A Novel 'Domino-Click Approach' to Unsymmetrical Bis-1*H*-1,2,3-triazoles

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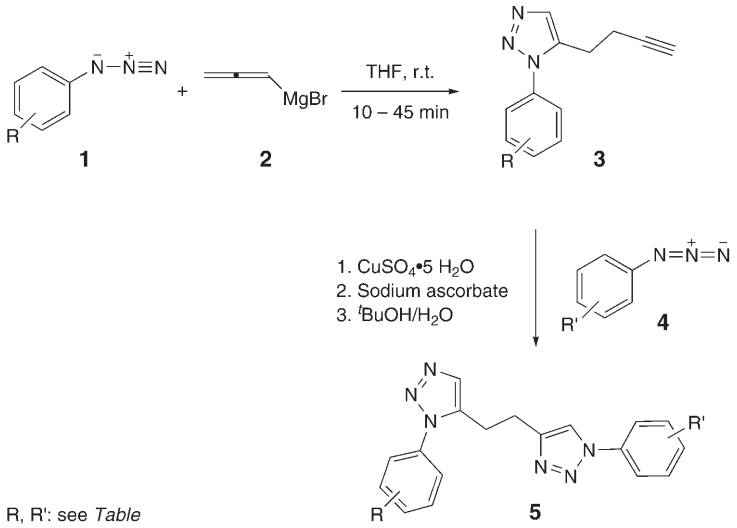
Aryl azides **1** were treated with allenylmagnesium bromide (**2**) to generate 1,5-disubstituted butynyl-1*H*-1,2,3-triazoles **3** in a domino fashion, which upon Cu^{I}-catalyzed 1,3-dipolar cycloaddition with aryl azides **4** afforded novel bis-1*H*-1,2,3-triazoles **5** in quantitative yields (*Scheme 1* and *Table*).

Introduction. – Nitrogen-containing compounds are part of the basis of life and constitute a major class of pharmacologically active compounds [1]. Amongst these, a large number of 1*H*-1,2,3-triazoles and their derivatives attracted considerable attention for the past few decades due to their chemotherapeutical value. Many 1*H*-1,2,3-triazoles, including bis-triazoles, are found to be potent antimicrobial, analgesic, anti-inflammatory, local-anesthetic, anticonvulsant, antineoplastic, antimalarial, and antiviral agents [2]. Some of them exhibited antiproliferative, anticancer activity, and several are used as DNA-cleaving agents and potassium-channel activators. Such diverse biological functions are also reported for a variety of bis-triazoles. The 'click chemistry' approach has been the most widely used method for the synthesis of libraries of a large number of biologically active molecular frameworks, particularly for the regioselective synthesis of 1*H*-1,2,3-triazoles, which involves the copper(I)-catalyzed cycloaddition reaction between azides and terminal alkynes (CuAAC). This reaction has been termed the 'cream of the crop' of 'click reactions' and has found application in various facets of drug discovery as it enables a modular approach to generate novel pharmacophores utilizing a collection of reliable chemical reactions [3]. Thus, the development of the copper(I)-catalyzed 'triazole click chemistry' has led to many interesting applications in synthetic and medicinal chemistry, molecular biology, and material science. The bioorthogonality of azide and alkynes [4] has allowed the use of their [3 + 2] cycloaddition in various biological applications including target-guided synthesis [5] and activity-based protein profiling [6]. Of particular interest would be the dimeric heterocycle-based ligands which are designed for specific target interactions. Various approaches reported for the synthesis of biologically relevant bis-triazoles include the Cu^{I}-catalyzed 1,3-dipolar cycloaddition of monoazides with diacetylenes or that of monoacetylenes with diazides. For example, the synthesis of bis-triazoles is reported by the reactions of bis(azidomethyl)benzenes with several substituted acetylenes [7]. Recently, due attention has been paid towards the synthesis and pharmacological evaluation of triazoles and bis-triazoles as potent HIV-1 protease inhibitors [8] and size-specific ligands for mRNA hairpin loops [9], respectively.

