ACADEMIA ROMÂNĂ

Revue Roumaine de Chimie

https://www.icf.ro/rrch/

Rev. Roum. Chim.,
2026, *71*(3–4), 275–283
DOI: 10.33224/rrch.2026.71.3-4.11

A FACILE AND REGIOSELECTIVE ONE-POT SYNTHESIS OF NEW 1,4-DISUBSTITUTED 1,2,3-TRIAZOLES USING CLICK CHEMISTRY

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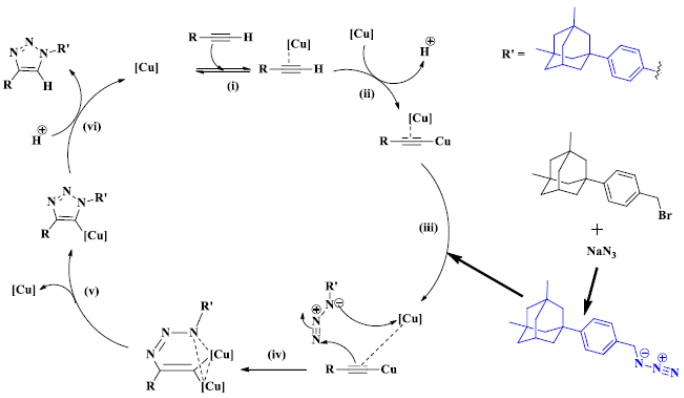
Received November 8, 2025

In this study, a series of new 1,4-disubstituted 1,2,3-triazole derivatives was efficiently synthesized from the precursor 1-(4-(bromomethyl)phenyl)-3,5-dimethyladamantane through a one-pot azidation/Click strategy. The reaction involves the *in situ* formation of the corresponding benzyl azide, followed by Cu(I)-catalyzed cycloaddition with various terminal alkynes at room temperature. This practical one-pot approach offers several advantages, including short reaction times, operational simplicity, scalability, high to excellent yields, and the use of inexpensive starting materials. The method proceeds without the need for additional additives or harsh reaction conditions, making it an attractive alternative to classical multistep protocols. The structures of all synthesized compounds were fully characterized by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy, and selected derivatives were further confirmed by mass spectrometric analysis.



INTRODUCTION

1,2,3-Triazoles have emerged as highly valuable nitrogen-containing heterocycles owing to their exceptional chemical stability and broad spectrum of applications in medicinal, biological, and materials chemistry.[1,2] Compounds incorporating the triazole ring exhibit diverse pharmacological activities, including antimicrobial,[3] antiprotozoal,[4] anti-HIV,[5] antiallergic,[6] antitubercular,[7] and anticancer activities.[8,9] Among them, 1,4-disubstituted 1,2,3-triazoles are especially attractive because of their excellent regioselectivity, metabolic stability, and favorable bioactivity profiles across diverse therapeutic targets.[10,11]

The development of click chemistry, especially the copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC),[12] has provided a convenient and powerful method for assembling triazole frameworks.[13,14] This reaction proceeds efficiently under mild conditions, offering excellent regioselectivity, high yields, and compatibility with

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various functional groups. Consequently, CuAAC has become an indispensable tool in modern synthetic and medicinal chemistry.[15,16]

The adamantyl moiety, a bulky and lipophilic structural motif, is frequently incorporated into bioactive molecules to enhance their lipophilicity, metabolic stability, and membrane permeability.[17,18] Its inclusion often leads to improved pharmacological profiles and increased biological activity.[19] Adamantane-based compounds have demonstrated antiviral, antimicrobial, and central nervous system effects, highlighting their significance in drug design.[20,21]

Despite the well-established value of both triazoles and adamantane units in medicinal chemistry, the rational design of hybrid structures often depends on the incorporation of an appropriate linker capable of modulating physicochemical and biological properties. In this context, benzyl linkers were deliberately selected as structural connectors because they provide conformational flexibility while increasing lipophilicity and enabling aromatic π–π interactions with biological targets.[22,23]

Such linkers have been reported to improve membrane permeability and reinforce binding affinity within enzyme active sites or receptor pockets, rendering benzyl-adamantane architectures promising scaffolds for further biological evaluation.

In line with this rationale, triazole-containing adamantyl benzyl derivatives have recently been explored for their antimicrobial,[24] antiproliferative,[25] and central nervous system-related activities, further supporting the design of new derivatives within this structural class.[26]

In the present study, the design of the target compounds was guided by their potential as biologically relevant scaffolds, particularly for antimicrobial and antiproliferative applications. The strategic combination of an adamantyl core, a bioactive 1,2,3-triazole ring capable of hydrogen-bonding and dipolar interactions, and a benzyl linker offering conformational adaptability and aromatic interactions was envisaged to afford hybrid structures suitable for interaction with diverse biological targets. Although biological evaluation is not reported at this stage, the synthesized compounds were conceived as promising candidates for future biological screening.

Motivated by the anticipated synergistic potential effects arising from the combination of a pharmacologically relevant adamantyl core, a triazole heterocycle, and a benzyl linker capable of fine-tuning biological interactions, and as part of our ongoing interest in developing novel adamantane–triazole hybrids, we sought to design an efficient and regioselective synthetic approach to new 1,4-disubstituted (3,5-adamantylbenzyl) -1,2,3-triazoles.

