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A convenient synthesis and crystal structure of disubstituted 1,2,3-triazoles having ether functionality

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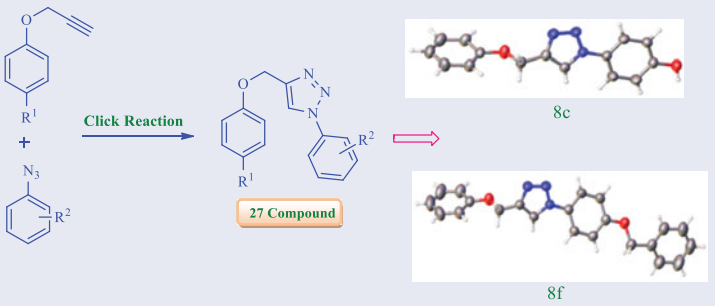
ABSTRACT

A series of 27 ether-linked 1,4-disubstituted 1,2,3-triazoles (**8a–8z$_1$**) has been synthesized by 1,3 dipolar cycloaddition of 1-substituted-4-(prop-2-yn-1-yloxy)benzene (**3a–3c**) and aromatic azides (**5a–5c, 7a–7f**). The synthesized compounds were explicated by FTIR, ^{1}H NMR, ^{13}C NMR and HRMS techniques. The structures of synthesized triazoles **8c** (CCDC 1840219) and **8f** (CCDC 1840220) were also confirmed by X-ray crystallography.

GRAPHICAL ABSTRACT



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Introduction

The microbial strains are steadily developing resistance toward the existing microbicidal through a brain-storming task for the synthetic chemists to develop new effective entities with spectacular mode of action. Therefore, the synthesis of new moieties and assessing their biological activities are the prime concern in the present scenario. In this respect, heterocyclic rings are considered as potent entities, endowed with key biological and pharmaceutical properties.[1,2] A quantum research on synthesis and biological activities of triazoles is in full swing from the last few years, proving it as a significant pharmaceutical motif reflecting the importance of this heterocyclic nucleus.[3]

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Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lsyc.
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Literature also reveals 1,2,3-triazoles as highly privileged structure which exhibit excellent biological activities in form of antimicrobial,[4–7] antiviral,[8–10] antitubercular,[11–14] antimalarial,[15–18] antihistaminic,[19] anticancer,[20–22] antioxidant,[23–26]immune potentiators[27] and anti-inflammatory[28] agents. For the synthesis of 1,4-disubstituted 1,2,3-triazoles, Huisgen's 1,3-dipolar cycloaddition reaction between terminal alkynes and azides was put forwarded by Sharpless and Meldal[29–31] by using copper(I) as catalyst. In continued to this, biological importance of ether-linked 1,4-disubstituted 1,2,3-triazoles was also highlighted by the various researchers.[32,33]

Encouraged from above considerations, we have synthesized 27 ether linked disubstituted 1,2,3-triazoles from click reaction of 1-substituted-4-(prop-2-yn-1-yloxy)benzene (**3a–3c**) and azides (**5a–5c, 7a–7f**) using copper(I) as a catalyst and characterized by FTIR, ^{1}H NMR, ^{13}C NMR and HRMS techniques. The structures of synthesized triazoles **8c** (CCDC 1840219) and **8f** (CCDC 1840220) were also confirmed by X-ray crystallography.

Result and discussion

Chemistry

The synthetic strategy for the synthesis of compound (**8a–8z$_1$**) was outlined in Scheme 1. The terminal alkynes i.e. 1-substituted-4-(prop-2-yn-1-yloxy)benzene[34] (**3a–3c**) were synthesized by reaction of 4-substituted phenol (**1a–1c**) in dimethylformamide with propargyl bromide in the presence of potassium carbonate as base.

The aromatic azides[35] (**5a–5c**) were synthesized from reaction of aminophenol (**4a–4c**) in a dilute hydrochloric acid with sodium nitrite and sodium azide. Further, for the synthesis of substituted azides (**7a–7f**) the aromatic azides (**5a–5c**) were reacted with (bromomethyl)benzene (**6a**)/(2-bromoethyl)benzene (**6b**) using potassium carbonate as base at room temperature with continuous stirring for 5–6 h.

