Green microwave versus conventional synthesis, crystal structure of 1-(4-(Benzothiazol-2-yl)piperazin-1-yl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)ethenone and HS-Analysis

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ABSTRACT

This study reports an efficient eco-friendly microwave assisted synthesis of 1-(4-(benzothiazol-2-yl)piperazin-1-yl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)ethanone (4) through the click cyclocondensation of 2-azido-1-(4-(benzod[d]thiazol-2-yl)piperazin-1-yl)ethanone (3) with phenyl acetylene. The synthesis was carried out under optimized copper catalyst copper(II) sulfate pentahydrate/sodium ascorbate, t-BuOH/water (1:1, v/v) to afford the regioselective 1,4-disubstituted 1,2,3-triazole isomer. The reactions were greatly accelerated using microwave irradiation. The new designed 1,2,3-triazole was fully characterized by IR, NMR, MS spectral data and X-ray diffraction. The crystal structure of 4 demonstrated a conventional chair conformation for the piperazinering. Interesting Hirshfeld Surface Analysis (HAS) was conducted showing clear agreement with the XRD analysis.

ARTICLE HISTORY

Received 4 October 2019
Revised 27 March 2020
Accepted 28 March 2020

KEYWORDS

Benzothiazole; 1,2,3-triazole; microwave irradiation; X-ray structure; HAS

1. Introduction

The benzothiazole cores are considered as important classes of nitrogen heteroarenes and possess substantial biological related properties, for instance anticonvulsant [1], antimicrobial [2], antidiabetic [3], analgesic [4] and anti-cancer [5].

1,2,3-Triazoles rings are well recognized as versatile synthons for the design of novel bioactive molecules [6]. In addition, the 1,2,3-triazole centred derivatives have gained paramount interest due to their significant pharmaceutical activities including antimicrobial [7], antioxidant [8], antitubecular [9], anti-inflammatory [10], antiproliferative [11] and anticancer [12]. Recent research in drug design has been directed to the building of single molecular frameworks of enhanced biological activity through molecular hybridization approach by the combination of two or more pharmacophores with complementary medicinal potenitalities [13,14]. Recently, we have synthesized novel hybrid compounds comprising of benzothiazole and 1,2,3-triazole moieties dotted with promising biological properties [15,16].

The Cu(I) catalyzed 1,3-dipolar cycloaddition reaction of azides with alkynes group has reported as the most effective and practical approach for the regioselective production of 1,2,3-triazoles with 1,4-disubstituted [17,18].

Microwave irradiation (MW) technique well known as useful approach for assisting organic synthesis in term of reduction in reaction time as well the improvement in reaction yields compared to classical synthesis [19,20].

Based on the above observations and by taking the advantages of MW, we herein report the click synthesis of novel benzothiazole based 1,2,3-triazole moiety by both conventional and microwave irradiation as a valuable addition to our interest on the development of new polyheterocyclic compounds [21–29]. Microwave technique has been used in this study because it improves reaction rates, environmentally friendly and operational simplicity [30]. Studies shows that molecules exposed to electromagnetic radiation are extremely agitated as solvents arrange in a line and re-align with the electric-field, generating a concentrated internal heat. Nonpolar solvents such as benzene, diethyl ether and toluene are microwave inactive, while polar solvents such as methanol, CH2Cl2, DMF, H2O and acetonitrile are microwave-active because polar solvents are capable to align themselves with the electric-field leading to fast heating and hence offering several advantages over traditional heating [31].
2. Results and discussion

2.1. Synthesis

The target 1,2,3-triazole tagged benzothiazole ring has been prepared started from 2-(piperazin-1-yl)benzo[d]thiazole (1) through multi-step synthesis as outlined in Scheme 1.

Thus, base-assisted acylation of compound 1 with bromoacetyl bromide at RT for 6 h, in the presence of triethylamine and dichloromethane, gave the bromoacetyl piperazine derivative 2 in 89%, which upon azidolysis for overnight, furnishing the desired compound (3) in 91%. A significant reduction in reaction time has been achieved when the MW has been used as an alternative source of energy (See experimental section).

