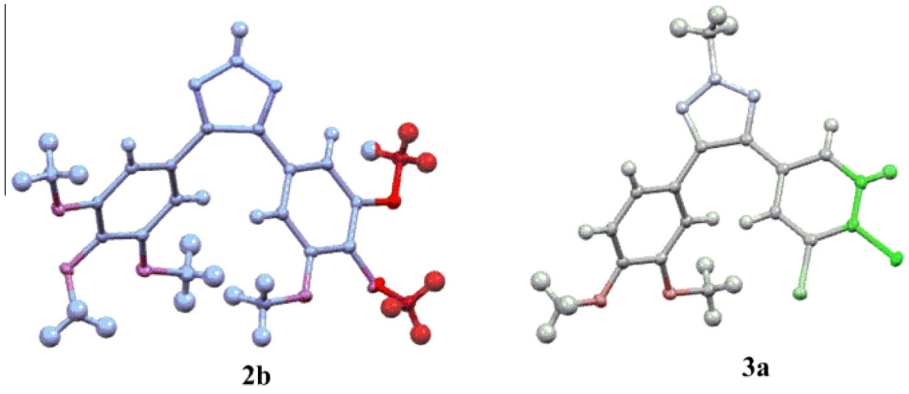
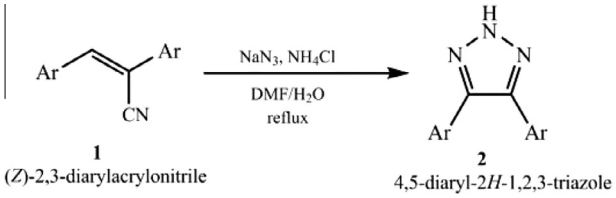


Figure 2. X-ray Crystal structures of compounds **2b** and **3a**.

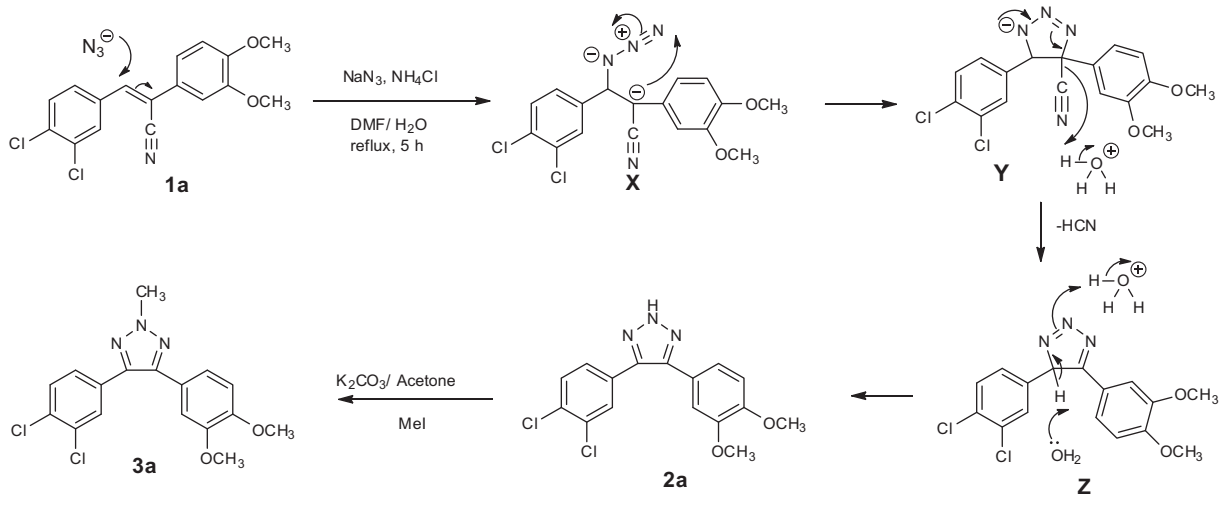


Scheme 1. Synthesis of 4,5-disubstituted 2*H*-1,2,3-triazoles from (*Z*)-2,3-diarylacrylonitriles.