Finally, targeted 1,4-disubstituted 1,2,3-triazoles with ether functionality were synthesized by click reaction of aromatic azides (**5a–5c, 7a–7f**) and 1-substituted-4-(prop-2-yn-1-yloxy)benzene (**3a–3c**) in dimethylformamide using catalytic amount of copper sulfate pentahydrate and sodium ascorbate.[5]

All the synthesized 1,4-disubstituted 1,2,3-triazoles (**8a–8z$_1$**) were characterized by FTIR, ^{1}H NMR, ^{13}C NMR and HRMS. In FTIR spectra, the emergence of band at 3380–3362 cm^{-1} was due to OH stretching of phenol. Absorption band appeared at 3186–3125 cm^{-1} due to C–H stretching vibration of triazole ring, while absorption band due to C–H stretching vibration of aromatic ring appeared at 3088–3045 cm^{-1}. The absorption band owing to N=N of triazole ring was observed at 1542–1528 cm^{-1}. Strong bands due to C–O asymmetric and symmetric stretching appeared at 1267–1228 and 1060–1001 cm^{-1}, respectively.

In ^{1}H NMR spectra, singlet due to triazole proton displayed in the region at δ 8.58–8.99 and OH proton resonated at δ 9.95–10.62. Methylene protons attached to C_4 of triazole appeared as singlet at δ 5.20–5.42, whereas, aromatic protons appeared in region δ 6.90–8.25.

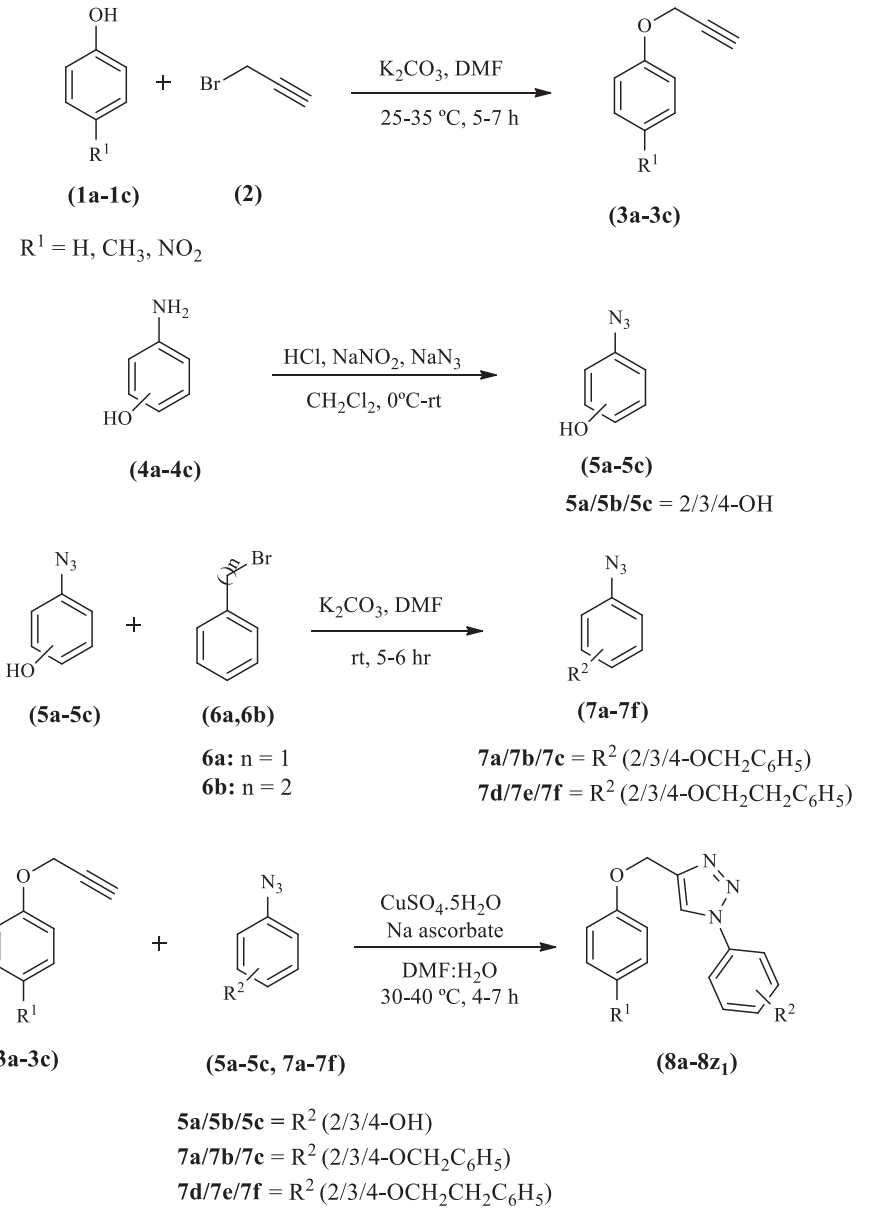
Moreover, in ^{13}C NMR spectra signal in region δ 141.9–144.5 and δ 121.1–124.9 were attributed to C_4 and C_5 of triazole ring, respectively. Peak due to aromatic carbon

