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A facile access for the synthesis of 1-hetero(aryl)-1,2,3-triazoles linked to equol under mild conditions

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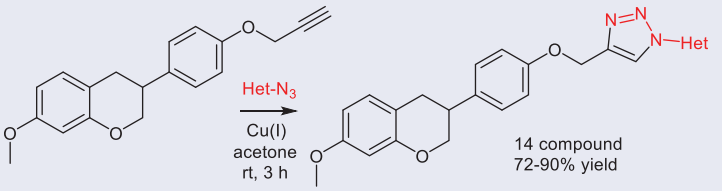
ABSTRACT

We herein report a convenient methodology for the synthesis of 1-hetero(aryl)-1,2,3-triazoles linked with equol by utilizing copper-catalyzed azide-alkyne cycloaddition reaction under exceptionally mild conditions. The salient features of this developed protocol include: easy isolation process, good to excellent yield of the products and appendage diversity of heteroaryl triazoles.

GRAPHICAL ABSTRACT



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KEYWORDS
Copper; cycloaddition; equol; 1,2,3-triazole

Introduction

Equol is an isoflavonoid that belongs to the class of polyphenols which exist in two enantiomeric forms. They exhibit a wide range of biological activities like anti-androgenic, antioxidant and anti-inflammatory potencies.[1] Equol significantly reduces bone loss and is reported to improve skin health and regeneration because of its antioxidative, phytoestrogenic and epigenetic characteristics.[2] In living organisms, equol is metabolized from the isoflavone daidzein by intestinal bacteria. Equol is also synthesized in the laboratories from the last 50 years; initially in racemic form and recently as separate enantiomers.[3] Highly functionalized molecules comprising of linearly connected heterocyclic rings have received considerable interest in recent years owing to their diverse pharmacological activity[4] and their applications in organic synthesis as well as material chemistry.[5] Among these, 1,2,3-triazole derivatives are highly important because of their varied biological and chemical properties.

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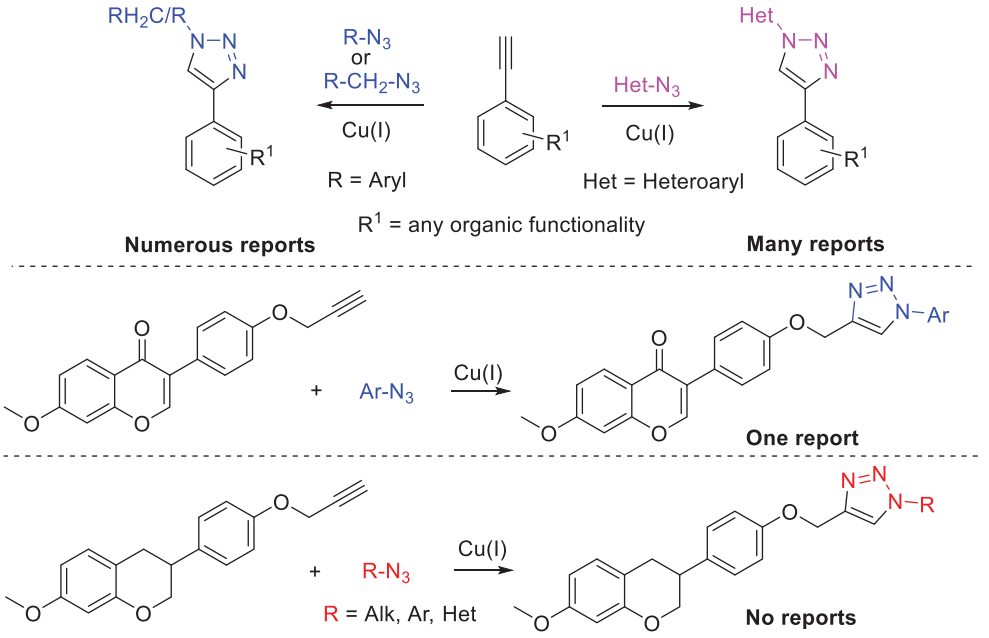
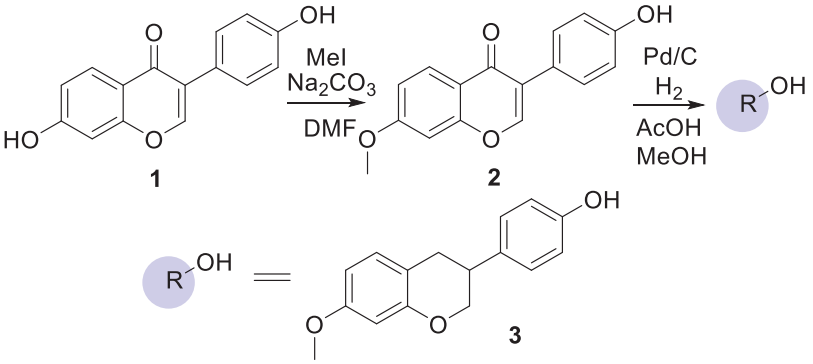