Table 1
Optimization of the reaction conditions for the synthesis of 4-(3,4-dichloro)-5-(3,4-dimethoxyphenyl)-2*H*-1,2,3-triazole

Entry	Solvent	Reaction conditions	Yield[a] (%)
1	DMF[c]	Reflux, 5 h, 3 equiv NH_4Cl/3 equiv NaN_3	24
2	DMF/H_2O[b]	Reflux, 5 h, 3 equiv NH_4Cl/3 equiv NaN_3	81
3	DMF/H_2O[b]	Reflux, 5 h, 1 equiv NH_4Cl/1 equiv NaN_3	45
4	DMF/H_2O[b]	Reflux, 5 h, 3 equiv NaN_3	32
5	THF[c]	Reflux, 5 h, 3 equiv NH_4Cl/3 equiv NaN_3	0

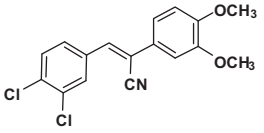
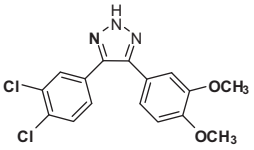
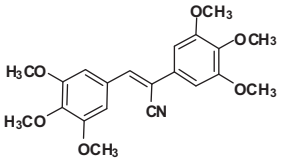
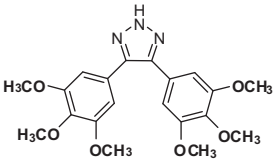
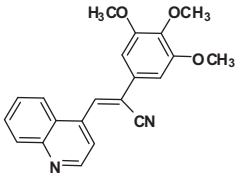
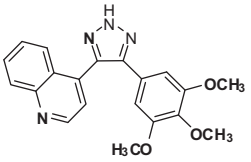
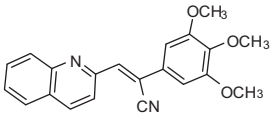
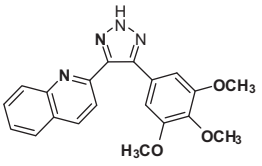
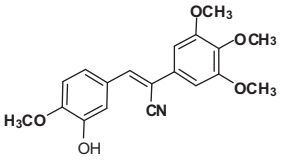
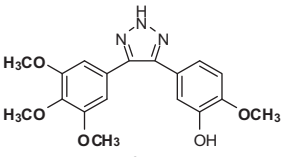
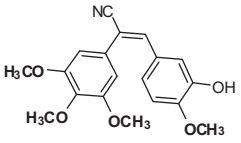
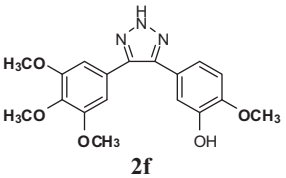
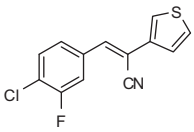
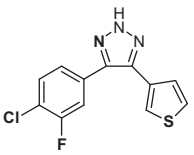
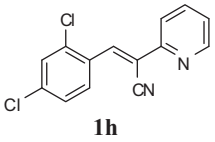
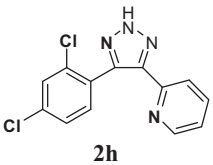
[a] Isolated yields.
[b] 10:1 volumes of DMF/H_2O.
[c] Anhydrous.



Scheme 2. Proposed mechanism and optimization of the reaction conditions for the synthesis of 4-(3,4-dichloro)-5-(3,4-dimethoxyphenyl)-2*H*-1,2,3-triazole and synthesis of its methylated product.