Herein, we report a convenient one-pot azidation/CuAAC protocol starting from readily accessible 1-(4-(bromomethyl)phenyl)-3,5-dimethyladamantane. The strategy involves in situ generation of the benzyl azide followed by Cu(I)-catalyzed cycloaddition with diverse terminal alkynes at room temperature, affording the desired triazole derivatives in good to excellent yields (Scheme 1). This streamlined and modular approach simplifies the synthetic sequence while improving operational efficiency, scalability, and overall practicality, providing rapid access to structurally diverse adamantane–triazole hybrids with potential medicinal relevance.

EXPERIMENTAL

General instrumentation.

Melting points were measured in open capillary tubes with an Electrothermal-9200 melting point apparatus and are uncorrected. ^{1} H NMR and ^{13}C NMR spectra were recorded using a Varian As 400 Merkur spectrometer operating at 400 MHz (^{1}H), 100 MHz (^{13}C) in $CDCl_3$ with tetramethylsilane as an internal reference. Coupling constants (*J* values) are given in hertz. High-resolution mass spectra (DIP-EI) were recorded with a QTOF Agilent 7200 instrument for the exact mass and Agilent 7890B for the GC.

General Procedure for the Synthesis of Adamantanetoluene (1)

In a round bottom flask, under argon atmosphere 1-bromo-3,5-dimethyladamantane (1 eq.) was dissolved in toluene (3.5 ml), and a catalytic amount of $InBr_3$ (5.0 mol%) was then added. After stirring for 48h at room temperature, the mixture was washed with water (3 × 10 ml) and then extracted with diethyl ether (3 × 25 ml). The gathered organic layers were dried over anhydrous $MgSO_4$ and concentrated under vacuum.

Preparation of 1,3-dimethyl-5-adamantanetoluene (1)

Yield: 70%, colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.16 (d, *J* = 8.2 Hz, 2H, $C_6H_4CH_3$), 7.02

(d, J = 8.1 Hz, 2H, $C_6H_4CH_3$), 2.22 (s, 3H, $C_6H_4CH_3$), 2.09–2.06 (m, 1H, H_{Ad}), 1.63 (d, J = 2.6 Hz, 2H, H_{Ad}), 1.42 (t, J = 8.3 Hz, 3H, H_{Ad}), 1.35–1.25 (m, 4H, H_{Ad}), 1.12–1.06 (m, 2H, H_{Ad}), 0.77 (s, 6H, $Ad(CH_3)_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ = [147.4, 135.6, 127.8, 126.7] (Ar–C), [50.3, 49.8, 44.4, 43.6, 31.4] (C_{Ad}), 28.8($2CH_3$), 21.6 (CH_3).

General Procedure for the Synthesis of Adamantyl Bromide Salts (2)

In a round bottom flask, compound (**1)** (1 g, 4.42 mmol) was added successively at room temperature to *N*-bromosuccinimide (NBS) (0.86 g, 4.86 mmol), 2,2'- azobisisobutyronitrile (AIBN) (0.018 g, 0.11 mmol), and cyclohexane (7 ml). The mixture was stirred and refluxed for 2 h. The reaction was monitored by TLC. Then, the mixture was allowed to cool at room temperature, water (30 ml) was added, and the residue was extracted with ethyl acetate (3 × 10 ml), dried over anhydrous $MgSO_4$ and concentrated under vacuum. The product was filtered in a small silica column to give the title compound.

Preparation of 1-(4-bromomethyl) Benzyl-3,5 Dimethyl Adamantane (2)

Yield: 66%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31 (s, 4H, $CH_2C_6H_4Ad(CH_3)_2$), 4.46 (s, 2H, $CH_2C_6H_4Ad(CH_3)_2$), 2.18–2.13 (m, 1H, H_{Ad}), 1.71 (d, J = 2.5 Hz, 2H, H_{Ad}), 1.50 (q, J = 12.6Hz, 5H, H_{Ad}), 1.39 (s, 3H, H_{Ad}), 1.21 (dd, J = 13.4, 11.4 Hz, 2H, H_{Ad}), 0.87 (s, 6H, $CH_2C_6H_4Ad(CH_3)_2$).^{13}C NMR (100 MHz, $CDCl_3$) δ = 151.03 (C_{Ad}), 137.32 (C), 134.76 (C), 128.74 (C), 128.46 (C), 126.25 (CH), 125.68 (CH), 125.39 (CH), 125.22 (CH), 50.76 (CH_2), [42.87, 41.54, 37.96, 34.19, 33.59, 31.44, 30.69, 29.87] CH and C_{Ad} (2 CH_3).