Scheme 1. An overview of reports on CuAAC.

The discovery of copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction by the groups of Meldal and Sharpless paved the way for the synthesis of a wide variety of monocyclic, spirocyclic and fused 1,2,3-triazoles.[5g,6] Moreover, several 1,2,3-triazole derivatives linearly connected to other heterocycles were found to exhibit potential antiviral,[4c,5h] anticancer and antibacterial properties.[4d,g] In the design and development of new drugs, the molecular hybridization strategy involving the combination of two or more pharmacophores in a single entity is presumed to generate new compounds with interesting biological profiles.[4d,7] Although the synthesis of 1,2,3-triazoles by CuAAC is a well-explored area in synthetic chemistry for the past two decades, the reaction of electron-deficient heteroaryl azides has always been a challenging problem.[8] Moreover, the synthesis of hybrids of 1-heteroaryl-1,2,3-triazoles and equol is surprisingly undone whereas the preparation of 1-aryl-1,2,3-triazoles linked with daidzein is limited to only one example (Scheme 1).[9] These observations enlightened us about the challenges associated with their synthesis and hence we directed our attention towards developing a facile and convenient one-pot approach for the synthesis of hybrids of 1-heteroaryl-1,2,3-triazoles and equol linearly connected via flexible oxymethylene linker.

Results and discussion

As depicted in Scheme 2, we started our synthetic route by the selective methylation of daidzein **1**. The intermediate thus obtained was then reduced to equol intermediate **3** by hydrogenation reaction. This methylated equol intermediate **3** was then treated with propargyl bromide and various azides sequentially in one-pot for obtaining a series of 1-hetero(aryl)-1,2,3-triazoles linked with equol.

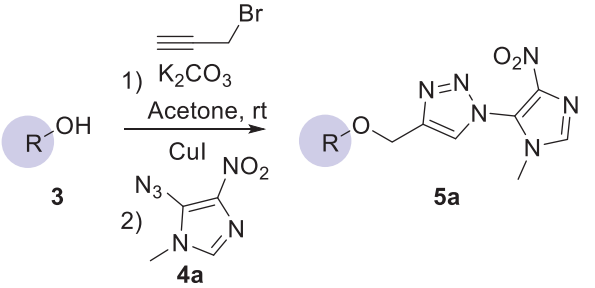


Scheme 2. Synthesis of methylated equol intermediate **3**.

