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Synthesis of a Novel 2-((4,5-Diphenyl-4*H*-1,2,4-triazol-3-yl)thio) acetaldehyde as a Bisulfite Adduct

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Abstract: The scope of the current work was to synthesize an *S*-alkylated 1,2,4-triazole-3-thiol derivative. Synthesis was carried out in two steps: in the first step, 4,5-diphenyl-4*H*-1,2,4-triazole-3-thiol was *S*-alkylated using a halogenated acetal and cesium carbonate. In the second step, several acetal deprotection procedures were tested, and the aldehyde obtained was isolated as a bisulfite adduct. The structures of the new compounds were characterized by FT-IR, 1D, and 2D NMR spectroscopic methods.

Keywords: 1,2,4-triazole-3-thiol; *S*-alkylation; acetal deprotection; bisulfite adduct

1. Introduction

The chemistry of 1,2,4-triazoles and their substituted and fused derivatives has received considerable attention in the last decades due to their economic importance, including as compounds with biological activity [1,2]. This pharmacological potential has already been valued in some drugs that contain the 1,2,4-triazole scaffold, such as Fluconazole, Alprazolam, and many more. The number and nature of the substituents or of the fused heterocycles allow a wide range of biological activities of 1,2,4-triazoles, some of them being: antianxiety, antimicrobial, antimycotic, anticancer, diuretic, antifungal, and many more. Due to their usefulness, the developments in the medicinal chemistry of 1,2,4-triazoles are constantly reviewed, at a rate of several reviews per year.

In the present work, our scope was to synthesize some 1,2,4-triazole thiol derivatives containing biologically important functional groups [3]: acetal and aldehyde (isolated as bisulfite adduct).

2. Results and Discussion

Several methods are available for the synthesis of 1,2,4-triazole thiols. Some of them involve: carboxylic acid chloride reactions with thiosemicarbazide (or a substituted derivative) followed by thermal cyclization of the obtained intermediary [4–6]; acyl halide reaction with lead (II) thiocyanate and hydrazine hydrate [7]; or thermolysis of thiosemicarbazones [8].

1,2,4-Triazole thiols can be further functionalized by *S*-alkylation using different reagents. The most common methods use different activated halogenated compounds in basic medium [9–11].

In the literature, there are many reported methods for acetal synthesis [12]. For our purposes, we chose to use a reagent that already had the acetal functional group for the *S*-alkylation of 1,2,4-triazole thiol. The *S*-alkylation of 4,5-diphenyl-4*H*-1,2,4-triazole-3-thiol was performed using a modified procedure from the literature [13].

Acetals can be converted to the corresponding aldehydes using different reagents and conditions [12], mainly Brønsted and Lewis acids, used in catalytical amounts or in excess.

For isolation and purification, the bisulfite method is known [14,15]. By reacting the aldehyde with sodium bisulfite, an α-hydroxy sulfonic acid is obtained as sodium salt, and

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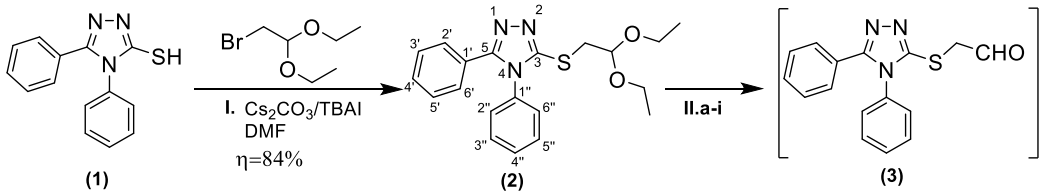
thus the aldehyde can be isolated from the reaction mixture. The bisulfite adduct can be purified by recrystallization, and the aldehyde functional group can be regenerated later.

Taking into consideration the data from the literature, we conducted the synthesis as follows.

1. In the first step, 1,2,4-triazole-3-thiol (**1**) was alkylated using 2-bromo-1,1-diethoxyethane (bromoacetaldehyde diethyl acetal) in basic medium provided by cesium carbonate, in 84% yield. The reaction follows a nucleophilic substitution mechanism via the sulfur atom. The resulting *S*-alkylated intermediary (**2**) was isolated and characterized using spectroscopic methods.
2. The obtained acetal (**2**) was deprotected by using various reagents and conditions. For the preliminary analysis, we used TLC or ^{1}H-NMR. TLC indicated whether the starting material was consumed, while the ^{1}H-NMR analysis showed the absence or presence of the aldehydic proton. The aldehyde was separated from the reaction mixture by conversion into its bisulfite adduct. The resulting α-hydroxy sulfonic acid sodium salt (**4**) was isolated and characterized.

