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Short Note

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

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Abstract: 4-(4-Methoxyphenyl)-5-phenyl–4*H*-1,2,4-triazole-3-thiol (**4**) was alkylated to 2-{[4-(-4-methoxyphenyl)-5-phenyl-4*H*-1,2,4-triazol-3-yl]thio}-1-phenylethan-1-one (**5**) in alkaline conditions using 2-bromo-1-phenylethanone. The alkylated compound (**5**) was reduced at the carbonyl group to the corresponding racemic secondary alcohol with an asymmetric carbon, (*R*,*S*)-2-{[4-(4-methoxyphenyl)-5-phenyl-4*H*-1,2,4-triazol-3-yl]thio}-1-phenyl-1-ethanol (**6**). Both synthesized compounds, ketone (**5**) and secondary alcohol (**6**), are new and have not been reported yet in the literature. All the synthesized compounds were characterized by IR, 1D and 2D NMR ^{1}H-^{1}H, ^{1}H-^{13}C and ^{1}H-^{15}N-NMR spectroscopy and by elemental analysis.

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

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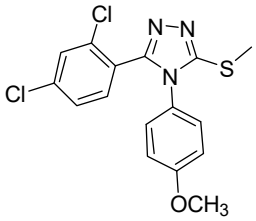
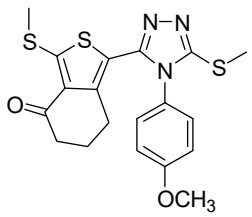
1. Introduction

The recent literature reveals that the mercapto- and thione-substituted 1,2,4-triazole moieties should be an important structural feature of a wide range of synthetic medicines [1]. A variety of medicinal actions have been reported, ranging from anti-tubercular action [2] to protein inhibitory action involved in the mechanism of diseases such as diabetes, obesity and cancer [3]. Other *S*-alkylated compounds derived from 4*H*-1,2,4-triazole-3-thiol 4,5-disubstituted show proven antifungal [4], antimicrobial and antibiotic activity [5] (Scheme 1).



3-(2,4-dichlorophenyl)-4-(4-methoxyphenyl) -5-(methylthio)-4*H*-1,2,4-triazole

Antifungical activity [4]

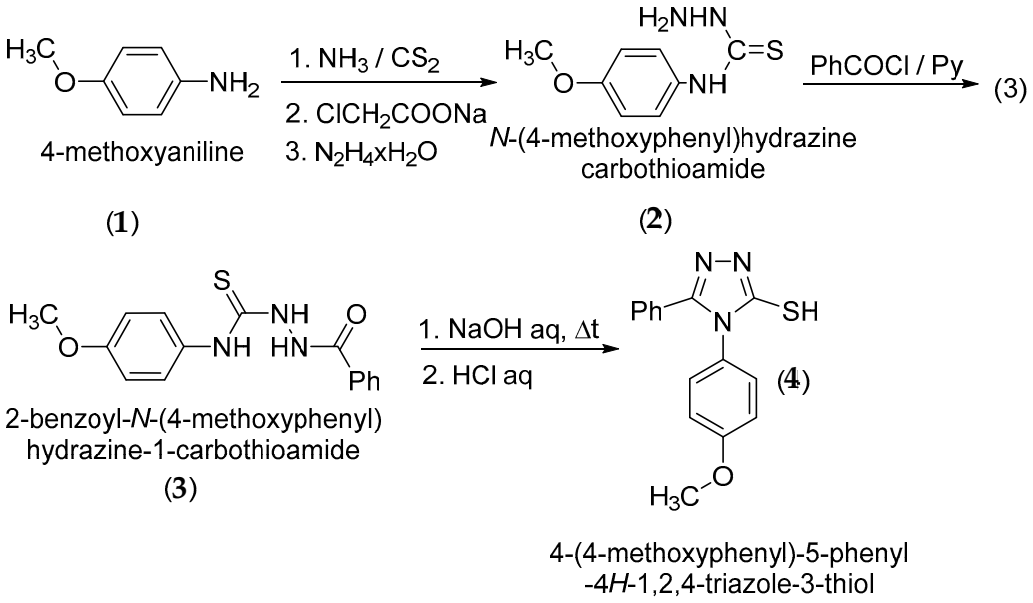


1-(4-(4-methoxyphenyl)-5-(methylthio)-4*H*-1,2,4-triazol-3-yl) -3-(methylthio)-6,7-dihydrobenzo[*c*]thiophen-4(5*H*)-one