Results and Discussions. – The wide range of pharmacological activities and application potential [5][10] of triazole and bis-triazole systems prompted us to design the synthesis of a library of unsymmetrical bis-1*H*-1,2,3-triazoles **5** based on a stepwise synthetic route involving domino addition of allenylmagnesium bromide (**2**) to aryl azides **1** resulting in a serendipitous formation of 5-butynylated triazoles **3** in good yields (>70%) instead of 4-butynylated triazoles (*Scheme 1*). The 5-butynylated triazoles upon Cu^{I}-catalyzed 1,3-dipolar cycloaddition with aryl azides **4** ('click reaction') generated bis-1*H*-1,2,3-triazoles **5** in quantitative yields, which were isolated in pure form after precipitation (*Table*). The products together with the approach for their synthesis being novel, the intermediate 5-butynylated triazoles **3** and the final products, the bis-triazoles **5**, were characterized by IR, ^{1}H- and ^{13}C-NMR, and MS analysis.

Scheme 1



A plausible mechanisms for the formation of the 5-butynyltriazoles **3** *via* a *Schlenk* complex is depicted in *Scheme 2*.

In conclusion, we have developed an unprecedented, convenient strategy for the synthesis of novel, structurally diverse, biologically important bis-1*H*-1,2,3-triazoles employing a domino reaction followed by the copper-catalyzed 'click chemistry' protocol.

A. H. B. and *B. S. A.* thank the *CSIR/UGC*, New Delhi, for the award of fellowships.

Table. *Bis-triazoles Prepared by 'Domino-Click' Reaction*

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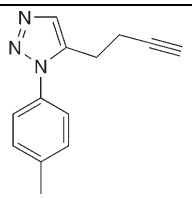
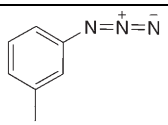
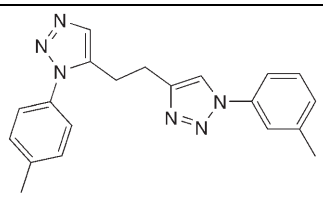
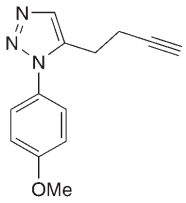
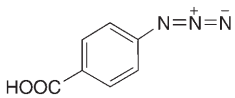
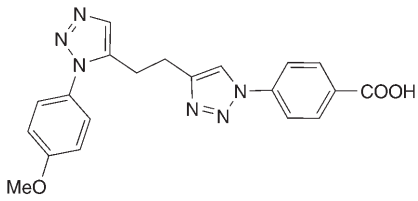
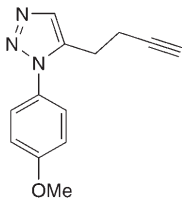
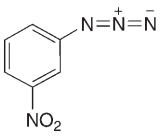
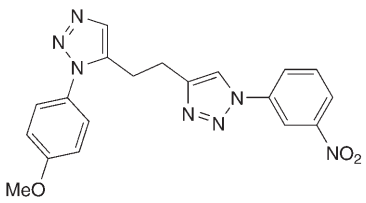
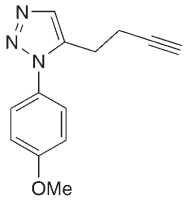
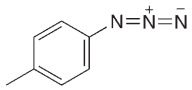
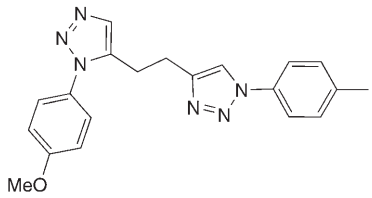
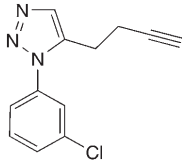
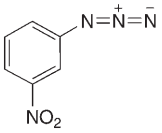
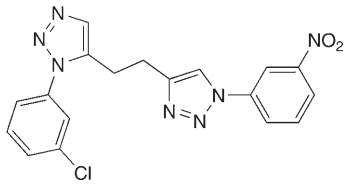
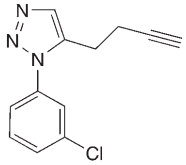
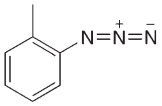
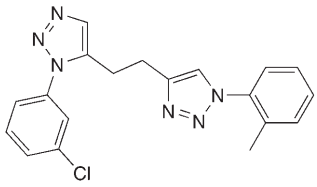
1				92
2				91[b])
3				89
4				91
5				88
6				92

Table (cont.)