As a model reaction, we took the equol intermediate **3** and 5-azido-1-methyl-4-nitro-1*H*-imidazole **4a** for performing the synthesis of 1,2,3-triazoles. The initial optimization studies were focused on synthesizing the desired compounds in two steps: by initial synthesis of O-propargylated intermediate and then treating that alkyne with heteroaromatic azides (see supporting info). Nevertheless, we were grateful to obtain the desired products in a one-pot methodology after careful screening of the reaction parameters (see supporting info for more details). The reaction proceeded smoothly at room temperature in the presence of CuI as a catalyst, potassium carbonate as the base and acetone as solvent (Table 1, entry 4). When potassium carbonate was replaced with organic bases, the yield of the required product decreased significantly (Table 1, entries 6 and 7). The use of CuBr instead of CuI also diminished the yield of the expected 1,2,3-triazole product (Table 1, entry 8). Among the solvents screened, acetone was found to be essential for better conversions (Table 1, entries 9 and 10). The detailed optimization studies are described in the Supporting Information and the optimum reaction conditions were as illustrated in entry 4 of Table 1. Gratifyingly, this developed methodology eased us to achieve the otherwise two-step synthesis of required products in one step in excellent yield.

After establishing a facile protocol for the one-pot synthesis of equol linked with 1,2,3-triazole, we directed our attention towards evaluating the substrate scope of the developed protocol. Accordingly, we treated the methylated equol intermediate **3** with propargyl bromide and different heteroaryl azides **4a–l** in our optimized reaction conditions. To our delight, we obtained the desired 1-heteroaryl-1,2,3-triazoles **5a–l** in good to excellent yields in all these reactions (Scheme 3). The various heterocyclic azides of uracil, thiophene, isoxazole, pyrazole, and imidazole reacted well efficiently to procure the desired products in excellent yields. The azides of benzothiazole and thiazole rendered the desired product in good yield only when stoichiometric amount of CuI was used which could be rationalized by the existence of those azides in its tetrazole form.[10] Moreover, our developed methodology also procured the expected products (**5k** and **5l**) in satisfactory yield when the antiretroviral drug, azidothymidine (Zidovudine) and its methyl derivative were employed for the CuAAc reaction. The utilization of hitherto unreported aromatic azides **4m–n** also procured the corresponding products **5m–n** in good yield.

Table 1. Optimization of the reaction conditions.[a]



Entry	(equiv.)	K_2CO_3 (equiv.)	Azide (equiv.)	Yield[b] 5a (%)
1	1	1	1	50
2	1.5	1	1	60
3	1.5	2	1	80
4	**1.5**	**3**	**1**	**90**
5	1.5	3	1.5	75
	Deviation from the above standard conditions (entry 4)			
6	TEA instead of K_2CO_3 (35% of **3** recovered)			50
7	DIPEA instead of K_2CO_3 (30% of **3** recovered)			60
8	CuBr instead of CuI			40
9	DMF instead of acetone (60% of **3** recovered)			25
10	H_2O instead of acetone (90% of **3** recovered)			NR

[a]Reaction conditions: **3** (1.0 mmol), propargyl bromide (1.5 mmol), base (3.0 mmol), solvent (3 mL), rt, 10 h. **4a** (1.0 mmol), catalyst (0.1 mmol), rt, 3 h. [b]Isolated yield.

The newly synthesized compounds **5a–n** was recrystallized from EtOH without any additional purification techniques and the structure of all the final compounds was characterized by the NMR and mass spectral analysis. Moreover, the structure of **5h**[11] was confirmed by single crystal XRD analysis (Figure 1).

In order to check the feasibility of the developed methodology at higher dimensions, a scale-up reaction was carried out at the later stage. Gratifyingly, the gram-scale reaction procured the expected product **5a** in satisfactory yield (85% isolated yield) as the same reaction in small-scale furnished the desired product in 90% yield (Scheme 3).