The involved reactions are presented in Scheme 1.



Scheme 1. Synthesis scheme for the novel compounds (**2**) and (**3**).

In Table 1, all the tested methods for acetal deprotection of **2** are listed.

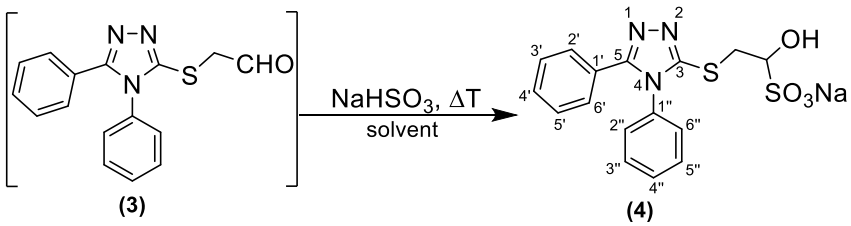
Table 1. Methods tested for the acetal deprotection of **2**.

No.	Method	Conversion, %	Ref.
1.	I_2, acetone, r.t., and reflux	n.o. [a]	[16]
2.	CF_3COOH, DCM, r.t., and reflux	100	[17]
3.	concd. HCl, THF-H_2O, reflux	100	[18]
4.	$Na_2S_2O_4$, THF-H_2O, reflux	n.o.	[19]
5.	$FeCl_3/SiO_2$, acetone, r.t.	n.o.	[20]
6.	$HClO_4/SiO_2$, EtOH 96%-H_2O, r.t.	n.o.	[21]
7.	$HClO_4/SiO_2$, THF-H_2O, reflux	n.o.	-
8.	TsOH, acetone, r.t.	n.o.	[22]
9.	HCOOH 80%, r.t.	27	-
10	HCOOH 98%, r.t.	47	[23]

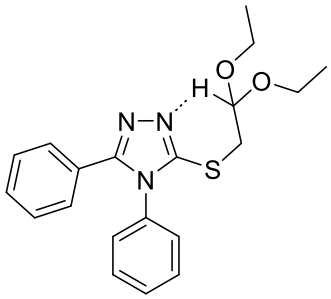
Note: [a]. n.o. = not observed.

In Scheme 2, the isolation of intermediary aldehyde (**3**) as a bisulfite adduct (**4**) is presented.

As can be seen from Table 1, the deprotection of diethyl acetal **2** failed when attempted with catalytical amounts of Lewis acids (entries 1 and 5) and strong Brønsted acids (entries 6–8), or under reducing conditions (entry 4). We hypothesize a hydrogen bond between the acetal H and 2-N of the pyrazole ring (structure **5**). This interaction would lessen the partial positive charge on the acetal carbon, rendering it less electrophilic, and thus significantly reducing the reaction rate.



Scheme 2. Isolation of aldehyde (**3**) as a bisulfite adduct (**4**).



(5)

When employing strong protic acids in excess, acetal **2** was converted quantitatively (entries 2 and 3). Concentrated hydrochloric acid in THF-water was very effective, as the reaction reached completion in less than 1 h. Trifluoroacetic acid in dichloromethane required approximatively 1 day to achieve complete conversion. In both cases, though, aldehyde **3** could not be observed in the crude reaction product by ^{1}H NMR analysis. We suspect that under these conditions or while in storage, aldehyde **3** undergoes further reactions, e.g., self-condensation or oxidation, to form other, unidentified products.

The desired product was isolated as its bisulfite adduct **4** when the reaction was conducted in formic acid 98%. Aldehyde **3** was also identified in the reaction mixture from the reaction performed in formic acid 80% by ^{1}H NMR analysis. Had this procedure been applied in methods two and three, it is possible that adduct **4** could also have been isolated in these cases.

3. Materials and Methods

The reagents used were purchased from commercial sources and used as received. 4,5-diphenyl-4*H*-1,2,4-triazole-3-thiol was synthesized earlier in our laboratory following the modified procedure from the literature [24–26].

The ^{1}H-NMR, ^{13}C-NMR, and ^{15}N-NMR spectra were recorded on Bruker Avance III 500 MHz and Bruker Fourier 300 MHz spectrometers. Chemical shifts (δ) were measured in ppm and coupling constants (*J*) in Hz. Samples were dissolved in $CDCl_3$ and DMSO-*d*6. TMS was used as an internal standard.