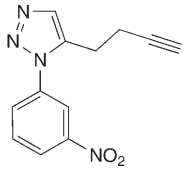
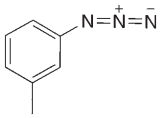
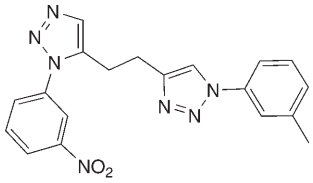
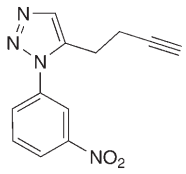
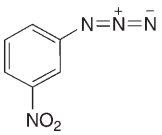
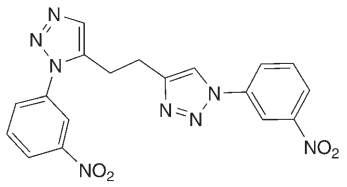
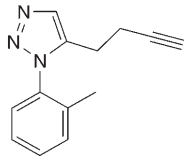
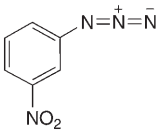
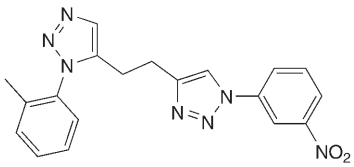
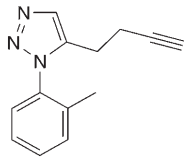
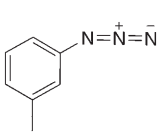
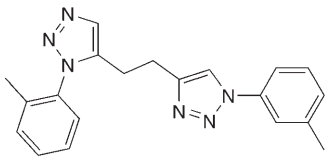
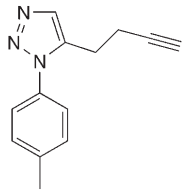
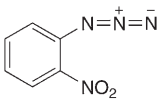
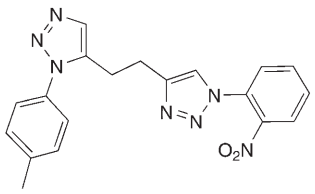
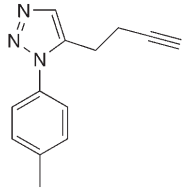
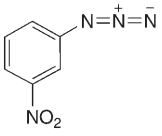
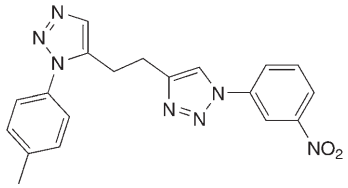
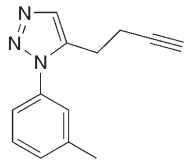
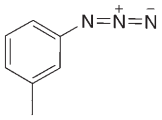
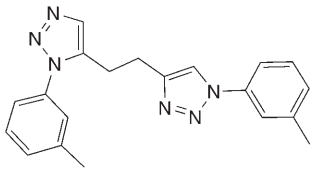
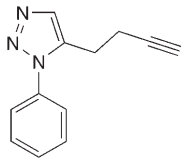
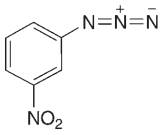
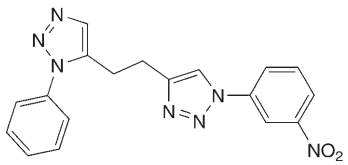
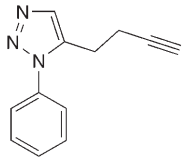
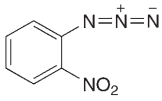
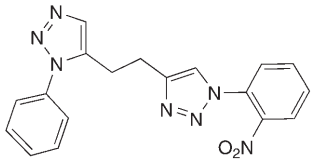
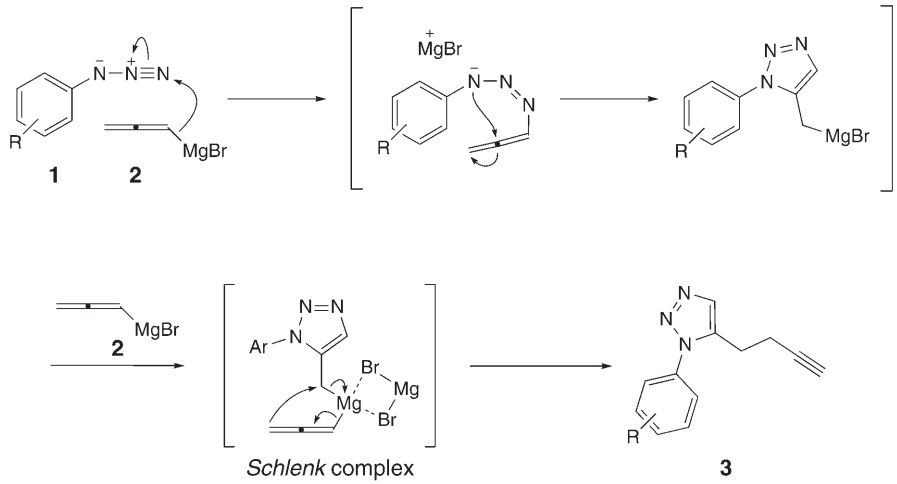
Entry	Triazole **3**	Azide **4**	Bis-triazole **5**[a])	Yield [%]
7				90
8				90
9				91
10				93
11				92
12				89
13				90[c])