General Procedure for the Synthesis of 1,2,3-Triazoles 3a–f

To a 20 mL round-bottomed flask equipped with a magnetic stirrer, were charged $Cu(OAc)_2{\cdot}H_2O$ (11mg, 0.057 mmol, 5 mol%), 1,10-phenanthroline monohydrate (10 mg, 0.057 mmol, 5 mol%), and sodium L-ascorbate (224 mg, 1.14 mmol). After addition of a EtOH/H_2O mixture (4:1 v/v, 7 mL), the resulting suspension was stirred for five minutes at room temperature. Subsequently, alkyne (1.14 mmol), sodium azide (90 mg, 1.40 mmol), and **(2)** (0.16 mL, 1.40 mmol) were added to the reaction mixture, which was stirred during 18 h at room temperature. H_2O (5 mL) was added to the reaction mixture and the precipitate was filtered off, washed thoroughly with H_2O, petroleum ether, and dried under vacuum. The crude product was purified by flash column chromatography [silica gel, EtOAc–PE (1:3)].

***ethyl 1-(4-(3,5-dimethyladamantan-1-yl)benzyl)-1H-1,2,3-triazole-4-carboxylate* (3a):**

Yield: 80%, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.05 (s, 1H, H-5 triazole), 7.17 (d, J = 8.1 Hz, 2H, C_6H_4), 7.06 (d, J = 8.1 Hz, 2H, C_6H_4), 5.52 (s, 2H, N–CH_2–C_6H_4), 4.40 (q, J = 7.1 Hz, 2H, O–CH_2–-CH_3), 2.20–2.15 (m, 1H, H_{Ad}), 1.71 (d, J = 2.5 Hz, 2H, H_{Ad}), 1.50 (q, J = 12.6 Hz, 5H, H_{Ad}), 1.40 (t, J = 7.1 Hz, 3H, O–CH_2–CH_3), 1.39 (s, 3H, H_{Ad}), 1.22 (dd, J = 13.4, 11.4 Hz, 2H, H_{Ad}), 0.87 (s, 6H, $Ad(CH_3)_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.5 (C=O), 148.5 (C-4 triazole), 147.4 (C_6H_4 C–Ar), 137.0 (C-5 triazole), 135.6 (C_6H_4 C–Ar), 127.8 (C_6H_4 CH), 126.7 (C_6H_4 CH), 61.2 (O–CH_2–CH_3), 54.5 (N–CH_2–C_6H_4), [50.3, 49.8, 44.4, 43.6, 31.4] (C_{Ad}), 28.8 ($Ad(CH_3)_2$), 21.6 ($C_6H_4CH_3$), 14.3 (O–CH_2–CH_3). HRMS (ESI+): m/z $[M+H]^+$ Calc.Mass for $C_{24}H_{32}N_3O_2$ 394.2416, found. 394.2406.

***diethyl 2-(1-(4-(3,5-dimethyladamantan-1-yl)benzyl)-1H-1,2,3-triazol-4-yl)malonate* (3b)**

Yield: 72%, Green oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52 (s, 1H, H-5 triazole), 7.16 (d, J = 8.1 Hz, 2H, C_6H_4), 7.05 (d, J = 8.1 Hz, 2H, C_6H_4), 5.51 (s, 2H, N–CH_2–C_6H_4), 5.10 (s, 1H, $CH(COOEt)_2$), 4.25 (m, 4H, 2×O–CH_2–CH_3), 2.20–2.14 (m, 1H, H_{Ad}), 1.71 (d, J = 2.5 Hz, 2H, H_{Ad}), 1.50 (q, J = 12.6 Hz, 5H, H_{Ad}), 1.39 (s, 3H, H_{Ad}), 1.30 (t, J = 7.1 Hz, 6H, 2×O–CH_2–CH_3), 1.22 (dd, J = 13.4, 11.4 Hz, 2H, H_{Ad}), 0.87 (s, 6H, $Ad(CH_3)_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.0 (2C, 2×C=O), 148.0 (C-4 triazole), 147.4 (C_6H_4 C-Ar), 135.6 (C_6H_4 C–Ar), 127.8 (C_6H_4 CH), 126.7 (C_6H_4 CH), 61.5 (2×O–CH_2–CH_3), 58.0 (C-5 triazole), 54.5 (N–CH_2–C_6H_4), 52.0 ($CH(COOEt)_2$), [50.3, 49.8, 44.4, 43.6, 31.4] (CAd), 28.8 ($Ad(CH_3)_2$), 21.6 ($C_6H_4CH_3$), 14.1 (2×O–CH_2–CH_3). HRMS (ESI^+): m/z $[M+H]^+$ Calc.Mass for $C_{28}H_{38}N_3O_4$ 480.2784, found. 480.2774.

