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Short Note

(±)-2-{[4-(4-Bromophenyl)-5-phenyl-4*H*-1,2,4-triazol-3-yl]sulfanyl}-1-phenyl-1-ethanol

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Abstract: The novel racemic secondary alcohol (±)-2-{[4-(4-bromophenyl)-5-phenyl-4*H*-1,2,4-triazol-3-yl]sulfanyl}-1-phenyl-1-ethanol (**12**) has been successfully synthesized through *S*-alkylation of 4-(4-bromophenyl)-5-phenyl-4*H*-1,2,4-triazole-3-thiol (**10**) in alkaline medium with 2-bromo-1-phenylethanone followed by reduction of the corresponding ketone **11**. All the synthesized compounds were characterized by IR, 1D (^{1}H, ^{13}C, DEPT135) and 2D (^{1}H-^{1}H, ^{1}H-^{13}C and ^{1}H-^{15}N) NMR spectroscopy, elemental analysis and HRMS spectrometry.

Keywords: 1,2,4-triazole-3-thiol; *S*-alkylation; secondary heterocyclic alcohol; racemic

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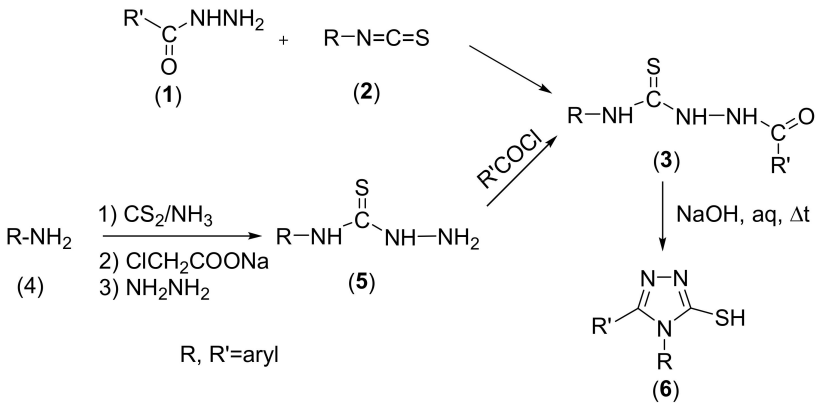
1. Introduction

Triazoles are an important class of compounds due to their numerous biomedical applications [1], such as antibacterial activity [2,3], antifungal [4] anticancer [5,6], antioxidant activity and anticonvulsant effects [7]. Grafting different substituents on the heterocyclic ring leads to a variation of the type of biological activity and the intensity with which it manifests itself [8]. The recent literature reveals that the presence of 4,5-disubstituted-4*H*-1,2,4-triazole-3-thiol moiety in chemical compounds is associated with numerous biological properties such as antimicrobial [9–13], anti-inflammatory [9] and antifungal [13] activities.

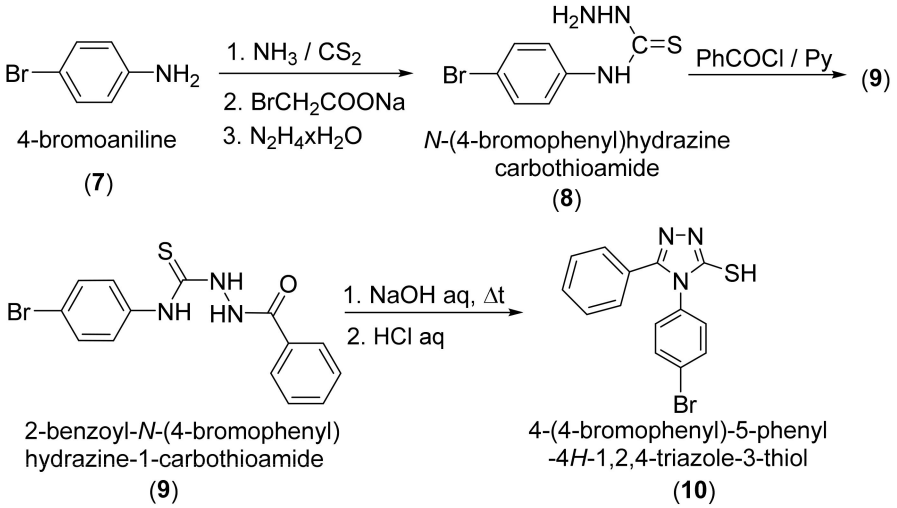
The general method of synthesis of 4,5-disubstituted-4*H*-1,2,4-triazole-3-thiols **6** is carried out by cyclization of the corresponding 2-acyl-*N*-(4-aryl)hydrazine-1-carbothioamides **3** [14,15]. The required 2-acyl-*N*-(4-aryl)hydrazine-1-carbothioamides **3** can be obtained by reaction of the appropriate carboxylic acid hydrazides **1** with (aryl)isothiocyanates **2** [16,17] or by a one-pot reaction starting from an aromatic amines **4** by successive reaction with carbon sulphide, sodium chloroacetate and hydrazine with the intermediate obtaining of *N*-(aryl)hydrazinecarbothioamides **5** [18,19], followed by their acylation with acyl chlorides (Scheme 1).