Table (cont.)

Entry	Triazole **3**	Azide **4**	Bis-triazole **5**[a])	Yield [%]
14				90
15				89

[a]) All compounds are syrupy liquids/semi-solids unless otherwise mentioned. [b]) Amorphous white solid, m.p. 195–197°. [c]) Amorphous brown solid, m.p. 175–177°.

Scheme 2. *Plausible Mechanism for the Formation of 5-Butynyltriazoles* **3**



Experimental Part

General. IR Spectra: *Bruker Vector 22* apparatus; in cm^{-1} (%T). ^{1}H-NMR Spectra: *Bruker DPX* apparatus; at 200 (^{1}H) and 50 MHz (^{13}C); chemical shifts δ in ppm rel. to Me_4Si, coupling constants J in Hz. ESI-MS: *ESI-esquire 3000 Bruker Daltonics* apparatus; in *m/z*. Elemental analyses: *Yamaco-CHN CORDER-MT-3 analyzer*; in %.

General Procedure. To a suspension of Mg turnings (1.6 g, 0.66 mol, 10 equiv.) in specially dried THF with $HgCl_2$ (5 mg, 1 wt.-% of propargyl bromide) was added propargyl bromide (= 3-bromoprop-1-yne; 3.05 ml of an 80 wt.-% soln. in toluene, 4 mmol, 5 equiv.) in small portions while stirring the mixture at r.t. (note: a small grain of $HgCl_2$ is generally required to promote formation of the reagent). The mixture was

stirred at r.t. for 2 h to give a cloudy light green soln. The allenylmagnesium bromide (= bromo(propa-1,2-dien-1-yl)magnesium) generated as above was cooled to 0–5° and added dropwise to a soln. of 3-methylphenyl azide (= 1-azido-3-methylbenzene; 1 g, 0.007 mol) maintaining the temp. between 0–5°. The mixture was allowed to attain r.t., and stirring was continued at r.t. for 30 min, followed by quenching with aq. NH_4Cl soln. (10 ml) and diluting with AcOEt (50 ml). The aq. layer was extracted with AcOEt (2×20 ml), the combined org. layer dried (Na_2SO_4) and concentrated, and the crude product subjected to chromatography (silica gel (60–120 mesh), hexane/AcOEt gradient): pure 5-(but-3-yn-1-yl)-1-(3-methylphenyl)-1*H*-1,2,3-triazole **3** (*Entry 13* in *Table*) as a colorless liquid.