IR spectra were recorded on a Jasco FT/IR-410 spectrophotometer (Jasco Corporation, Tokyo, Japan) in KBr pellets.

Melting points were measured on a Böetius PHMK apparatus (Veb Analytik, Dresden, Germany) and were uncorrected.

TLC analysis was performed on 60 F_{254} silica gel plates from Merck using hexane-ethyl acetate = 1:1 (*v*/*v*) as eluent. The samples were withdrawn and applied onto the plates using the Pintea device [27].

4. Experimental

*4.1. Synthesis of 3-((2,2-Diethoxyethyl)thio)-4,5-diphenyl-4H-1,2,4-triazole (**2**)*

In a round-bottom flask equipped with a reflux condenser, thermometer, and magnetic stirring, 4,5-diphenyl-4*H*-1,2,4-triazole-3-thiol (1.393 g, 5.5 mmol) together with Cs_2CO_3 (1.792 g, 5.5 mmol) and tetrabutylammonium iodide (2.03 g, 5.5 mmol) were partially

dissolved in 25 mL of DMF (white suspension). The reaction mixture was kept under argon atmosphere and was stirred for 30 min at room temperature, and then it was cooled to 0 °C.

2-Bromo-1,1-diethoxyethane **2** (0.985 g, 5 mmol) was added dropwise to the reaction mixture under stirring. Stirring was continued for 2.5 h at 0 °C, and a pink coloration of the suspension was observed. The reaction mixture was stirred at room temperature for 12 h, after which it was heated to 60 °C for 3 h. The yellow-colored suspension was poured into 100 mL of distilled water under stirring.

The obtained mixture was then extracted with 3 × 20 mL of ethyl acetate, and the organic extract was washed with 9 × 10 mL of 5% NaOH. The obtained solution was dried over anhydrous Na_2SO_4, and the solvent was evaporated.

Next, 1.566 g of slightly yellow powder was obtained; the isolation yield was 84%, and the melting point was: 125–127 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 7.50–7.46 (m, 3H, 2″-H, 6″-H, 4′-H); 7.41–7.39 (m, 2H, 2′-H, 6′-H); 7.32–7.31 (t, 1H, J_m = 1.35 Hz, J_o = 7.35 Hz, 4″-H); 7.28–7.22 (m, 4H, 3′-H, 5′-H, 3″-H, 5″-H); 4.85 (t, 1H, J = 5.4 Hz, -C<u>H</u>-CH_2-); 3.73–3.68 (m, 2H, O-C<u>H_{2a}</u>-CH_3); 3.62–3.58 (m, 2H, -O-C<u>H_{2b}</u>-CH_3); 3.43 (d, 2H, -S-CH_3); 1.20 (t, 6H, 2 × CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 155.0 (3-C); 152.8 (5-C); 134.2 (1″-C); 129.9 (2″-C, 6″-C); 129.8 (4′-C); 129.6 (4″-C); 128.4 (3′-C, 5′-C); 128.1 (2′-C, 6′-C); 127.3 (3″-C, 1″-C); 126.6 (1′-C); 101.2 (-CH_2-<u>C</u>H-O); 62.8 (-O-CH_2 -); 35.3 (-S-CH_2); 15.2 (-CH_3); FT-IR (cm^{-1}): 3057, 2975, 2928, 1593, 1475, 773, 696.

Elemental analysis for $C_{20}H_{23}N_3O_2S$ Calcd. (%): C, 65.02; H, 6.27; N, 11.37; S, 8.68. Found (%): C, 65.0; H, 6.25; N, 11.32; S, 8.65.

*4.2. Synthesis of 2-((4,5-Diphenyl-4H-1,2,4-triazol-3-yl)thio)acetaldehyde (**3**)*

4.2.1. Method A

In a round-bottom flask, 3-((2,2-diethoxyethyl)thio)-4,5-diphenyl-4*H*-1,2,4-triazole (0.185 g, 0.5 mmol) was added together with 5 mL of 80% formic acid. The obtained solution was stirred, and then it was poured over 20 mL of distilled water. Then, the mixture was extracted with 3 × 10 mL of ethyl acetate, after which the organic extract was dried over anhydrous sodium sulfate. The solvent was evaporated, and the preliminary ^{1}H-NMR analysis showed that the hydrolysis reaction occurred with a conversion of 27%.