Antibiotic activity [5]

Scheme 1. Biological activity of similar compounds.

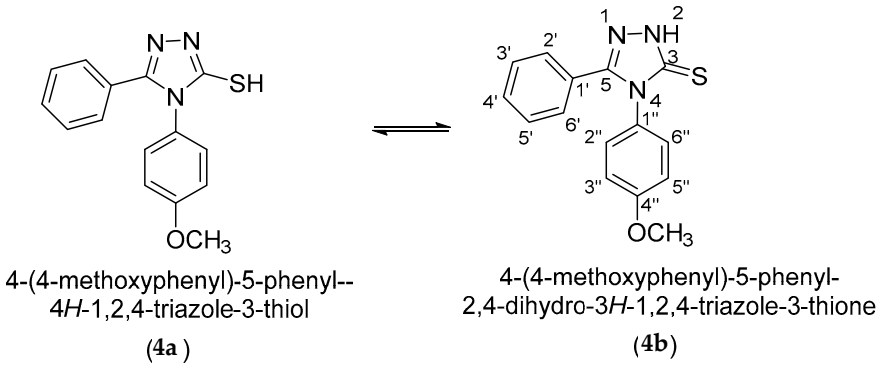
4-(4-Methoxyphenyl)-5-phenyl-4*H*-1,2,4-triazole-3-thiol (**4**) was synthesized starting from 4-methoxyaniline (**1**) via the corresponding *N*-(4-methoxyphenyl)hydrazinecarbothioamide (**2**), followed by acylation to 2-benzoyl-*N*-(4-methoxyphenyl)hydrazine-1-carbothioamide (**3**) and cyclization of (**3**) to 4-(4-methoxyphenyl)-5-phenyl-4*H*-1,2,4-triazole-3-thiol (**4**) according to the literature methods (Scheme 2) [6–10]. The *S*-alkylation was performed using cesium carbonate as an alkaline base [11,12] and the reduction of the ketone group to the corresponding secondary alcohol was carried out with sodium borohydride [13].



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

2. Results and Discussion

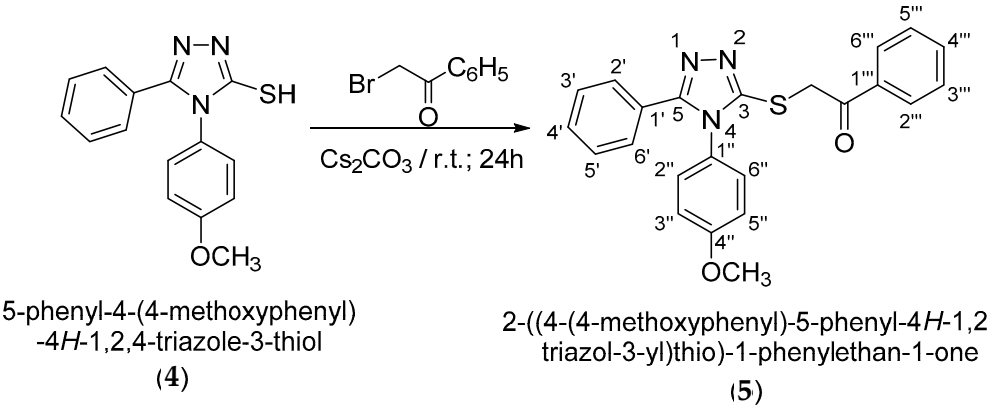
3-Mercaptotriazole (**4**) can theoretically have two tautomeric forms: the thiol form (**4a**) and the thione form (**4b**). As a result, alkylation in a basic medium can theoretically occur as *S*-alkylation at the tautomeric form (**4a**) or as *N*-alkylation at the tautomeric form (**4b**) (Scheme 3).



