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An efficient one-pot synthesis of C_2-symmetric triazolophanes by copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction

R. Rajesh, G. Periyasami, R. Raghunathan *

Department of Organic Chemistry, University of Madras, Chennai 600 025, India

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ABSTRACT

A facile and efficient one-pot synthesis of 12–15-membered triazolophanes has been accomplished using CuAAC methodology. The formation of triazolophanes was confirmed by spectral analysis and the products were isolated in good yield. The effect of solvents on this reaction was also studied.

The Cu (I)-catalyzed reaction of terminal alkynes with organic azides via 1,3-dipolar cycloaddition reaction to give 1,4-disubstituted 1,2,3-triazoles is an example of a click reaction.[1,2] This reaction is well utilized for the synthesis of a variety of triazoles with high yields and regiospecificity under simple reaction conditions.[2] The efficiency and versatility of this reaction opened new opportunities in various fields such as biology,[3] medicinal chemistry,[2b] material science,[4] and polymer science.[5]

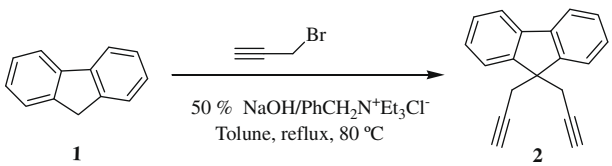
In 2002, Sharpless and Meldal independently discovered the Cu(I)-catalyzed click reaction which led to a regioselective formation of 1,4-disubstituted 1,2,3-triazole as the exclusive product, and the reaction is termed as Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC).[6] Triazoles are important class of compounds because of their interesting chemical properties, which include high aromatic stabilization, tolerance to acidic and basic as well as oxidative and reductive conditions, high dipole moment (~5 D)[7] and π-stacking interaction.[8] Moreover, this scaffold constitutes a wide range of applications in medicinal chemistry: as antiasthmatic[9], antiviral[10], antibacterial[11], anti-HIV,[12] amoebicidal, and antiallergic drugs.[13] Furthermore, triazole-containing macromolecules are rigid and have greater efficiency for binding guest molecules.[14]

In view of the above-mentioned importance of triazoles, we aimed to synthesize a series of macrocyclic compounds namely triazolophanes, using CuAAC reaction. To the best of our knowledge, only a few reports are available for the synthesis of triazolophanes.[15,16] In an elegant approach Haridas et al. recently reported the synthesis of novel triazolophanes containing peptidic and non-peptidic backbones.[15] Hence we expect that CuAAC reaction to be an efficient and convergent method for the construction of macrocyclic compounds containing triazole moiety.

The synthetic approach depicted in Schemes 1 and 2 outlines the preparation of triazolophanes. The requisite dipropargylfluorene (DPF) **2**, which was obtained from fluorene and propargyl bromide according to the literature procedure[17] (Scheme 1), was utilized as a dipolarophile for the first time.

Xylyl azide **3a** which was readily prepared from commercially available xylene dibromide on reaction with DPF **2** in the presence of CuI and DIPEA in dry acetonitrile under N_2 atmosphere at 40 °C for 12 h afforded the 15-membered triazolophane **4a** in moderate yield.[18] To improve the yield, the above-mentioned reaction was carried out in the presence of $CuSO_4{\cdot}5H_2O$ and sodium ascorbate in THF/water (1:1) at 60 °C for 12 h,[18] and the expected macrocycles were obtained in good yield (Tables 1).

The products were fully characterized by ^1H, ^{13}C, DEPT 135, 2D NMR and mass spectrometry. The ^1H NMR spectrum of the compound **4a** showed two singlets at δ 3.57 and 5.19 corresponding



Scheme 1. Synthesis of dipropargylfluorene (DPF).

* Corresponding author. Tel.: +91 44 22202811; fax: +91 44 22300488.
E-mail address: ragharaghunathan@yahoo.com (R. Raghunathan).