The 5-butynyl-1-(3-methylphenyl) triazole **3** (10 mmol) was stirred in ^{t}BuOH/H_2O 1:1 (10 ml), then $CuSO_4$ (12 mmol) and sodium ascorbate (50 mmol) were added. After 15 min, 3-methylphenyl azide (10 mmol) was added, and the mixture, was stirred for 8 h. The mixture was diluted with AcOEt, the aq. layer extracted with AcOEt (2×20 ml), the combined org. layer dried (anh. Na_2SO_4), and the solvent evaporated: crude **5**. Precipitation from hexane/AcOEt afforded pure bis-triazole **5** (90%; *Entry 13* in *Table*) as an amorphous brown solid.

Similarly, other triazoles **3** and bis-triazoles **5** were prepared (see *Table*): anal. data of a representative product of type **3** and **5** are given below.

*5-(But-3-yn-1-yl)-1-(3-methylphenyl)-1*H*-1,2,3-triazole* (*Table*, *Entry 13*): Syrupy brown liquid. IR (KBr): 3292 (2), 2923 (10), 2853 (43), 2361, 2337 (52), 2118, 1738, 1611 (35), 1592 (30), 1542, 1493, 1384, 1257, 1157, 1020 (2), 980, 877, 849, 790, 694 (53), 646. ^{1}H-NMR ($CDCl_3$): 2.05 (*t*, $J = 2.6$, 1 H); 2.44 (*s*, 3 H); 2.50 (2 H); 2.91 (*t*, $J = 7.2$, 2 H); 7.20–7.43 (*m*, 4 H); 7.72 (*s*, 1 H). ^{13}C-NMR (500 MHz, $CDCl_3$): 16.8; 20.3; 22.7; 69.6; 84.7; 121.3; 126.1; 128.3; 129.5; 131.6; 134.8; 136.6. ESI-MS: 233.9 ($[M + Na]^+$), 211.9 (78, $[M + 1]^+$). Anal. calc. for $C_{13}H_{13}N_3$ (211.27): C 73.91, H 6.20, N 19.89; found: C 74.09, H 6.10, N 20.06.

*1-(3-Methylphenyl)-4-{2-[1-(3-methylphenyl)-1*H*-1,2,3-triazol-5-yl]ethyl}-1*H*-1,2,3-triazole* (*Table*, *Entry 13*). Amorphous brown solid. M.p. 175°. IR (KBr): 3429 (23), 3138 (5), 2922 (50), 2860, 1612 (26), 1593 (29), 1549, 1494 (2), 1383, 1234 (30), 1165 (30), 1089, 1047 (5), 1017, 980, 873, 849, 786 (15), 690 (38), 618. ^{1}H-NMR ($CDCl_3$): 2.33 (*s*, 3 H); 2.43 (*s*, 3 H); 3.05 (*t*, $J = 6.2$, 2 H); 3.20 (*t*, $J = 6.2$, 2 H); 7.25–7.59 (*m*, 8 H); 7.73 (*s*, 1 H); 8.36 (*s*, 1 H). ^{13}C-NMR (500 MHz, $CDCl_3$): 19.8; 19.9; 22.9; 23.9; 117.0; 120.4; 122.2; 125.7; 129.2; 129.9; 130.4; 132.1; 135.9; 136.9; 137.8; 140.0; 146.3. ESI-MS: 367 (100, $[M + Na]^+$), 345 (43, $[M + 1]^+$). Anal. calc. for $C_{20}H_{20}N_6$ (344.42): C 69.75, H 5.85, N 24.40; found: C 69.80, H 5.82, N 24.51.

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