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

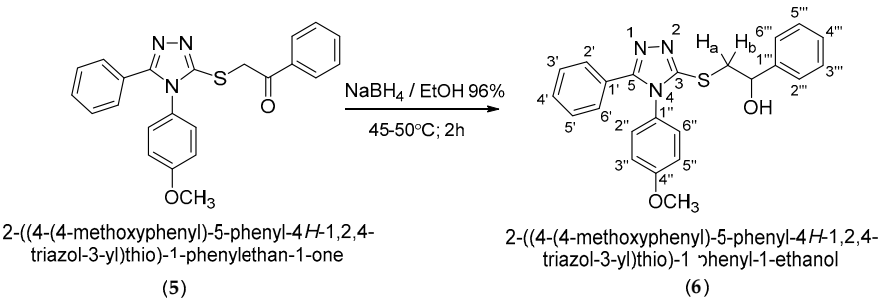
From the ^{1}H and ^{13}C-NMR spectra, it is confirmed that the tautomeric equilibrium is completely shifted to the tautomeric form (**4b**) in Py-*d5*. This shift of equilibrium is confirmed by the deshielded signal of the 2-N-H proton at 16.00 ppm, as well as by the deshielded signal of the 3-C carbon atom at 171.7 ppm, corresponding to a C=S thionic 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. This is observed from 2D NMR spectroscopic analysis by analyzing the couplings over two to three bonds in the HMBC spectrum as well as by the shifting of the signal of the triazolic carbon 3-C atom to a lower δ value at 151.7 ppm, corresponding to a thiol type carbon atom. *S*-Alkylation of 4-(4-methoxyphenyl)-5-phenyl-4H-1,2,4-triazole-3-thiol (**4**) was carried out using 2-bromo-1-phenylethanone in DMF in the presence of Cs_2CO_3 at room temperature. 2-{[4-(-4-Methoxyphenyl)-5-phenyl-4*H*-1,2,4-triazol-3-yl]thio}-1-phenylethan-1-one (**5**) resulting from *S*-alkylation was obtained in a yield of 79% after recrystallization from ethanol (Scheme 4).



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

Reduction of the carbonyl group in the ketone (**5**) to the racemic secondary alcohol (*R,S*)-2-{[4-(4-methoxyphenyl)-5-phenyl-4*H*-1,2,4-triazol-3-yl]thio}-1-phenyl-1-ethanol (**6**) was accomplished with sodium borohydride in ethanol 96%. Secondary alcohol (**6**) was obtained in a yield of 77.0% after recrystallization from ethanol (Scheme 5).



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

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 methylene protons in the obtained secondary alcohol (**5**) are diastereotopic and 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.

3. Materials and Methods

The chemical reagents were purchased from commercial sources and used in syntheses with no further purification. Melting points were determined on a Böetius PHMK (Veb Analytik Dresden, 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 Py-*d5* 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.

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

^{1}H-NMR (Py-d_5, 500 MHz): δ (ppm): 16.00 (s, 1H, -NH), 7.64-7.62 (m, 2H, 2′-H, 6′-H), 7.50 (d, 2H, *J* = 8.94 Hz, 2″-H, 6″-H), 7.38-7.31 (m, 3H, 3′-H, 4′-H, 5′-H), 7.03 (d, 2H, *J* = 8.94 Hz, 3″-H, 5″-H), 3.35 (s, 3H, -OCH$_3$);
^{13}C-NMR (Py-d_5, 125 MHz): δ (ppm): 171.7 (C=S), 160.8 (4″-C), 151.9 (5-C), 131.0 (4′-C); 130.7 (2″-C, 6″-C), 129.4 (3′-C, 5′-C), 129.3 (2′-C, 6′-C), 128.8 (1″-C), 127.6 (1′-C), 115.5 (3″-C, 5″-C), 55.8 (O-CH$_3$);
^{15}N-NMR (Py-d_5, 50 MHz) δ (ppm): 182.6 (4-N).
(All spectra are reported in Supplementary Materials)