A representative experimental procedure for the synthesis of 4-((4-(7-Methoxychroman-3-yl)phenoxy)methyl)-1-(1-methyl-4-nitro-1*H*-imidazol-5-yl)-1*H*-1,2,3-triazole (**5a**) is detailed here. To the solution of 4-(7-methoxychroman-3-yl)phenol **3** (0.256 g, 1 mmol, 1 equiv.) in acetone (3 mL), K_2CO_3 (0.415 g, 3 mmol, 3 equiv.) and propargyl bromide (0.178 g, 1.5 mmol, 1.5 equiv.) were added in inert atmosphere and the reaction mixture was stirred at room temperature for 10 h. After the completion of reaction monitored by TLC, azide **4a** (1 mmol, 1 equiv.) and CuI (0.019 g, 10 mol %, 0.1 equiv.) were added to the same reaction vessel and the mixture was stirred at room temperature for another 3–5 h. After the completion of reaction monitored by TLC, the reaction mixture was filtered through celite and distilled under reduced pressure to obtain the crude product. The crude product was further recrystallized from ethanol to obtain the titled compound **5a** as light yellow solid in 90% yield. Mp 201–203 °C. IR (KBr): 3849, 3122, 2919, 1611, 1580, 1527, 1504, 1461, 1433, 1378, 1355, 1319, 1288, 1262, 1232, 1196, 1156, 1111, 1017, 868, 827, 775, 648, 539 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): $\delta = 2.88–2.96$ (m, 2H), 3.12–3.15 (m, 1H), 3.55 (s, 3H), 3.70 (s, 3H), 4.01

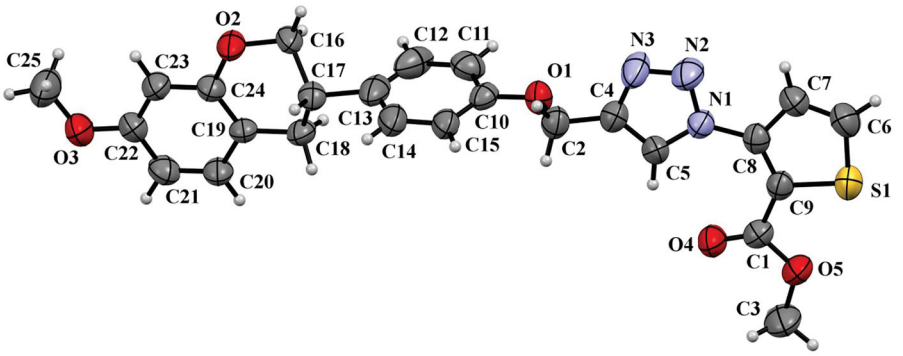
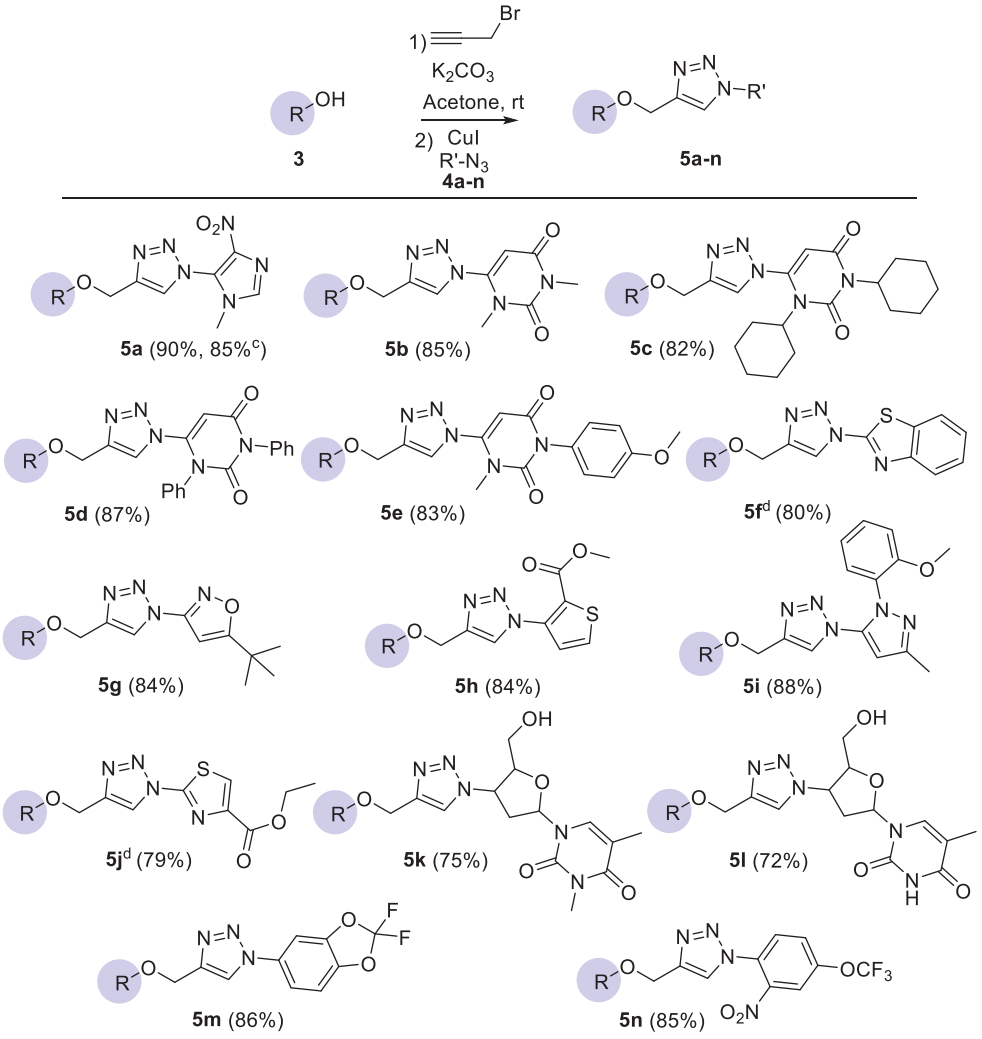