attached to oxygen of phenoxy ring appeared at δ 156.4–163.8, while other aromatic carbons displayed signal in region at δ 111.0–130.5.

The HRMS data of all the products were in good agreement with calculated values.

X-ray crystallographic study

Single crystals of 4-(4-(phenoxymethyl)-1H-1,2,3-triazol-1-yl)phenol **8c** (Fig. 1) and 1-(4-(benzyloxy)phenyl)-4-(phenoxymethyl)-1H-1,2,3-triazole **8f** (Fig. 2) were grown in



Scheme 1. Synthesis of ether linked 1,4-disubstituted 1,2,3-triazoles.

Scheme 1. Continued

Compound	R^1	R^2	Reaction time (h)	Yield %
8a	H	2-OH	4	86
8b	H	3-OH	5	90
8c	H	4-OH	5	86
8d	H	2-$OCH_2C_6H_5$	5	93
8e	H	3-$OCH_2C_6H_5$	6	84
8f	H	4-$OCH_2C_6H_5$	5	79
8g	H	2-$OCH_2CH_2C_6H_5$	4	93
8h	H	3-$OCH_2CH_2C_6H_5$	7	84
8i	H	4-$OCH_2CH_2C_6H_5$	7	79
8j	CH_3	2-OH	4	92
8k	CH_3	3-OH	6	84
8l	CH_3	4-OH	4	88
8m	CH_3	2-$OCH_2C_6H_5$	5	89
8n	CH_3	3-$OCH_2C_6H_5$	7	84
8o	CH_3	4-$OCH_2C_6H_5$	6	90
8p	CH_3	2-$OCH_2CH_2C_6H_5$	6	89
8q	CH_3	3-$OCH_2CH_2C_6H_5$	7	84
8r	CH_3	4-$OCH_2CH_2C_6H_5$	5	90
8s	NO_2	2-OH	4	94
8t	NO_2	3-OH	6	89
8u	NO_2	4-OH	5	84
8v	NO_2	2-$OCH_2C_6H_5$	5	87
8w	NO_2	3-$OCH_2C_6H_5$	6	90
8x	NO_2	4-$OCH_2C_6H_5$	4	92
8y	NO_2	2-$OCH_2CH_2C_6H_5$	7	87
8z	NO_2	3-$OCH_2CH_2C_6H_5$	7	90
8z$_1$	NO_2	4-$OCH_2CH_2C_6H_5$	6	92

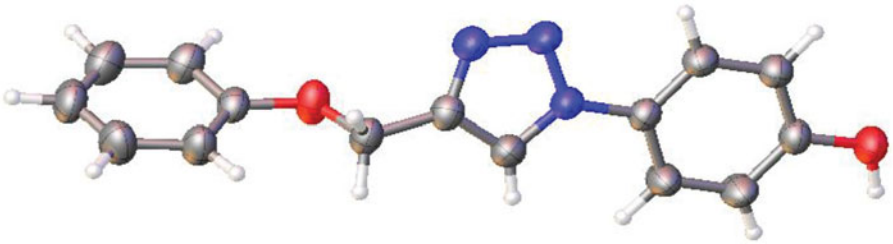


Figure 1. Crystal structure of compound **8c**.