The formation of the piperazine acetyl derivative 2 has been clearly evidenced by the spectroscopic characterization data. The IR spectrum revealed the disappearing of the piperazine amino group and the appearance of the acetyl carbonyl (C=O) group at 1685 cm\(^{-1}\). Moreover, its \(^1\)H NMR supported the structure of compound 2 by the absence of NH proton. A diagnostic singlet has been observed at 3.33 ppm attributed to the acetyl methylene protons (CH\(_2\))CO. All remaining protons were resonated at their respected chemical shift (See experimental section). The \(^13\)C NMR spectrum revealed two distinct signals assigned to the C = O and CH\(_2\) carbons at \(\delta\)C 169.7 and \(\delta\)C 59.8 ppm, respectively, attributed to the acetyl side chain of compound 2.

The resulted azide 3 has been used as precursor in the synthesis of the desired compound 4. Thus, copper assisted cycloaddition reaction for 1,3-dipolar of the azide 3 with phenyl acetylene using sodium ascorbate in DMSO/H\(_2\)O (1:1) required stirring for 8 h at 80 °C and afforded selectively the 1,4-disubstituted benzothiazole-piperazine-1,2,3-triazole hybrid 4 in 86% yield. When the azide–alkyne click synthesis has been assisted by microwave irradiation, the click product 4 was prepared in 94% yield within 8 min, without any change in regioselectivity.

2.2. Crystallography and Hirshfeld Surface Analysis (HAS)

The structure of the newly designed 1,2,3-triazole 4 was in accordance with its NMR (\(^1\)H and \(^13\)C) and mass spectra. Its \(^1\)H NMR spectrum (Figure 1) recorded a singlet in the aromatic region at \(\delta\)H 8.47 ppm attributable to the triazolyl proton. In addition, the \(^13\)C NMR spectrum (Figure 2) showed the presence of new aromatic signals related to the phenyl carbons, which supported the success of the click reaction. Table 1.

The structure of 4 is further confirmed by X-ray diffraction analysis. An ORTEP perspective view of compound 4 is shown in Figure 3. It is a linear molecule with the piperazine ring occupying approximately the centre of the molecule. As anticipated, the ring in piperazine prefers, energetically a chair conformation. The N atoms electron pairs are in trans-configuration to each other in the solid state with both the organic substituents equatorial. In a similar compound, the piperazine ring acted as a strong coordinating species where the piperazine ring adopted boat conformation forming a 1:1 metal chelate complex [32]. In the planar triazolyl ring, the N4 = N5 and N5 = N6 bond lengths, 1.337(2) and 1.311(3) Å respectively, may be well compared with the standard N = N bond distance of 1.24 Å and with the single bond length of 1.40 Å [32,33]. Selected bond angles (°) and distances (Å) for 4 are given in Table 2. The sulfur atom is in the cis configuration with respect to the oxygen atom of the molecule falling within 0.26 Å of the plane (C1-C12, N1-N3, S1 and O1). The interplanar angle between (C14-C21, N4-N6) and (C1-C8, N1, N2, S) planes is 85.22°. This explains the poor π ... π stacking arrangement between the molecules. The partial packing in Figure 2 sheds more light on the twisted molecule preventing better π ... π stacking. Figure 4.

Figures 5 and 6 elucidates the molecular interactions in compound 4 with the aid of HASA [35]. HASA reveals the presence of red areas around some atoms (Figure 5a), indicating strong internal and external interactions. The H−H contact shows the highest interaction in compound 4, (42.8%). The C−H/H−C interaction acts as a secondary interaction with no sharp peaks (24.0%). While H−N/N−H contact shows a normal role (14.0%), yet it is more important than O−H/H−O contact (6.7%) with total di+ de = 2.3 Å (Figure 3). The H−S contact is obtained mainly by the middle peaks (with tips at di + de = 2.4 Å), (7.9%). Interestingly, no distinct C−C interaction is obtained for 4, (0.7%), indicating weak π−π stacking. Thus, HAS findings are in agreement with XRD analyses. In general, the shortest di and de combination is 2.25 Å.