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

4-(4-Methoxyphenyl)-5-phenyl-4*H*-1,2,4-triazole-3-thiol (**4**) (0.00125 moles, 0.35 g) was magnetically stirred with cesium carbonate (0.00138 mol, 0.45 g) dissolved in ethanol (0.351 moles, 20.00 mL), at room temperature. After the cesium salt was dissolved, a solution of 2-bromo-1-phenylethanone (0.0012 moles, 0.25 g) in ethanol (0.263 moles, 15.00 mL) was added in the reaction mixture. The resulting mixture was left to stir for 24 h and after that was precipitated in water. The solid formed was collected by filtration, washed with water, dried and recrystallized from EtOH. The ketone (**5**) was obtained in a yield of 79.0%.
m.p.: 150–152 °C.
IR (KBr, cm^{-1}): 3062, 2975, 2900, 1672, 1589; 1510, 1446, 1386, 1253, 1189, 837, 756, 692.
^{1}H-NMR (DMSO-d_6, 500 MHz): *δ* (ppm): 8.04 (d, 2H, *J* = 8.26 Hz, 2‴-H, 6‴-H), 7.69 (t, 1H, *J* = 7.44 Hz, 4‴-H), 7.57 (t, 2H, *J* = 7.90 Hz, 3‴-H, 5‴-H), 7.41-7.34 (m, 7H, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H, 2″-H, 6″-H), 7.08 (dt, 2H, *J* = 8.90 Hz, *J* = 2.05 Hz, 3″-H, 5″-H) 4.94 (s, 2H, -CH$_2$); 3.82 (s, 3H, -OCH$_3$);
^{13}C-NMR (DMSO-d_6, 125 MHz): *δ* (ppm): 193.0 (C=O), 159.9 (4′-C), 154.4 (5-C), 151,7 (3-C), 135.2 (1‴-C), 133.6 (4‴-C), 129.6 (4′-C), 128.8 (2″-C, 5″-C), 128.7 (3‴4-C, 5‴-C); 128.5 (3′-C, 5′-C), 128.3 (2‴-C, 6‴-C), 127.7 (2′-C, 6′-C), 126.6 (1′-C); 126.1 (1″-C), 115.0 (3″-C, 5″-C), 55.4 (-OCH$_3$), 40.0 (-CH$_2$);
^{15}N-NMR (DMSO-d_6, 50 MHz): δ (ppm): 177.2 (4-N).
(All spectra are reported in Supplementary Materials)
Elemental analysis for $C_{23}H_{19}N_3O_2S$ Calcd. (%): C, 68.81; H, 4.77; N, 10.47; S, 7.99
Found (%): C, 68.75; H, 4.69; N, 10.40; S, 7.90.

*3.3. Synthesis of 2-{[4-(4-methoxyphenyl)-5-phenyl-4H-1,2,4-triazol-3-yl]thio}-1-phenyl-1-ethanol (**6**)*