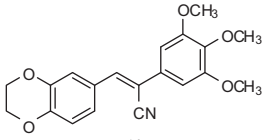
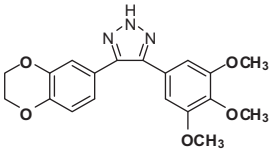
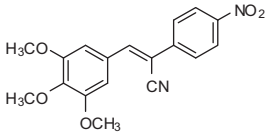
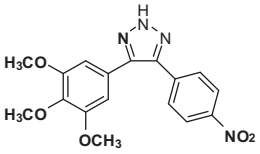
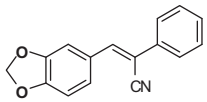
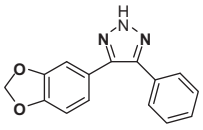
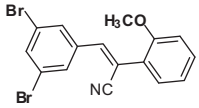
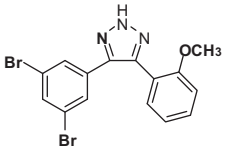
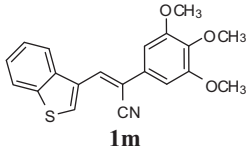
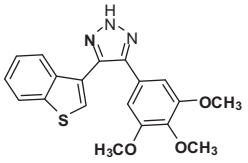
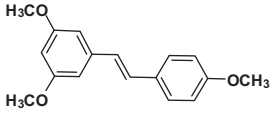
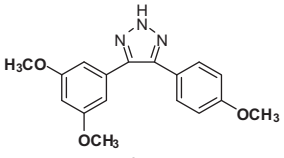
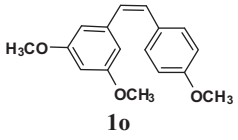
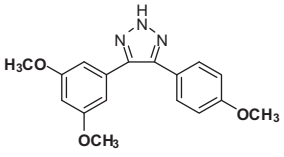
Please cite this article in press as: Madadi, N. R.; et al. *Tetrahedron Lett.* (2014), http://dx.doi.org/10.1016/j.tetlet.2014.05.045

Table 2
Synthesis of 4,5-disubstituted-2*H*-1,2,3-triazoles from their corresponding (*Z*)-2,3-diaryl substituted acrylonitriles with reaction times and isolated yields

Entry	Substrate	Time (h)	Triazole	Yield (%)
1	 **1a**	5	 **2a**	81
2	 **1b**	12	 **2b**	65
3	 **1c**	5	 **2c**	69
4	 **1d**	5	 **2d**	74
5	 **1e**	12	 **2e**	59
6	 **1f**	12	 **2f**	21
7	 **1g**	5	 **2g**	64
8	 **1h**	5	 **2h**	78

(*continued on next page*)

Table 2 (*continued*)

Entry	Substrate	Time (h)	Triazole	Yield (%)
9	 **1i**	12	 **2i**	60
10	 **1j**	3	 **2j**	80
11	 **1k**	12	 **2k**	66
12	 **1l**	5	 **2l**	78
13	 **1m**	5	 **2m**	87
14	 **1n**	12	 **2n**	0
15	 **1o**	12	 **2o**	0

10:1 volumes of DMF/H_2O. X-ray crystallographic studies on compounds **2b** and **3a** confirmed the presence of a 2*H*-1,2,3-triazole ring system and the position of *N*-methylation (Fig. 2).

Previous reports have not elaborated on the mechanism of formation of the 2*H*-1,2,3-triazole ring in cyanostilbenes of structure **1**.[14,15] Triazole ring formation initially involves Michael addition of azide ion at the unsubstituted sp^2 olefinic carbon to afford **X** followed by cyclization to **Y** (Scheme 2). Acid-catalyzed elimination of the cyano moiety then affords **2a**. It is evident from the optimization studies that NH_4Cl and water are essential components in the reaction (Scheme 2). All the reactions were conducted with (*Z*)-2,3-diarylacrylonitriles. However, we did examine the relative usefulness of utilizing (*E*)-2,3-diarylacrylonitriles in these reactions. Thus, (*E*)-3-(3-hydroxy-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-acrylonitrile, the corresponding (*E*)-isomer of **1e**, was used as a starting material for the synthesis of compound **2e**. The yield of the resulting 2*H*-1,2,3-triazole **2e** was 21% compared to 59% when the (*Z*)-isomer was utilized under similar reaction conditions (Table 2, entry 5), indicating that (*E*)-2,3-diarylacrylonitriles are less useful than their (*Z*)-counterparts in the synthesis of 2*H*-1,2,3-triazoles of structure **2**.