3. Experimental section

3.1. General

Melting points were performed on a variable heater (Stuart) melt-temp apparatus and are uncorrected. The Infrared spectra were recorded in a KBr matrix using a Perkin-Elmer 1430 series FT-IR spectrometer. NMR spectra were done using an Advance Bruker spectrometer at 100 MHz (for \(^13\)C) and 400 MHz (for \(^1\)H). Tetramethylsilane was used as the internal reference. The assignment of the EI mass spectra has been achieved using a Finnigan MAT 95XL spectrometer. Elemental analyses were done using GmbH-Vario EL III Elemental Analyzer.

Synthesis and characterization of compound 2

Conventional Method (CM). (10 mmol) of Bromoacetyl bromide was added slowly (dropwise) to a solution of compound 1 (10 mmol) in dichloromethane
Scheme 1.

(30 mL), in the presence of containing triethylamine (10 mmol) at 0 °C. The reaction mixture was stirred at RT for 6 h, and the solid thus formed was separated, washed with water and recrystallized from ethanol to yield compound 2 as white pellets in 89% yield. Anal. Calcd (found) for C₁₃H₁₄BrN₃OS: C 45.89 (45.77); H 4.15 (4.22); N 12.35 (12.25).

**Microwave Method (MWI).**
A mixture of (1 mmol) of compound 1, triethylamine (1 mmol), bromoacetyl bromide (10 mmol) and dichloromethane (5 mL) in a sealed borosilicate glass container equipped with silicone top, was treated by MW for 4 min. The obtained reaction mixture was treated as shown in the conventional method to afford compound 2 in 95% yield.

**Synthesis and characterization of compound 3,**

**Conventional Method (CM).** (10 mmol) of compound 2 was mixed with sodium azide (NaN₃) (12 mmol) in acetone:water (100 mL) in (4:1) was stirred at room temperature (RT) for a day. Evaporation of the excess of solvent

**Table 1.** Crystallographic data for compound 4.

| Chemical formula | C₂₁H₂₀N₆OS |
|------------------|-------------|
| Formula weight   | 536.24      |
| Crystal system, space group | Monoclinic, P₂₁/c |
| Temperature (K)  | 296         |
| a, b, c (Å)      | 17.9403 (4), 10.1828 (2), 10.8856 (3) |
| β (°)            | 90.934 (1)  |
| V (Å³)           | 1988.34 (8) |
| Z                | 4           |
| Radiation type   | Cu Kα       |
| μ (mm⁻¹)         | 1.00        |
| Crystal size (mm)| 0.24 × 0.16 × 0.01 |
| Diffractometer   | Bruker X8 PROSPECTOR APEX2 CCD |
| Rint             | 0.034       |
| Number of parameters | 276         |
| Number of restraints | 81          |

**Figure 1.** $^1$H NMR spectrum of compound 4.
Figure 2. $^{13}$C NMR spectrum of compound 4.

Figure 3. ORTEP perspective view and labelling scheme of compound 4 with 30% probability level. The piperazine ring, S1 and N1 atoms are shown as the major components of the disordered parts (both fully resolved). The ratio of major:minor configurations in the piperazidinering refined to 0.626:0.374, and in the thiazole ring the ratio was 0.932:0.068.
Table 2. Selected bond distances and angles (Å, °)