Scheme 1. Synthetic route to 4,5-disubstituted-4*H*-1,2,4-triazole-3-thiols.

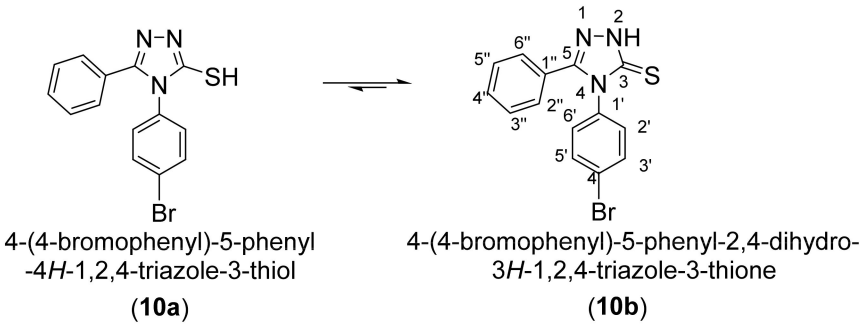
2. Results and Discussion

4-(4-Bromophenyl)-5-phenyl-4*H*-1,2,4-triazole-3-thiol (**10**) was synthesized starting from 4-bromoaniline according to the literature methods (Scheme 2). The *S*-alkylation of the triazole **10** was performed with 2-bromo-1-phenylethanone in the presence of cesium carbonate [11,16] followed by the reduction of the corresponding ketone **11** with sodium borohydride to give the secondary alcohol **12** [20,21] (Scheme 2).



Scheme 2. Synthetic route to 4-(4-bromophenyl)-5-phenyl-4*H*-1,2,4-triazole-3-thiol.

Theoretically 4-(4-bromophenyl)-5-phenyl-4*H*-1,2,4-triazole-3-thiol (**10**) can have two tautomeric forms: the thiol form **10a** and the thione form **10b**. As a result, alkylation in a basic medium can occur in fact as *S*-alkylation at the tautomeric form **10a** or as *N*-alkylation at the tautomeric form **10b** (Scheme 3).

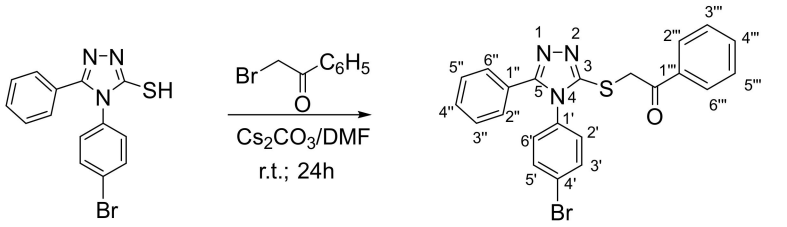


Scheme 3. Tautomeric equilibrium of 4-(4-bromophenyl)-5-phenyl-4*H*-1,2,4-triazole-3-thiol (**10**).