A variety of cyano-CA4 analogs were subjected to treatment with NaN_3/DMF/H_2O under the above optimized reaction conditions, and their corresponding 4,5-disubstituted 2*H*-1,2,3-triazoles (**2a**–**2m**) were obtained in modest to good yields (Table 2). No significant side products are formed in the reactions shown in Table 2. It should be noted that when either *E*- or *Z*-diarylstilbenes that lack the cyano group (Table 2, entries 14 and 15, **1n** and **1o**) are utilized

in the above reaction no detectable amounts of the corresponding 2*H*-1,2,3-triazole were observed.

In summary, we have developed a facile procedure for the synthesis of 4,5-diaryl-2*H*-1,2,3-triazoles bearing a broad range of aryl moieties from their corresponding (*Z*)-2,3-diarylacrylonitriles. The method does not require an inert atmosphere, is economical, can be applied to a wide range of aryl groups and aromatic ring substitutions, and is a viable alternative to the Huisgen cycloaddition reaction of alkynes with azides.

Acknowledgments

The authors thank the NIH/National Cancer Institute (CA140409) United States, and the Arkansas Research Alliance for financial support, and acknowledge Grants UL1TR000039 and KL2TR000063 for the UAMS Translational Research Institute support of the Bioanalytical Core.

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General experimental procedure: A typical experimental procedure entailed refluxing a mixture of the (Z)-2,3-diarylacrylonitrile (**1**), NaN_3, and NH_4Cl in a mole ratio of 1:3:3 in 10:1 volumes of DMF/H_2O for 5–12 h. The reaction was monitored by TLC and GC. When the starting material had completely disappeared, cold water was added and the mixture stirred over 10–15 min, during which the final product precipitated out. In the absence of a precipitate, the product was extracted into ethyl acetate, the organic extract washed with copious amounts of water, and the resulting organic liquor evaporated to dryness on a rotavaporator. The residue obtained was purified by flash column chromatography to afford the corresponding triazole (**2**). Yields of the synthesized triazoles are presented in Table 2.

*Spectral data for selected products: 5-(3,4-dichlorophenyl)-4-(3,4-dimethoxyphenyl)-2H-1,2,3-triazole (**2a**):* Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$-*d*): δ 3.82 (s, 3H, –OCH_3), δ 3.93 (s, 3H, –OCH_3), 6.87–6.89 (d, *J* = 8 Hz, 1H, ArH), 7.05–7.07 (d, *J* = 12 Hz, 2H, ArH),), 7.42 (s, 2H, ArH), 7.78 (s, 1H, ArH). ^{13}C NMR (100 MHz, DMSO-d_6): 55.87, 55.96, 111.05, 127.31, 129.80, 129.89, 130.54, 132.60, 132.86, 149.15, 149.754. HRMS (ESI): *m*/*z* calcd for $C_{16}H_{14}Cl_2N_3O_2$ [M−H] 350.0463; found 350.0480.

*4,5-Bis(3,4,5-trimethoxyphenyl)-2H-1,2,3-triazole (**2b**):* Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$-*d*): δ 3.77 (s, 12H, –OCH_3), 3.88 (s, 6H, –OCH_2), 6.85 (s, 4H, ArH). ^{13}C NMR (100 MHz, DMSO-d_6): 56.09, 60.97, 105.58, 125.59, 138.28, 153.27. HRMS (ESI): *m*/*z* calcd for $C_{20}H_{24}N_3O_6$ [M−H] 402.1665; found 402.1659.

*4-(4-(3,4,5-Trimethoxyphenyl)-2H-1,2,3-triazol-5-yl)quinoline (**2c**):* Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$-*d*): δ 3.47 (s, 6H, –OCH_3), 3.81 (s, 3H, –OCH_3), 6.65 (s, 2H, ArH), 7.50–7.52 (t, *J* = 8 Hz, 1H, ArH), 7.54–7.56(d, *J* = 4.4 Hz, 1H, ArH), 7.76–7.77 (t, *J* = 1.6 Hz, 1H, ArH), 7.82–7.84 (d, *J* = 8 Hz, 1H, ArH), 8.27–8.29 (d, *J* = 8.8 Hz, 1H, ArH), 9.03–9.04 (d, *J* = 4.4 Hz, 1H, ArH). ^{13}C NMR (100 MHz, DMSO-d_6):55.70, 55.79, 0.85, 60.95, 104.47, 104.55, 122.68, 122.76, 124.69, 125.95, 126.66, 127.52, 129.42, 130.21, 138.21, 138.45, 148.15, 149.63, 149.69, 153.24. HRMS (ESI): *m*/*z* calcd for $C_{20}H_{19}N_4O_3$ [M−H] 363.1457; found 363.1445.