***(1-(4-(3,5-dimethyladamantan-1-yl)benzyl)-1H-1,2,3-triazol-4-yl)methylbenzoate* (3c):**

Yield: 75%, Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.10 (d, J = 7.2 Hz, 2H, C_6H_5), 7.85

(s, 1H, H-5 triazole), 7.60 (t, *J* = 7.4 Hz, 1H, C_6H_5), 7.45 (t, *J* = 7.7 Hz, 2H, C_6H_5), 7.16 (d, *J* = 8.1 Hz, 2H, C_6H_4), 7.05 (d, *J* = 8.1 Hz, 2H, C_6H_4), 5.55 (s, 2H, O–CH_2-triazole), 5.51 (s, 2H, N–CH_2–C_6H_4), 2.20–2.14 (m, 1H, $_{HAd}$), 1.71 (d, *J* = 2.5 Hz, 2H, H_{Ad}), 1.50 (q, *J* = 12.6 Hz, 5H, H_{Ad}), 1.39 (s, 3H, H_{Ad}), 1.22 (dd, *J* = 13.4, 11.4 Hz, 2H, H_{Ad}), 0.87 (s, 6H, Ad(CH_3)$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.5 (C=O), 147.4 (C_6H_4 C-Ar), 145.5 (C-4 triazole), 135.6 (C_6H_4 C-Ar), 133.5 (C_6H_5 C-para), 130.5 (C-5 triazole), 129.8 (C_6H_5 C-ortho), 128.5 (C_6H_5 C-meta), 129.0 (C_6H_5 C-ipso), 127.8 (C_6H_4 CH), 126.7 (C_6H_4 CH), 62.5 (O–CH_2-triazole), 54.5 (N–CH_2–C_6H_4), [50.3, 49.8, 44.4, 43.6, 31.4] (CAd), 28.8 (Ad(CH_3)$_2$), 21.6 ($C_6H_4CH_3$).

***(1-(4-(3,5-dimethyladamantan-1-yl)benzyl)-1H-1,2,3-triazol-4-yl)methyl 4-chloro benzoate* (3d)**

Yield: 77%, White solid . ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.00 (d, *J* = 8.5 Hz, 2H, C_6H_4Cl), 7.85 (s, 1H, H-5 triazole), 7.40 (d, *J* = 8.5 Hz, 2H, C_6H_4Cl), 7.16 (d, *J* = 8.1 Hz, 2H, C_6H_4), 7.05 (d, *J* = 8.1 Hz, 2H, C_6H_4), 5.55 (s, 2H, O–CH_2-triazole), 5.51 (s, 2H, N–CH_2–C_6H_4), 2.20–2.14 (m, 1H, H_{Ad}), 1.71 (d, *J* = 2.5 Hz, 2H, H_{Ad}), 1.50 (q, *J* = 12.6 Hz, 5H, H_{Ad}), 1.39 (s, 3H, H_{Ad}), 1.22 (dd, *J* = 13.4, 11.4 Hz, 2H, H_{Ad}), 0.87 (s, 6H, Ad(CH_3)$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.0 (C=O), 147.4 (C_6H_4 C-Ar), 145.5 (C-4 triazole), 140.5 (C_6H_4Cl C–Cl), 135.6 (C_6H_4 C–Ar), 131.0 (C_6H_4Cl), 130.5 (C-5 triazole), 129.2 (C_6H_4Cl C-ipso), 128.9 (C_6H_4Cl), 127.8 (C_6H_4 CH), 126.7 (C_6H_4 CH), 62.5 (O–CH_2-triazole), 54.5 (N–CH_2–C_6H_4), [50.3, 49.8, 44.4, 43.6, 31.4] (C_{Ad}), 28.8 (Ad(CH_3)$_2$), 21.6 ($C_6H_4CH_3$).

***(1-(4-(3,5-dimethyladamantan-1-yl)benzyl)-1H-1,2,3-triazol-4-yl)methyl 4-methyl benzoate* (3e)**

Yield: 86%, Brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.95 (d, *J* = 8.1 Hz, 2H, $C_6H_4CH_3$), 7.80 (s, 1H, H-5 triazole), 7.25 (d, *J* = 7.9 Hz, 2H, $C_6H_4CH_3$), 7.16 (d, *J* = 8.1 Hz, 2H, C_6H_4), 7.05 (d, *J* = 8.1 Hz, 2H, C_6H_4), 5.50 (s, 2H, O–-CH_2-triazole), 5.51 (s, 2H, N–CH_2–C_6H_4), 2.40 (s, 3H, C_6H_4–CH_3), 2.20–2.14 (m, 1H, H_{Ad}), 1.71 (d, *J* = 2.5 Hz, 2H, H_{Ad}), 1.50 (q, *J* = 12.6 Hz, 5H, H_{Ad}), 1.39 (s, 3H, H_{Ad}), 1.22 (dd, *J* = 13.4, 11.4 Hz, 2H, H_{Ad}), 0.87 (s, 6H, Ad(CH_3)$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.5 (C=O), 147.4 (C_6H_4 C-Ar), 145.5 (C-4 triazole), 144.5 ($C_6H_4CH_3$), 135.6 (C_6H_4 C–Ar), 130.0 ($C_6H_4CH_3$ C-ortho), 130.5 (C-5 triazole), 129.5 ($C_6H_4CH_3$ C-meta), 127.8 (C_6H_4 CH), 126.7 (C_6H_4 CH), 126.5 ($C_6H_4CH_3$ C-ipso), 62.5 (O–CH_2-triazole), 54.5 (N–CH_2–C_6H_4), [50.3, 49.8, 44.4, 43.6, 31.4] (C_{Ad}), 28.8 (Ad(CH_3)$_2$), 21.7 (C_6H_4–CH_3), 21.6 ($C_6H_4CH_3$).