The corresponding ^{1}H NMR and ^{13}C NMR spectra confirmed that the tautomeric equilibri is confirmed by the deshielded signals of the 2-N-H proton at 14.11 ppm and of the 3-C carbon atom at 168.9 ppm which corresponds to a thione-type (C=S) carbon atom.

Following alkylation using cesium carbonate as a base in *N*,*N*-dimethylformamide, it has been observed that the alkylation occurs exclusively at the thiol group as *S*-alkylation [22] (Scheme 4). This is observed from 2D NMR spectroscopic analysis by analyzing the couplings over two or three bonds in the HMBC spectrum, as well as by the shift of the signal of the triazole carbon 3-C atom to a lower δ value at 152.0 ppm, corresponding to a thiol (C-SH)-type carbon atom. The alkylation is proved by the existence of a ^{1}H NMR signal at 4.98 ppm corresponding to the methylene proton (S-CH_2) and the ^{13}C NMR signal at 193.0 ppm corresponding to the carbonyl carbon atom (C=O) from the ketone (**11**). The 2D ^{1}H-^{15}N HMBC spectrum does not show the cross-peak over two bonds between the 2-N carbon atom and the methylene protons (-CH_2) that could have been observed in the case

of *N*-alkylation, which confirms that *S*-alkylation has occurred. In the case of *S*-alkylation the long-range coupling over 4 bonds between the 2-N atom and the methylene protons is not observable.



4-(4-bromophenyl)-5-phenyl -4*H*-1,2,4-triazole-3-thiol

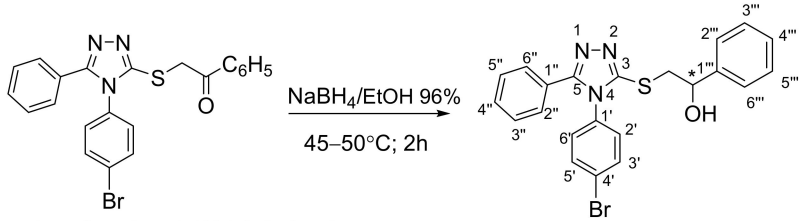
(**10**)

2-{[4-(4-bromophenyl)-5-phenyl-4*H*-1,2,4-triazol-3-yl]thio}-1-phenylethan-1-one

(**11**)

Scheme 4. Synthetic route to 2-{[4-(4-bromophenyl)-5-phenyl-4*H*-1,2,4-triazol-3-yl]thio}-1-phenylethan -1-one (**11**).

Reduction of the carbonyl group to the secondary alcohol group was accomplished with sodium borohydride in ethanol. Secondary alcohol **12** was obtained in a yield of 57.0% after recrystallization from ethanol (Scheme 5).



2-{[4-(4-bromophenyl)-5-phenyl-4*H*-1,2,4-triazol-3-yl]thio}-1-phenylethan-1-one

(**11**)

2-{[4-(4-bromphenyl)-5-phenyl-4*H*-1,2,4-triazol-3-yl]thio}-1-phenyl-1-ethanol

(**12**)

Scheme 5. Synthetic route to (±)-2-{[4-(4-bromophenyl)-5-phenyl-4*H*-1,2,4-triazol-3-yl]thio}-1-phenyl-1-ethanol (**12**).

From the correlative ^{1}H-^{15}N HMBC spectra the signal for the 4-N nitrogen atom in all the synthesized compounds could be identified, by its coupling over three bonds with hydrogen atoms in the *ortho* positions of the phenyl ring attached to this atom. This long-range coupling was very useful in the assignment of the corresponding ^{1}H NMR signals for the *ortho* protons on the phenyl ring bound to the 4-*N* nitrogen atom. The reduction of ketone **11** to secondary alcohol **12** is evidenced from the ^{1}H NMR spectrum by the doublet at 4.94 ppm attributed to the hydroxyl proton (OH), the multiplet at 5.20–5.18 ppm attributed to the methine proton (CH) and the doublets of doublets at 3.47 and 3.62 respectively attributed to the two diastereotopic protons of the methylene group (S-CH2). The ^{13}C NMR spectrum shows the disappearance of the deshielding signal at 193.0 ppm corresponding to the carbonyl carbon atom and the appearance of the signal at 73.3 ppm attributed to the methine carbon atom (CH-O).