Figure 1. Compound **5h** according to XRD data in the thermal ellipsoids of 50% probability level.



Scheme 3. Substrate scope of the developed methodology.[a] [a]Reaction conditions: (1) **3** (1.0 mmol), propargyl bromide (1.5 mmol), K_2CO_3 (3.0 mmol), acetone (3 mL), rt, 10 h; 2) **4a–n** (1.0 mmol), CuI (0.1 mmol), rt, 3 h. [b]Isolated yield. [c]The gram-scale reaction yield. [d]1.0 mmol of CuI used.

(t, $J = 10.4$ Hz, 1H), 4.22 (d, $J = 10.4$ Hz, 1H), 5.29 (s, 2H), 6.37 (d, $J = 2.4$ Hz, 1H), 6.46 (dd, $J = 2.4$, 8.4 Hz, 1H), 7.01 (d, $J = 8.4$ Hz, 1H), 7.06 (d, $J = 8.4$ Hz, 2H), 7.29 (d, $J = 8.8$ Hz, 2H), 8.14 (s, 1H), 8.79 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 31.1$, 32.3, 36.9, 55.0, 60.8, 70.1, 101.1, 106.8, 114.1, 114.9, 123.4, 128.4, 128.5, 130.2, 134.0, 136.1, 139.0, 143.2, 154.6, 156.8, 158.6. MS (EI): m/z (%) = 462 (1) $[M]^+$, 137 (100). Anal. Calcd for $C_{23}H_{22}N_6O_5$: C, 59.73; H, 4.80; N, 18.17. Found: C, 59.39; H, 4.45; N, 17.88.

Conclusion

A facile and convenient methodology has been developed for the sequential one-pot synthesis of 1-hetero(aryl)-1,2,3-triazoles linked with equol under mild conditions. The reaction was found to be tolerant with a wide variety of heteroaryl azides which point toward its broad scope and diversity. The protocol described here can be extended for the synthesis of diverse triazole hybrids linked to other complex molecules in future.

The detailed experimental procedure and characterization data including spectra are available in the Supporting information uploaded along with the manuscript.

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[11] Deposition numbers for compounds **5h** (CCDC 1993494) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/pages/Home.aspx.