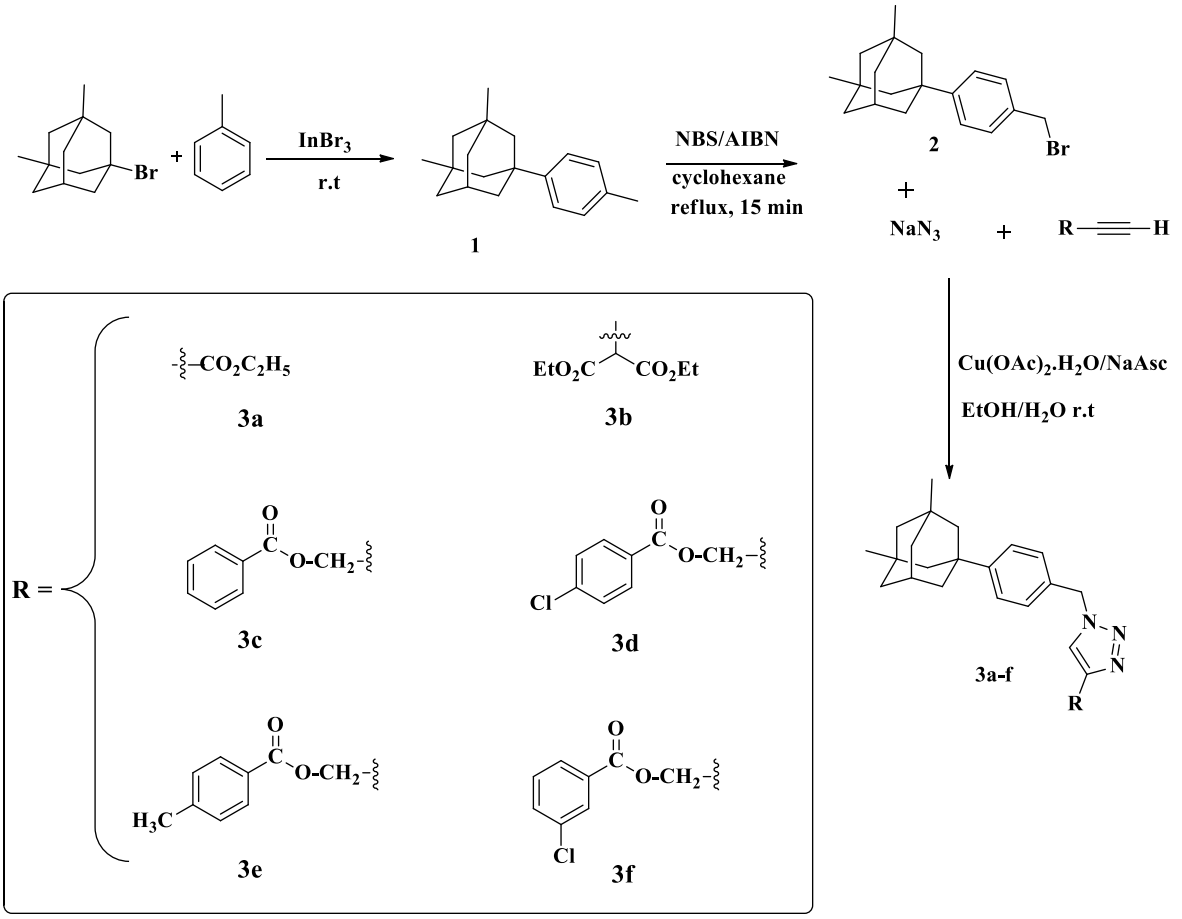
***(1-(4-(3,5-dimethyladamantan-1-yl)benzyl)-1H-1,2,3-triazol-4-yl)methyl 3-chloro benzoate* (3f)**

Yield: 79%, White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.05 (t, *J* = 1.8 Hz, 1H, C_6H_4Cl H-2), 7.95 (dt, *J* = 7.8, 1.4 Hz, 1H, C_6H_4Cl H-4), 7.85 (s, 1H, H-5 triazole), 7.55 (dt, *J* = 7.9, 1.3 Hz, 1H, C_6H_4Cl H-6), 7.40 (t, *J* = 7.9 Hz, 1H, C_6H_4Cl H-5), 7.16 (d, *J* = 8.1 Hz, 2H, C_6H_4), 7.05 (d, *J* = 8.1 Hz, 2H, C_6H_4), 5.55 (s, 2H, O–CH_2-triazole), 5.51 (s, 2H, N–CH_2–C_6H_4), 2.20-2.14 (m, 1H, H_{Ad}), 1.71 (d, *J* = 2.5 Hz, 2H, H_{Ad}), 1.50 (q, *J* = 12.6 Hz, 5H, H_{Ad}), 1.39 (s, 3H, H_{Ad}), 1.22 (dd, *J* = 13.4, 11.4 Hz, 2H, H_{Ad}), 0.87 (s, 6H, Ad(CH_3)$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.0 (C=O), 147.4 (C_6H_4 C–Ar), 145.5 (C-4 triazole), 135.6 (C_6H_4 C–Ar), 134.5 (C_6H_4Cl C-3), 133.0 (C_6H_4Cl C-1), 131.0 (C_6H_4Cl C-6), 130.5 (C-5 triazole), 128.5 (C_6H_4Cl C-4), 128.0 (C_6H_4Cl C-5), 127.5 (C_6H_4Cl C-2), 127.8 (C_6H_4 CH), 126.7 (C_6H_4 CH), 62.5 (O–CH_2–triazole), 54.5 (N–CH_2–C_6H_4), [50.3, 49.8, 44.4, 43.6, 31.4] (C_{Ad}), 28.8 (Ad(CH_3)$_2$), 21.6 ($C_6H_4CH_3$).