| Bond                  | Distance   | Angle       |
|-----------------------|------------|-------------|
| S1A—C1                | 1.7163(14) | N2—C8A—C9A | 111.1(5)    |
| S1A—C7                | 1.767(2)   | N3—C9A—C8A | 108.5(4)    |
| O1—C12                | 1.224(2)   | N3—C10A—C11A| 107.3(5)    |
| N1A—C6                | 1.386(2)   | N2—C11A—C10A| 110.1(5)    |
| N1A—C7                | 1.272(3)   |             | 107.27(17)  |
| N2—C7                 | 1.357(3)   | N6—C15—C16 | 122.49(16)  |
| N2—C8A                | 1.458(7)   | C14—C15—C16| 130.03(16)  |
| N2—C11A               | 1.467(8)   | C14—C15     | 1.368(3)    |
| N3—C12                | 1.340(3)   | C8A—C9A     | 1.495(10)   |
| N3—C9A                | 1.478(4)   | C10A—C11A   | 1.527(10)   |
| N3—C10A               | 1.502(4)   | N6—N5—N4    | 107.01(15)  |
| N4—N5                 | 1.337(2)   | N5—N6—C15   | 109.30(15)  |
| N4—C13                | 1.445(2)   | C2—C1—S1A   | 128.55(9)   |
| N4—C14                | 1.330(2)   | C6—C1—S1A   | 111.44(9)   |
| N5—N6                 | 1.311(3)   | N1A—C6—C1   | 113.32(13)  |
| N6—C15                | 1.354(3)   | N1A—C6—C5   | 126.60(13)  |
| C12—C13               | 1.516(3)   | N1A—C7—S1A  | 115.75(17)  |
| C1—S1A—C7            | 87.60(9)   | N1A—C7—N2   | 125.02(18)  |
| C7—N2—C8A            | 118.7(3)   | N2—C7—S1A   | 119.22(14)  |
| C7—N2—C11A           | 119.9(4)   | O1—C12—N3   | 122.96(19)  |
| C8A—N2—C11A          | 113.8(5)   | O1—C12—C13  | 120.26(18)  |
| C12—N2—C9A           | 124.6(2)   | N3—C12—C13  | 116.78(16)  |
| C12—N3—C10A          | 118.3(2)   | N4—C12—C13  | 111.14(15)  |
| C9A—N3—C10A          | 111.4(3)   | N4—C14—C15  | 105.67(15)  |
| N5—N4—C13            | 120.49(15) | C14—N4—C13  | 128.76(15)  |

Figure 4. The crystal partial packing of 4 showing the distance between calculated centroids. Hydrogen atoms are omitted for clarity using Mercurypackage [34]. The distances between the centroids are 5.959 and 5.933 Å left to right respectively.

under reduced pressure, filtration, washing with water and recrystallization from ethanol gave compound 3 as white pellets in 91% yield. Anal. Calcd (found) for C13H14N6OS: C 51.64 (51.73); H 4.67 (4.60); N 27.80 (27.74).

Microwave Method (MWI). A mixture (1 mmol) of compound 2, sodium azide (NaN3) (1.2 mmol) and acetone:water (10 mL) in (4:1) in a sealed borosilicate glass container equipped with silicone top, was treated by MW for 6 min. The reaction mixture was processed as shown above to afford compound 3 in 96% yield.

Synthesis and characterization of 4

**Conventional Method (CM).** A solution (11 mmol) of sodium ascorbate and copper sulfate (8 mmol) in water (10 mL) was added with stirring to a solution of phenylacetylene (10 mmol) and benzothiazole azide 3 (10 mmol) in DMSO (10 mL). Then, the reaction mixture was heated at 80 °C for 8 h. The reaction was periodically monitored by TLC. The reaction mixture was poured on crushed ice and the precipitate thus formed was filtered, washed with saturated solution of ammonium chloride and recrystallized from ethanol to afford the 1,2,3-triazole 4 as colourless needles in 86% yield.

**Microwave Method (MWI).** A mixture (1 mmol) of phenylacetylene, sodium ascorbate (1.1 mmol), copper sulfate (0.8 mmol), benzothiazole azide 3 (1 mmol), DMSO and water (5 mL) in a sealed borosilicate glass container equipped with silicone top, was treated by MW for 8 min. The obtained reaction mixture was treated as described in the conventional method to afford the 1,2,3-triazole 4 in 94% yield.

Analytical and physical data for compounds 2, 3 and 4 are given in Table 3.