*5-(Benzo[b]thiophen-3-yl)-4-(3,4,5-trimethoxyphenyl)-2H-1,2,3-triazole (**2m**):* Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$-*d*): δ 3.57 (s, 6H, –OCH_3), δ 3.84 (s, 3H, –OCH_3), 6.80 (s, 2H, ArH), 7.34–7.39 (m, *J* = 20 Hz, 1H, ArH), 7.61 (s, 1H, ArH), 7.75–7.77 (d, *J* = 7.6 Hz, 1H, ArH), 7.90–7.92(d, *J* = 8 Hz, 1H, ArH). ^{13}C NMR (100 MHz, DMSO-d_6):55.72, 55.85, 60.85, 60.99, 104.57, 104.64, 122.61, 122.73, 123.65, 123.77, 124.66, 124.74, 124.83, 124.94, 125.28, 127.21, 127.37, 137.56, 138.12, 139.89, 153.24. HRMS (ESI): *m*/*z* calcd for $C_{19}H_{18}N_3O_3S$ [M−H] 368.1069; found 368.1075.

*5-(Benzo[d][1,3]dioxol-5-yl)-4-phenyl-2H-1,2,3-triazole (**2i**):* Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$-*d*): δ 6.00 (s, 2H, –CH_2), 6.80–6.82 (d, *J* = 8.8 Hz, 1H, ArH), 7.03–7.05 (d, *J* = 6.8 Hz, 2H, ArH), 7.38–7.40 (t, *J* = 5.2 Hz, 3H, ArH), 7.56–7.58 (m, *J* = 9.6 Hz, 1H, ArH). ^{13}C NMR (100 MHz, DMSO-d_6): 101.25, 108.58, 108.70, 122.23, 128.24, 128.70, 147.85. HRMS (ESI): *m*/*z* calcd for $C_{15}H_{12}N_3O_2$ [M−H] 266.0930; found 266.0918.

*4-(3,4-Dichlorophenyl)-5-(3,4-dimethoxyphenyl)-2-methyl-2H-1,2,3-triazole (**3a**):* A mixture of 5-(3,4-dichlorophenyl)-4-(3,4-dimethoxyphenyl)-2*H*-1,2,3-triazole (**2a**) (1 mmol), K_2CO_3 (10 mmol) and MeI (2 mmol) in 10 volumes of acetone was refluxed for 5 h. 2M aqueous HCl was then added to quench the reaction and the resulting mixture was evaporated to dryness on a rotavaporator. The resulting residue was dissolved in ethyl acetate, filtered, and the filtrate submitted to ethyl acetate/hexane flash column chromatography to yield 4-(3,4-dichlorophenyl)-5-(3,4-dimethoxyphenyl)-2-methyl-2*H*-1,2,3-triazole (**3a**) as a pale yellow solid; 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$-*d*): δ 3.83 (s, 3H, –OCH_3), 3.92 (s, 3H, –OCH_3), 4.25 (s, 3H, –CH_3), 6.86–6.88 (d, *J* = 8 Hz, 1H, ArH), 7.05–7.07 (dd, *J* = 15.2 Hz, 2H, ArH),), 7.42–7.26 (dd, *J* = 16.8 Hz, 2H, ArH), 7.74–7.74 (d, *J* = 1.6 Hz, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$-*d*): 41.98, 56.08, 111.40, 121.07, 123.09, 127.45, 129.97, 130.59, 131.376, 132.41, 132.91, 141.99, 144.87, 149.25, 149.63.