RESULTS AND DISCUSSION

The synthesis of the target 1,4-disubstituted 1,2,3-triazoles (**3a–f**) was accomplished through an efficient three-step sequence starting from 1-bromodimethyladamantane. Initially, indium tribromide promoted a mild and highly selective Friedel–Crafts alkylation of toluene at room temperature, yielding the *para*-substituted adamantylbenzyl intermediate (**1**) via generation of a stabilized adamantyl carbocation. Subsequent benzylic bromination of intermediate (**1**) with NBS and AIBN under refluxing cyclohexane afforded the corresponding bromide (**2**) through a selective radical chain mechanism. In the final step, compound (**2**) underwent nucleophilic substitution with sodium azide, and without isolation of the intermediate, the resulting benzyl azide directly participated in a Cu(I)-catalyzed azide–alkyne cycloaddition ($Cu(OAc)_2$/Na ascorbate) with a series of terminal alkynes, thus enabling a practical one-pot azidation/Click transformation to furnish triazoles **3a–f** in good overall yields. This

streamlined synthetic route provides a convenient, regioselective, and versatile platform for generating structurally diverse adamantyl-based triazole derivatives of potential medicinal interest.



Scheme 1 – Synthesis of 1,4-disubstituted 3,5 dimethyl1-[4-(1-adamantyl)benzyl]-1*H*-1,2,3-triazoles (**3a–f**).

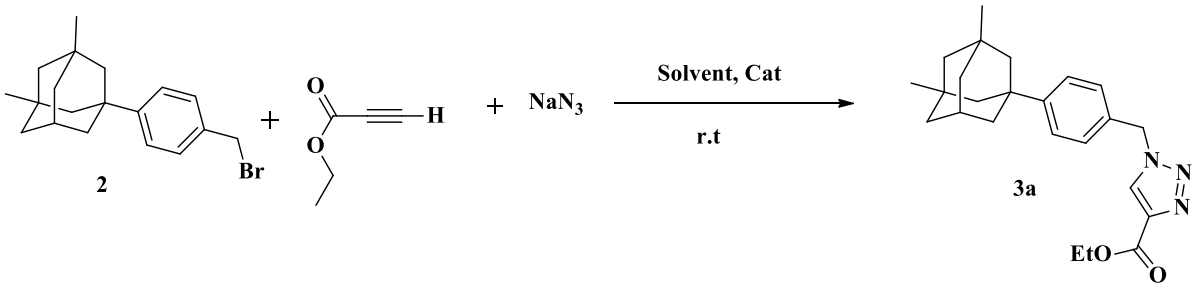
The optimization data in Table 1 identify the one-pot azidation/CuAAC conditions (Scheme 2) that maximize conversion of 1-(4-(bromomethyl)phenyl)-3,5-dimethyladamantane to triazole **3a**: entry 12 (EtOH/H_2O, $Cu(OAc)_2 \cdot H_2O$/NaAsc, 18 h, r.t.) gave the best isolated yield (80%). Two clear trends emerge. First, the oxidation state and form of the copper source matter: preformed Cu(I) salts (CuCl, CuBr, CuI; entries 1–3) afford moderate yields because they can directly catalyze the cycloaddition, whereas Cu(II) salts ($CuSO_4.5H_2O$, entry 4) perform poorly unless reduced in situ. Addition of sodium ascorbate (entries 8–12) converts Cu(II) to the active Cu(I) species and substantially improves performance, $Cu(OAc)_2.H_2O$/NaAsc in polar aprotic DMF (entry 9) approaches good yield (71%), but the best results are obtained in a protic, mixed solvent (EtOH/H_2O, entry 12).

This solvent effect can be attributed to the complementary properties of water and ethanol in the reaction mixture, which together provides a favorable protic environment that, facilitates the azidation step by improving azide solubility and promotes the subsequent CuAAC reaction, ultimately resulting in a faster and cleaner one-pot sequence.

Increasing reaction time in less optimal media (entry 6) produced only marginal gain, indicating that solvent/catalyst choice (not time) limits conversion. Lower yields with $CuSO_4.5H_2O$ alone or in CH_2Cl_2/H_2O (entries 4–6) likely reflect incomplete in-situ reduction and phase-transfer limitations, whereas poor performance in THF (entry 11) stems from limited azide solubility. Finally, common side processes (protodehalogenation, hydrolysis, or over-oxidation) are minimized under the optimized EtOH/H_2O/$Cu(OAc)_2 \cdot H_2O$/NaAsc conditions, which furnish a practical, regioselective, and operationally simple one-pot protocol; further modest improvements might be obtained by tuning

catalyst loading, alkyne stoichiometry or adding a minimal ligand to stabilize Cu(I) if desired.