The secondary alcohol **12** has two diastereotopic protons at the methylene group which appear in the ^{1}H NMR spectrum at different δ values as two distinct doublets of doublets. This is specific for a methylene group attached to an asymmetric carbon atom. From the ^{1}H-^{13}C HMBC spectrum, the long-range coupling over three bonds of the methylene diastereotopic protons with the 3-C triazole carbon atom is observed, thus further confirming the *S*-alkylation.

In conclusion we obtained two novel compounds that have not yet been reported in the literature, 2-{[4-(4-bromophenyl)-5-phenyl-4*H*-1,2,4-triazol-3-yl]thio}-1-phenylethan-1-one

(**11**) and (±)-2-{[4-(4-bromphenyl)-5-phenyl-4*H*-1,2,4-triazol-3-yl]thio}-1-phenyl-1-ethanol (**12**) whose structures were confirmed by 1D and 2D NMR spectroscopy.

3. Materials and Methods

The chemical reagents were purchased from commercial sources and used in the various syntheses with no further purification. Melting points were determined on a Böetius PHMK (Veb Analytik. Dresden, Germany) melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded as KBr disks on a Jasco FT/IR-410 spectrometer (JASCO Corporation, Tokyo, Japan). NMR spectra were recorded on a Bruker AVANCE III 500 MHz spectrometer (Bruker BioSpin GmbH, Rheinstetten, Germany), in DMSO-d_6 and $CDCl_3$ using TMS as an internal standard for protons and carbons. Chemical shifts are reported in ppm units and the coupling constants are given in Hz. High resolution MS (HRMS) spectra were recorded on a Bruker Maxis II QTOF spectrometer (Bruker Daltonics, Bremen, Germany) with electrospray ionization (ESI) in positive mode. The compounds have been dissolved in acetonitrile. MS spectra processing and isotope pattern simulations were performed with Compass Data Analysis V.4.4 (Bruker Daltonics).

*3.1. NMR Characterization of 4-(4-Bromophenyl)-5-phenyl-4H-1,2,4-triazole-3-thiol (**10**)*

^{1}H NMR (500 MHz, DMSO-d_6) δ(ppm): 14.18 (s, 1H, -NH); 7.70 (dt, 2H, *J* = 8.7 Hz, *J* = 2.0 Hz, 2′-H, 6′-H,); 7.43 (tt, 1H, *J* = 7.2 Hz, *J* = 1.34 Hz, 4′-H); 7.39–7.32 (m, 6H, 2″-H, 6″-H, 3″-H, 5″-H, 3′-H, 5′-H);

^{13}C NMR (125 MHz, DMSO-d_6) δ(ppm): 168.9 (3-C); 150.9 (5-C); 139.7 (1′-C); 132.3 (2′-C, 6′-C); 130.8 (3′-C, 5′-C); 130.3 (4″-C); 128.5 (3″-C, 5″-C); 128.3 (2″-C, 6″-C); 125.5 (1″-C); 122.5 (4′-C);

^{15}N NMR (50 MHz, DMSO-d_6) δ(ppm): 183.1 (4-N); 275.6 (1-N).

*3.2. Synthesis of 2-{[4-(4-Bromophenyl)-5-phenyl-4H-1,2,4-triazol-3-yl]sulfanyl}-1-phenylethan-1-one (**11**)*