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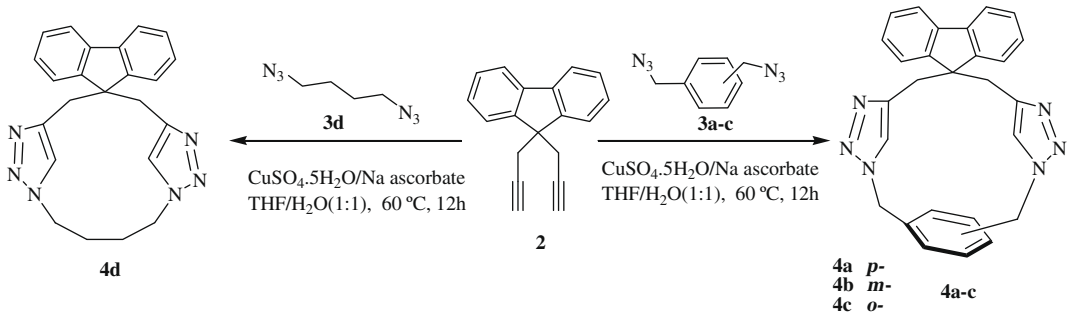

Scheme 2. Copper-catalyzed click reaction of **3a–d** with DPF.

Table 1
Click reaction of dipolar azides **3a–d** with DPF and DPA

Entry	Alkyne	Azide	Product	Yield[a] (%)	
				Method A	Method B
1	2	**3a**	**4a**	42	60
2	2	**3b**	**4b**	51	70
3	2	**3c**	**4c**	46	62
4	2	**3d**	**4d**	40	58
5	5	**3a**	**6a**	32	48
6	5	**3b**	**6b**	44	61
7	5	**3c**	**6c**	35	52
8	5	**3d**	**6d**	41	50

Method A: CuI, DIPEA, CH_3CN, N_2 atm, 40 °C, 12 h.
Method B: $CuSO_4.5H_2O$, Na ascorbate, THF/H_2O (1:1), 60 °C, 12 h.
[a] Yield of isolated product after column chromatography.

to dipropargylfluorenyl and xylyl methylene protons, respectively. The signals in ^{13}C NMR spectrum of compound **4a** exhibited two peaks at δ 34.4 and 52.9 corresponding to dipropargylfluorenyl and xylyl methylene carbons and at δ 121.6 for the triazole –CH carbon. These assignments were based on their C, H-COSY correlation data. The mass spectrum of the compound **4a** showed the molecular ion peak at *m/z*: 430.12 (M^+) which further confirmed the formation of triazolophane. The C_2-symmetric structure of the compound **4a** was assigned on the basis of ^1H and ^{13}C NMR spectra.[19] Encouraged by these results, the same reaction protocol was extended for the synthesis of 12–14-membered triazolophanes successfully by reacting **2** with various azides (Scheme 2).

Thus DPF **2** was further reacted with **3b–d** to yield 12–14-membered triazolophanes **4b–d**, respectively. Compounds **4b–d** exhibited C_2-symmetry as evidenced by ^1H and ^{13}C NMR spectroscopic data.[19] The reaction methodology was extended to dipropargylanthrone (DPA) **5** which was synthesized using the same procedure as for DPF. DPA underwent CuAAC reaction with azides **3a–d** to give 12–15-membered triazolophanes **6a–d** (Scheme 3).

The structures of the macrocycles **6a–d** were confirmed by spectral analysis. In the ^1H NMR spectrum of **6d**, the dipropargylanthrone methylene protons appeared as a singlet at δ 3.73 and –NCH_2 proton appeared as a multiplet at δ 3.81. The ^{13}C spectrum of **6d**, the triazole –CH resonated at δ 121.6 ppm. The C_2-symmetric structure of triazolophane **6d** was assigned on the basis of ^1H and ^{13}C NMR spectra.[19]

The reactions were carried out in different solvents such as *t*-BuOH, EtOH, DMSO and DMF water mixture (1:1). It was observed that the *t*-BuOH gave only poor yield, and other solvents failed to give the expected products. Of all the solvents only THF/H_2O (1:1) was proved to be the most efficient solvent system.

In conclusion, we have described an efficient one-pot synthesis of triazolophanes using Cu (I)-catalyzed 1,3-dipolar cycloaddition methodology. All the compounds were confirmed through spectral analysis. Study of biological activity and other properties of these macromolecules are currently in progress. This work describes a simple, one-pot method for the synthesis of triazolophanes using the CuAAC reaction.