The nature of the ligand is known to play a crucial role in copper(I)-catalyzed azide–alkyne cycloaddition reactions, as it can influence the stability and reactivity of the Cu(I) species. In the present study, 1,10-phenanthroline was selected as the ligand owing to its strong bidentate coordination ability, which efficiently stabilizes Cu(I) and enhances its catalytic activity under mild conditions. This ligand has been widely employed in CuAAC reactions and is known to promote high regioselectivity and reproducibility, particularly in one-pot and in situ azide generation protocols. Alternative ligands, such as bipyridine derivatives or other nitrogen-based chelating agents, were not evaluated in this work, as the main objective was to develop a simple, practical, and efficient one-pot methodology using a well-established catalytic system.



Scheme 2 – Optimization study of the one-pot protocol used for the synthesis of triazole derivative **3a**.

Table 1

Optimization of the Reaction Conditions for Synthesis of (**3a**) in One Pot

Entry	Solvent	Catalyst	time (h)	Yield (%)[a]
1	DMF	CuCl	18	73
2	DMF	CuBr	18	76
3	DMF	CuI	18	69
4	DMF	$Cu(SO)_4 \cdot 5H_2O$	18	44
5	CH_2Cl_2:H_2O	$Cu(SO)_4 \cdot 5H_2O$	18	50
6	CH_2Cl_2:H_2O	$Cu(SO)_4 \cdot 5H_2O$	24	52
7	DMF	$Cu(OAc)_2 \cdot H_2O$	18	49
8	CH_2Cl_2:H_2O	$Cu(OAc)_2 \cdot H_2O$/NaAsc	18	58
9	DMF	$Cu(OAc)_2 \cdot H_2O$/NaAsc	18	71
10	CH_3CN	$Cu(OAc)_2 \cdot H_2O$/NaAsc	18	65
11	THF	$Cu(OAc)_2 \cdot H_2O$/NaAsc	18	46
12	EtOH/H_2O	$Cu(OAc)_2 \cdot H_2O$/NaAsc	18	80

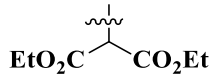
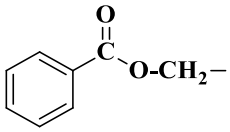
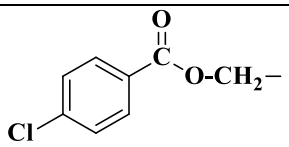
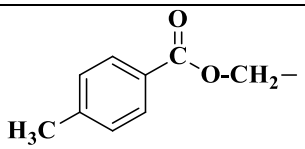
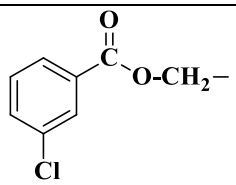
[a] Isolated yields.

With the optimized conditions in hand, the substrate scope of the one-pot azidation/CuAAC protocol was examined using a variety of terminal alkynes (Table 2). The reaction showed broad functional-group tolerance and delivered the desired 1,4-disubstituted 1,2,3-triazoles (**3a–f**) in consistently good to excellent yields ranging from 72% to 86%. Electron-deficient alkynes such as ethyl propiolate and diethyl 2-ethynylmalonate reacted smoothly, providing triazoles **3a** and **3b** in high yields, demonstrating that strong electron-withdrawing groups do not impede the cycloaddition. Alkynes bearing ester functionalities, including simple carboxylates (**3a**), malonate derivatives (**3b**), and substituted benzoates (**3c–3f**), were well tolerated under the optimized conditions, affording the desired 1,4-disubstituted 1,2,3-triazoles in good to excellent yields. These results demonstrate the excellent functional group tolerance of the protocol toward ester moieties.

Moreover, aromatic alkynes incorporating electron-neutral (**3c**), electron-donating (**3e**), and electron-withdrawing substituents (**3d, 3f**) reacted smoothly, delivering the corresponding products in 77–86% yield. The consistently high yields across all entries underscore the robustness of the optimized one-pot sequence and its efficiency in generating structurally diverse adamantyl-based triazoles from a broad range of alkyne partners.