In a round bottom flask 4-(4-bromophenyl)-5-phenyl-4*H*-1,2,4-triazole-3-sulfanyl (**10**, 2.11 g, 0.006 mol) was solubilized in DMF (41 mL). After complete dissolution of the compound, cesium carbonate (1.03 g, 0.0038 mol) was added in small portions. After 15 min. a solution of 2-bromo-1-phenylethanone (1.26 g, 0.006 mol) in DMF (20 mL), was slowly dropped over the reaction mass and then allowed to stir for approximately 24 h. The crude reaction was precipitated in distilled water. Compound **11** was purified by recrystallization from ethanol to give 1.75 g (61% yield) of a white powder pure product. M.p. 152–153 °C. TLC: Rf = 0.51 (*n*-hexane/ethyl acetate, 3:7). FT-IR (KBr, cm^{-1}): 758 ($\gamma_{sk.ar}$), 759 ($\gamma_{sk.ar}$), 1492 ($\nu_{Sk.ar}$), 1578 ($\nu_{Sk.ar}$), 1682 ($\nu_{C=O}$), 2915 ($\nu^{as}{}_{CH2}$), 3058 (ν_{CarH}), 3089 (ν_{CarH}). ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 8.04 (d,2H, *J* = 7.4 Hz, 2‴-H, 6‴-H); 7.65–7.60 (m, 3H, 3′-H, 5′-H, 4‴-H); 7.50 (t, 2H, *J* = 7.8 Hz, 3‴-H, 5‴-H); 7.41–7.35 (m, 3H, 2″-H, 6″-H, 4″-H); 7.30 (t, 2H, *J* = 7.6 Hz, 3″-H, 5″-H); 7.15 (d, 2H, *J* = 8.6 Hz, 2′-H, 6′-H); 4.98 (s, 2H, -CH_2); ^{13}C NMR ($CDCl_3$,125 MHz) δ (ppm): 193.0 (C=O); 154.9 (5-C); 152.0 (3-C); 135.2 (1‴-C); 134.0 (4‴-C); 133.3 (3′-C,5′-C); 133.0 (1″-C); 129.9 (4″-C); 128.85 (2′-C, 6′-C); 128.83 (3‴-C, 6‴-C); 128.6 (3″-C, 5″-C); 128.5 (2‴-C, 6‴-C); 128.2 (2″-C, 6″-C); 126.2 (1′-C); 124.2 (4′-C); 41.4 (CH_2); ^{15}N NMR ($CDCl_3$,50 MHz) δ (ppm): 175.1 (4-N).

(All spectra are reported in Supplementary Materials) Elemental analysis for $C_{22}H_{16}BrN_3OS$ Calcd. (%): C, 58.67; H, 3.58; Br, 17.74; N, 9.33; S, 7.12. Found (%): C, 58.62; H, 3.54; Br, 17.68; N, 9.20; S, 7.02. HRMS: calculated for $C_{22}H_{16}BrN_3OS$+Na: 472.0095; found: 472.0081.

*3.3. Synthesis of (±)-2-{[4-(4-Bromophenyl)-5-phenyl-4H-1,2,4-triazol-3-yl]sulfanyl}-1-phenyl-1-ethanol (**12**)*

Compound **11** (0.8 g, 0.00177 moles) was dissolved in ethanol (50 mL) with mild heating (45–50 °C. Then $NaBH_4$ (0.096 g, 0.0025 mol) was added in small five portions within 1.25 h. After 30 min from the last portion addition the conversion is monitored by TLC, and the obtained product precipitated in water. The purification was carried