In summary, we have reported a facile, fast and convenient green microwave-assisted click protocol for the production of new benzothiazole-piperazine-1,2,3-triazole hybrid. The preparation has the advantage of eco-friendly, excellent yield and significant reduction in...
reaction time. We hope that the convenience of this procedure will spur the investigation of the useful applications of the title compound.

3.2. Crystallography

Single Crystal XRD: X-ray diffraction measurements were collected at 296 K, on a Bruker X8 PROSPECTOR APEX2 CCD with a microfocus source (Cu Kα radiation). The absorption correction used was SADABS2014/5 (Bruker, 2014/5) [36–38]. \( wR^2_{\text{int}} \) was 0.0977 before and 0.0514 after correction. The Ratio of minimum to maximum transmission is 0.3526. The \( \lambda/2 \) correction factor is 0.00150. The scaling software applied was for multi-scan corrections. The structure was determined by intrinsic phasing methods with the SHELXT [39,40]. Full-matrix least-squares refinement against \( F^2 \) and Fourier calculations and were performed with the programme SHELXL [39,40]. Mercury package was used in this study to obtain centroids, angles and distances calculation [34].
Selected crystal parameters and data for compounds 2, 3 and 4.

Acknowledgment

We wish to thank Dr David L. Hughes from the University of East Anglia in the U.K. for useful discussion on the crystallographic aspects of this paper.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Table 3. Physical and analytical data for compounds 2, 3 and 4.

| Comp. No. | M.P. °C | IR (v, cm⁻¹) | ¹H NMR, ppm | ¹C NMR, ppm | EL MS (m/z) |
|-----------|---------|--------------|-------------|-------------|------------|
| 2         | 88–90   | 3045 (arCH), 2920 (alCH), 1685 (C = O), 1615 (C = N), 1570 (C = C) | 2.67 (4H, t, J = 4 Hz, 2x NC H2), 3.33 (2H, s, C2(CBr)2), 3.57 (4H, t, J = 4 Hz, 2x NC H2), 7.05–7.09 (1H, m, Ph–H), 7.26–7.30 (1H, m, Ph–H), 7.47 (1H, d, J = 8 Hz, Ph–H), 7.77 (1H, d, J = 8 Hz, Ph–H) | 47.9, 51.0, 58.0, 59.8 (CH2); 118.5, 121.1, 121.2, 125.9, 130.3, 152.4, 160.8, 169.7 (Ph–C, C = N, C = O) | 339.00 (M⁺) |
| 3         | 148–150 | 3070 (arCH), 2930 (al CH), 2170 (N2), 1690 (C = O), 1620 (C = N), 1560 (C = C) | 4.07–4.33 (3H, m, 4x NC H2), 4.22 (2H, s, CH2N2), 7.09–7.11 (1H, m, Ph–H), 7.27–7.31 (1H, m, Ph–H), 7.49 (1H, d, J = 8 Hz, Ph–H), 7.80 (1H, d, J = 8 Hz, Ph–H) | 40.7, 43.3, 47.6, 49.7 (CH2); 118.7, 121.2, 121.4, 126.0, 130.3, 152.2, 166.1, 167.9 (Ph–C, C = N, C = O) | 302.10 (M⁺) |
| 4         | 188–189 | 3070 (ar CH), 2925 (al CH), 1680 (C = O), 1615 (C = N), 1580 (C = C) | 3.63–3.74 (2H, m, 4x NC H2), 5.62 (2H, s, CH2CO), 7.09–7.13 (1H, m, Ph–H), 7.29–7.36 (2H, m, Ph–H), 7.44–7.52 (2H, m, Ph–H), 7.81 (1H, d, J = 8 Hz, Ph–H), 7.88 (1H, d, J = 8 Hz, Ph–H), 8.47 (1H, 1,2,3-triazole–CH) | 40.9, 43.5, 47.5, 47.7, 50.8 (CH2); 118.7, 121.2, 121.4, 125.0, 126.0, 127.7, 128.8, 130.4, 130.7, 146.1, 152.2, 164.5, 168.0 (Ph–C, C = N, C = O) | 404.19 (M⁺), 21050653. |
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