Table 2

One-pot preparation of 1,2,3-triazoles **3a–f**

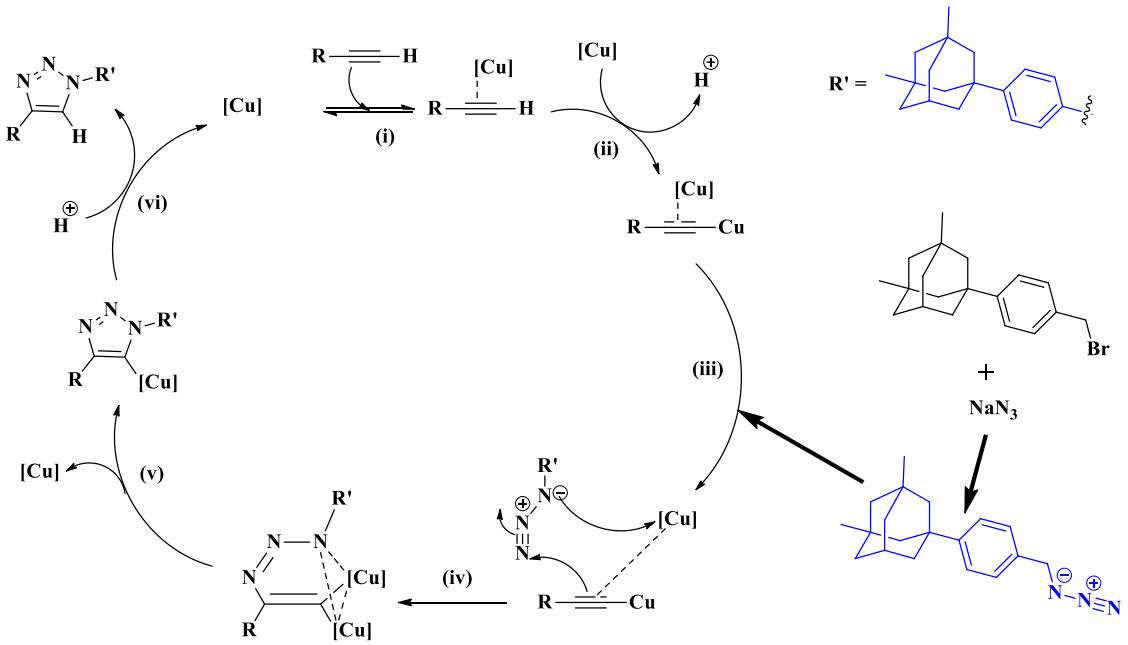
Entry	R	Compound	Time (h)	M.p. (˚C) Measured	Product (Yield)[a]
1	$-CO_2C_2H_5$	3a	18	142	80
2		3b	18	-	72
3		3c	18	-	75
4		3d	18	148	77
5		3e	18	163	86
6		3f	18	175	79

[a]Isolated yields.

Based on comparisons with earlier studies, we suggest a plausible reaction mechanism for the Cu-promoted one-pot synthesis of 1,4-Disubstituted 1,2,3-Triazole. The mechanistic foundation of the Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC) has been extensively examined since the seminal report by Sharpless and co-workers in 2002.[27] Subsequent theoretical and experimental studies, particularly those by Fokin and collaborators,[28,29] demonstrated that the participation of two copper centers markedly enhances the reaction rate and lowers the activation barrier. These findings firmly established the dinuclear Cu(I) pathway as the most plausible mechanistic model and underpin the interpretation adopted in Scheme 3.

In the present one-pot transformation, the benzylic bromide is first converted into the corresponding benzyl azide, which immediately enters the CuAAC catalytic cycle. The combination of $Cu(OAc)_2 \cdot H_2O$ and sodium ascorbate efficiently generates Cu(I) in situ under mild hydroalcoholic conditions, ensuring a continuous supply of the active catalytic species throughout the process. The ensuing cycloaddition proceeds through the established bimetallic pathway. Cu(I) first activates the terminal alkyne through π-coordination, followed by deprotonation to form the copper acetylide. A second Cu(I) center subsequently coordinates to the azide, yielding a μ-alkynyl–μ-azido dicopper intermediate that brings both reactants into an optimal geometric arrangement. This preorganization enables formation of the characteristic six-membered dicopper metallacycle, which then collapses to afford the 1,4-disubstituted triazolide intermediate. Final protonolysis releases the neutral triazole and regenerates both Cu(I) centers.

The overall efficiency, regioselectivity, and mild operating conditions of this one-pot process are consistent with the dinuclear Cu(I) mechanism. Although mononuclear alternatives may operate under strongly coordinating environments, the ligand-free aqueous ethanol system used here strongly favors the cooperative bimetallic pathway.



Scheme 3 – Plausible Mechanism for the One-Pot Synthesis of 1,4-Disubstituted 1,2,3-Triazoles Using Click Chemistry.

CONCLUSION

In summary, we have developed an efficient, regioselective, and operationally simple one-pot strategy for the synthesis of new 1,4-disubstituted 1,2,3-triazoles derived from 1-(4-(bromomethyl)phenyl)-3,5-dimethyladamantane using a sequential azidation/CuAAC process. The optimized EtOH/H_2O–$Cu(OAc)_2$/NaAsc system enabled smooth conversion under mild conditions, providing consistently high yields while avoiding additional additives or transition-metal preactivation steps. This methodology demonstrated broad functional-group tolerance toward a variety of terminal alkynes, affording the desired triazoles (**3a–f**) in 72–86% yields and highlighting its robustness and synthetic versatility. Given the pharmacological relevance of both adamantane and the triazole motif, the described one-pot protocol offers a valuable platform for the rapid generation of structurally diverse derivatives with potential medicinal interest. Future work will focus on expanding the substrate scope and evaluating the biological activities of the synthesized compounds.

Acknowledgements. This work was supported by the Ministry of higher education and scientific research (Algeria), and DGRSDT (DIRECTORATE GENERAL FOR SCIENTIFIC RESEARCH AND TECHNOLOGICAL DEVELOPMENT) for financial support.

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