out by recrystallization from 96% ethanol, finally giving 0.462 g (a yield of 57%) of 2-{[4-(4-bromophenyl)-5-phenyl-4*H*-1,2,4-triazol-3-yl]sulfanyl}-1-phenylethane-1-ol as a white powder. M.p. 183.5–185 °C. TLC Rf = 0.4 (*n*-hexane/ethyl acetate, 3:7). FT-IR (KBr, cm^{-1}): 695 ($\gamma_{sk.ar}$), 774 ($\gamma_{sk.ar}$), 826 ($\gamma_{sk.ar}$), 1269 (ν_{C-O}), 1427 ($\nu_{Sk.ar}$), 1492 ($\nu_{Sk.ar}$), 2853 (ν^{s}_{CH2}), 2935 (ν^{as}_{CH2}), 3032 (ν_{CarH}), 3057 (ν_{CarH}), 3087 (ν_{CarH}), 3197 (ν_{OH}). ^{1}H NMR (500 MHz, DMSO-d_6) δ(ppm): 7.61 (d, 2H, J = 8.6Hz, 3′-H, 5′-H); 7.45 (d, 2H, J = 7.4 Hz, 2‴-H, 6‴-H); 7.39–7.26 (m, 8H, 2′-H, 6′-H, 3′-H, 5′-H, 4′-H, 3‴-H, 5‴-H, 4‴-H); 7,10 (d, 2H, J = 8.6 Hz, 2′-H, 6′-H); 5.20–5.18(m, 1H, -CH); 4.94 (d, 1H, J = 3.8 Hz, -OH); 3.62 (dd, 1H, J = 14.4 Hz, J = 3.1Hz, H_a); 3.47 (dd, 1H, J = 8.2 Hz, J = 14.4 Hz, H_b); ^{13}C NMR (125 MHz, DMSO-d_6) δ(ppm): 154.9 (5-C); 153.7 (3-C); 142.8 (1‴-C); 133.3 (3′-C, 5′-C); 133.0 (1′-C); 130.1 (4″-C); 128.77 (2′-C, 6′-C); 128.72 (3″-C, 5″-C); 128.5 (3‴-C, 5‴-C); 128.1 (2″-C, 6″-C); 127.8 (4‴-C); 126.0 (1″-C); 125.9 (2‴-C, 6‴-C); 124.0 (4′-C); 73.3 (CH); 41,.6 (CH_2); ^{15}N NMR (50 MHz, DMSO-d_6) δ(ppm): 175.1 (4-N).

(All spectra are reported in Supplementary Materials) Elemental analysis for $C_{22}H_{18}BrN_3OS$ Calcd. (%): C, 58.41; H, 4.01; Br, 17.66; N, 9.29; S, 7.09. Found (%):C, 58.40; H, 3.99; Br, 17,58; N, 9.20; S, 7.01. HRMS: calculated for $C_{22}H_{18}BrN_3OS$+Na: 474.0252; found: 474.0347.

Supplementary Materials: The following are available online, Figure S1. ^{1}H NMR spectrum of compound (**10**) in DMSO-*d6*; Figure S2. ^{13}C NMR spectrum of compound (**10**) in DMSO-*d6*; Figure S3. HMBC ^{1}H-^{15}N spectrum of compound (10) in DMSO-*d6*; Figure S4. FT-IR spectrum of compound (**11**); Figure S5. ^{1}H NMR spectrum of compound (**11**) in $CDCl_3$; Figure S6. ^{13}C NMR spectrum of compound (**11**) in $CDCl_3$; Figure S7. COSY ^{1}H-^{1}H spectrum of compound (**11**) in $CDCl_3$; Figure S8. ^{13}C DEPT135 spectrum of compound (**11**) in $CDCl_3$; Figure S9. HMBC ^{1}H-^{13}C spectrum of compound (**12**) in $CDCl_3$ Figure S10. HMBC ^{1}H-^{15}N spectrum of compound (**11**) in $CDCl_3$; Figure S11. HSQCCED ^{1}H-^{13}C spectrum of compound (**11**) in $CDCl_3$; Figure S12. FT-IR spectrum of compound (**12**); Figure S13. ^{1}H NMR spectrum of compound (**12**) in $CDCl_3$; Figure S14. ^{13}C NMR spectrum of compound (**12**) in $CDCl_3$; Figure S15. COSY ^{1}H-^{1}H spectrum of compound (**12**) in $CDCl_3$; Figure S16. ^{13}C DEPT135 spectrum of compound (**12**) in $CDCl_3$; Figure S17. HMBC ^{1}H-^{13}C spectrum of compound (**12**) in $CDCl_3$; Figure S18. HMBC ^{1}H-^{15}N spectrum of compound (**12**) in $CDCl_3$; Figure S19. HSQCED ^{1}H-^{13}C spectrum of compound 6 (**12**) in $CDCl_3$; Figure S20. HRMS spectrum of compound (**11**); Figure S21. HRMS spectrum of compound (**12**).

Author Contributions: Designed the experiments, V.B.; performed the experiments, M.M.V. and V.B.; analyzed the spectral data, V.B.; wrote the manuscript, V.B. and M.M.V.; supervision and funding acquisitions, V.B. All authors have read and agreed to the published version of the manuscript.

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