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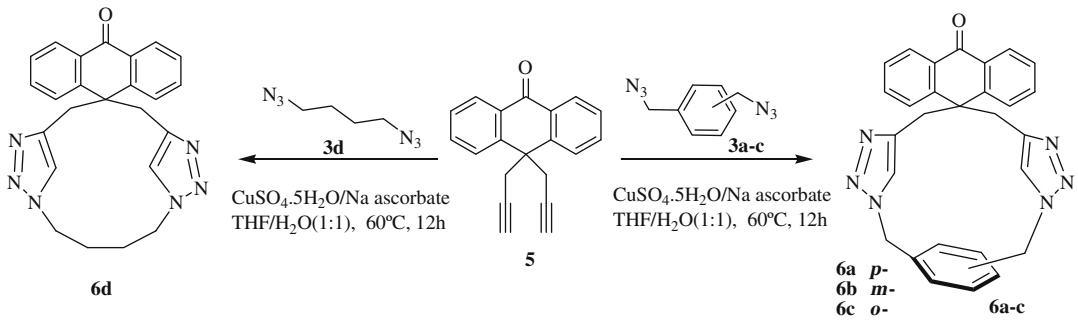

Scheme 3. Copper-catalyzed click reaction of **3a–d** with DPA.

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18. Representative procedure for the synthesis of triazolophanes **4a–d** using 'click reaction'.
    Method A: To the alkynyl compound **1a** (150 mg, 1 mmol) in dry acetonitrile (10 ml) in N_2 atm was added xylyl azide **2a** (1equiv) followed by diisopropylethylamine (DIPEA) (2.5 equiv) and CuI (3.0 equiv).The reaction mixture was stirred for 12 h at 40 °C After the completion of the reaction an aqueous solution of NH_4Cl (10 ml) was added and extracted with CH_2Cl_2. The organic layer was washed with water, and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the crude product was subjected to flash column chromatography using chloroform/methanol as eluent (9:1) to give **4a**.
    Method B: To a solution of DPF **1a** (150 mg, 0.62 mmol) and xylylazide **2a** (0.64 mmol) in THF (10 ml), H_2O (10 ml) were added $CuSO_4$ (0.24 mmol) and sodium ascorbate (0.51 mmol). The resulting solution was stirred for 12 h at 60 °C. The solvent was evaporated under vacuo and the residue was diluted with CH_2Cl_2, washed with water and brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel flash column chromatography using chloroform/methanol (9:1) to give the pure product **4a**.
19. Representative spectral data of the products.
    Compound **4a**: white solid; mp: 160–162 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.57 (s, 4H), 5.19 (s, 4H), 6.09 (s, 2H), 6.69 (s, 4H), 7.02–7.14 (m, 4H), 7.16 (d, 2H, J = 7.2 Hz), 7.34 (d, 2H, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.4, 52.9, 54.3, 119.5, 121.6, 123.8, 127.3, 127.5, 127.6, 135.1, 140.6, 143.9, 147.8. MS EI *m/z*: 430.12 (M+). Anal. Calcd for $C_{27}H_{22}N_6$: C, 75.33; H, 5.15; N, 19.52. Found: C, 75.47; H, 5.24; N, 19.65.
    Compound **4d**: white solid; mp: 165–167 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (m, 4H), 3.40 (m, 4H), 3.96 (s, 4H), 6.31 (s, 2H), 7.15–7.17 (m, 4H), 7.19–7.31 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.1, 33.7, 48.2, 52.9, 118.5, 120.8, 123.0, 126.3, 126.8, 139.4, 142.8, 147.4. MS EI *m/z*: 382.42 (M+). Anal. Calcd for $C_{23}H_{22}N_6$: C, 72.23; H, 5.80; N, 21.97. Found: C, 72.31; H, 5.69; N, 22.04.
    Compound **6d**: white solid; mp: 170–172 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.99 (m, 4H), 3.73 (m, 4H), 3.81 (s, 4H), 5.91 (s, 2H), 7.09 (m, 2H), 7.39 (d, 2H, J = 7.5 Hz,), 7.61 (m, 2H), 7.90 (d, 2H, J = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.4, 40.8, 46.9, 48.8, 121.6, 126.8, 127.1, 127.4, 132.2, 133.9, 142.7, 144.8, 182.3. MS EI *m/z*: 410.43 (M+). Anal. Calcd for $C_{24}H_{22}N_6O$: C, 70.23; H, 5.40; N, 20.47. Found: C, 70.12; H, 5.51; N, 20.58.