4.2.2. Method B

In a round-bottom flask, 3-((2,2-diethoxyethyl)thio)-4,5-diphenyl-4*H*-1,2,4-triazole (0.185 g, 0.5 mmol) was added together with 5 mL of 98% formic acid. The obtained solution was stirred for 1 h, and then it was poured over 20 mL of distilled water. Then, the mixture was extracted with 3 × 10 mL of ethyl acetate, after which the organic extract was dried over anhydrous sodium sulfate. The solvent was evaporated, and the preliminary ^{1}H-NMR analysis showed that the hydrolysis reaction occurred with a conversion of 47%.

*4.3. Synthesis of Sodium 2-((4,5-Diphenyl-4H-1,2,4-triazol-3-yl)thio)-1-hydroxyethane-1-sulfonate (Bisulfite Adduct) (**4**)*

The obtained residue (method **B**) was extracted in 2 × 10 mL of dichloromethane and washed with 10 mL of water. The solvent was evaporated, and then sodium bisulfite (0.097 g, 0.9 mmol) was added, together with 0.5 mL of distilled water, 2 mL of ethyl acetate, and 2 mL of 96% ethanol. The mixture was heated to 40 °C for 1 h, after which a white precipitate formation could be observed. The precipitate was separated from the mixture by vacuum filtration and then washed on filter with 10 mL of absolute ethanol.

Next, 66 mg of white powder was obtained: ^{1}H NMR (DMSO-*d*6, 300 MHz) δ (ppm): 7.55–7.53 (m, 3H, 2′-H, 6′-H, 4″-H); 7.42–7.30 (m, 7H, 3′-H, 5′-H, 2″-H, 3″-H, 6″-H); 6.03 (d, l, 1H, -OH); 4.15–4.12 (m, l, 1H, -CH_2-C<u>H</u>); 3.77 (dd, 1H, J_1 = 2.66 Hz, J_2 = 12.86 Hz, S-C<u>H_{2a}</u>-CH-); 3.21 (dd, 1H, J_1 = 10.40 Hz, J_2 = 12.86 Hz, -S-C<u>H_{2b}</u>-CH-); ^{13}C NMR (DMSO-d6, 75 MHz); δ (ppm): 154.6 (3-C); 152.9 (5-C); 134.3 (1′-C); 130.4 (4′-C); 130.3 (3′-C, 5′-C); 130.1 (4″-C); 128.9 (3″-C, 5″-C); 128.3 (2′-C, 6′-C); 128.2 (2″-C, 6″-C); 127.1 (1″-C); 81.6 (-CH_2-<u>C</u>H); 36.0 (-S-<u>C</u>H_2); FT-IR (cm^{-1}): 3429, 3062, 1592, 1499, 1450, 774, 696.

Elemental analysis for $C_{16}H_{14}N_3NaO_4S_2$ Calcd. (%): C, 48.11; H, 3.53; N, 10.52; S, 16.05. Found (%): C, 48.08; H, 3.51; N, 10.46; S, 16.02.

All spectra are reported in the Supplementary Materials.

5. Conclusions

We synthesized a novel 2-((4,5-diphenyl-4*H*-1,2,4-triazol-3-yl)thio)acetaldehyde (**3**) as a bisulfite adduct (**4**) by deprotecting its acetal, 3-((2,2-diethoxyethyl)thio)-4,5-diphenyl-4*H*-1,2,4-triazole (**2**), using several methods reported in the literature. Formic acid (98%) proved to be the most suitable reagent for acetal deprotection.

Supplementary Materials: The following supporting information can be downloaded. Figure S1: ^{1}H NMR spectrum of the compound (**2**), Figure S2: ^{13}C NMR spectrum of the compound (**2**), Figure S3: ^{13}C DEPT135 spectrum of the compound (**2**), Figure S4: COSY ^{1}H-^{1}H spectrum of the compound (**2**), Figure S5: HSQC ^{1}H-^{13}C spectrum of the compound (**2**), Figure S6: HMBC ^{1}H-^{13}C spectrum of the compound (**2**), Figure S7: ^{1}H NMR spectrum of the compound (**4**), Figure S8: ^{13}C NMR spectrum of the compound (**4**), Figure S9: ^{13}C DEPT135 spectrum of the compound (**4**), Figure S10: COSY ^{1}H-^{1}H spectrum of the compound (**4**), Figure S11: HSQC ^{1}H-^{13}C spectrum of the compound (**4**), Figure S12: HMBC ^{1}H-^{13}C spectrum of the compound (**4**), Figure S13: FT-IR spectrum of the compound (**2**), Figure S14: FT-IR spectrum of the compound (**4**).

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