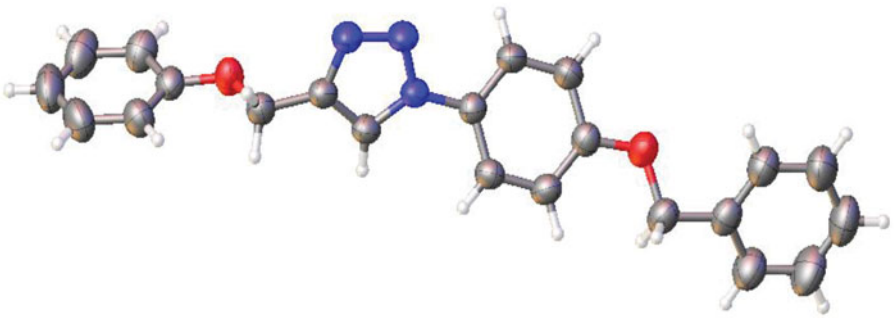


Figure 2. Crystal structure of compound **8f.**

ethyl acetate using the slow evaporation technique. Single crystal data for compounds **8c** and **8f** has been deposited in the Cambridge Crystallographic Data Center and assigned to the **CCDC 1840219** and **CCDC 1840220** numbers, respectively, which is available at www.ccdc.cam.ac.uk/conts/retrieving.html.

Experimental

The chemicals were purchased from Alfa-Aesar, Sigma-Aldrich, and used without further purification. Thin layer chromatography was used to monitor the progress of the reactions and visualized by UV light. Melting points were determined by capillary method and are uncorrected. IR spectra were recorded on a SHIMAZDU AFFINITY-I FT-IR spectrophotometer using KBr powder and the values are expressed in cm^{-1}. The ^{1}H NMR and ^{13}C NMR spectra of the synthesized compounds were recorded at 400 and 100 MHz, respectively, using Bruker Avance II 400 MHz NMR spectrometer in DMSO-d_6 solvent, and the chemical shifts were expressed in δ and coupling constants (J) in Hz. Splitting patterns were indicated as s: singlet, d: doublet, t: triplet, m: multiplet. HRMS were obtained using Waters Micromass Q-Tof Micro (ESI) spectrophotometer (Waters Corporation, MA) and values were quoted in *m/z*.

Procedure for the synthesis of 2-(4-(phenoxymethyl)-1H-1,2,3-triazol-1-yl) phenol (8a)

To a stirred solution of azido phenol[35] (**5a**) (1.0 mmol) and (prop-2-yn-1-yloxy)benzene (**3a**) (1.0 mmol) in dimethylformamide (15 mL), copper sulfate pentahydrate (0.2 mmol) and sodium ascorbate (0.5 mmol) were added. The reaction mixture was stirred for 4 h at 30–40 °C. After completion of reaction, ice cold water was added to reaction mixture. Product was precipitated, filtered and washed with ammonia solution. Crude product was dissolved in ethyl acetate and precipitated out by hexane, which was filtered and dried to get white solid product in 86% yield, mp: 152–154 °C; FTIR (KBr): 3362 (OH, str.), 3128 (C–H str., triazole ring), 3075 (C–H str., aromatic ring), 2937 (C–H str., aliphatic), 1580, 1477 (C=C str., aromatic ring), 1244, 1017 (C–O str., ether) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.23 (s, 2H, OCH_2), 6.95–7.14 (m, 5H, ArH), 7.31–7.36 (m, 3H, ArH), 7.61 (d, 1H, ArH, J= 8.0 Hz), 8.60 (s, 1H, CH-triazole), 10.59 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 61.3 (OCH_2), 115.2, 117.5, 120.0 (C_5 triazole), 121.3, 124.9, 125.74, 126.71, 130.0, 130.7, 142.9 (C_4 triazole), 150.2 (COH), 158.6 (CH_2OC); HRMS (*m/z*) calculated for $C_{15}H_{13}N_3O_2$ $[M+H]^+$: 268.101, found: 268.108.

X-ray crystallography

Single crystals of compounds **8c** and **8f** were selected and determined on a SuperNova, Single source at offset, Titan diffractometer. The crystal was kept at 293 K during data collection. Using Olex2, the structure was solved with the ShelXT[36] structure solution program using Direct Methods and refined with the ShelXL[37] refinement package using Least Squares minimization.

Conclusion

In this work, a series of 1,4-disubstituted 1,2,3-triazoles (**8a–8z$_1$**) have been synthesized through straightforward click reaction between terminal alkynes and azide. The synthesized compounds were characterized by various analytical techniques, further, the structures of synthesized compounds **8c** (CCDC 1840219) and **8f** (CCDC 1840220) were also confirmed by X-ray crystallography.

Full experimental details, ^{1}H NMR, ^{13}C NMR and HRMS data, this material can be found *via* the "Supplementary Content" section of this article webpage.

Disclosure statement

No potential conflict of interest was reported by the authors.

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