2-{[4-(-4-Methoxyphenyl)-5-phenyl-4*H*-1,2,4-triazol-3-yl]thio}-1-phenylethan-1-one (**5**) (0.0005 moles, 0.223 g) was dissolved in ethanol (0.386 moles, 22.00 mL) and heated in a water bath until the complete dissolution of the ketone. Afterwards, sodium borohydride (0.0008 moles, 0.03 g) was added in five stages at certain time intervals. After the last portion, the conversion of the reaction was checked, and the resulting mixture was precipitated in water. The solid formed was collected by filtration, washed with water, dried and recrystallized from ethanol. The secondary alcohol (6) was obtained in a yield of 77.0%.
m.p.: 170–172 °C;
IR (KBr, cm^{-1}): 3348, 3060, 2975, 2892, 2835, 1604, 1508, 1446, 1388, 1247, 1170, 831, 777, 700.
^{1}H-NMR (DMSO-d_6, 500 MHz) *δ* (ppm): 7.40–7.30 (m, 11H, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H, 2″-H, 6″-H, 2‴-H, 3‴-H, 5‴-H, 6‴-H), 7.26 (t, 1H, *J* = 7.06 Hz 4‴-H), 7.06 (d, 2H, *J* = 8.85 Hz, 3″-H, 5″-H), 5.80 (d, 1H, *J* = 4.78 Hz, -OH); 4.90-4.87 (m, 1H, -CH-OH), 3.80 (s, 3H, -OCH$_3$), 3.54 (dd, 1H, *J* = 12.99 Hz, *J* = 4.48 Hz, Ha), 3.39-3.32 (m, 1H, Hb).
^{13}C-NMR (DMSO-d_6, 125 MHz) *δ* (ppm): 159.8 (4″-C), 154.3 (5-C), 152.7 (3-C), 143.7 (1‴-C), 129.5 (4′-C), 128.9 (2″-C, 6″-C), 128.4 (3′-C, 5′-C), 128.0 (3‴-C, 5‴-C), 127.7 (2′-C, 6-C), 127.2 (4‴-C), 126.7 (1′-C), 126.2 (1″-C), 125.8 (2‴-C, 6‴-C), 114.9 (3″-C, 5″-C), 70.9 (-CH), 55.4 (O-CH$_3$), 40.5 (-CH$_2$).
^{15}N-NMR (DMSO-d_6, 50 MHz) δ (ppm): 176.9 (4-N).

(All spectra are reported in Supplementary Materials)
Elemental analysis for $C_{23}H_{21}N_3O_2S$ Calcd. (%): C, 68.46; H, 5.25; N, 10.41; S, 7.95. Found (%): C, 68.40; H, 5.20; N, 10.30; S, 7.90.

Supplementary Materials: The following are available online, Figure S1. ^{1}H-NMR spectrum of compound **4** in Py-*d5*; Figure S2. ^{13}C-NMR spectrum of compound **4** in Py-*d5*; Figure S3. FT-IR spectrum of compound **5**; Figure S4. ^{1}H-NMR spectrum of compound **5** in DMSO-d_6; Figure S5. ^{13}C-NMR spectrum of compound **5** in DMSO-d_6; Figure S6. COSY ^{1}H-^{1}H spectrum of compound **5** in DMSO-d_6; Figure S7. ^{13}C DEPT135 spectrum of compound **5** in DMSO-d_6; Figure S8. HMBC ^{1}H-^{13}C spectrum of compound **5** in DMSO-d_6; Figure S9. HMBC ^{1}H-^{15}N spectrum of compound **5** in DMSO-d_6; Figure S10. HSQCCED ^{1}H-^{13}C spectrum of compound **5** in DMSO-d_6; Figure S11. FT-IR spectrum of compound **6**; Figure S12. ^{1}H-NMR spectrum of compound **6** in DMSO-d_6; Figure S13. ^{13}C-NMR spectrum of compound **6** in DMSO-d_6; Figure S14. COSY ^{1}H-^{1}H spectrum of compound **6** in DMSO-d_6; Figure S15. ^{13}C DEPT135 spectrum of compound **6** in DMSO-d_6; Figure S16. HMBC ^{1}H-^{13}C spectrum of compound **6** in DMSO-d_6; Figure S17. HMBC ^{1}H-^{15}N spectrum of compound **6** in DMSO-d_6; Figure S18. HSQCCED ^{1}H-^{13}C spectrum of compound **6** in DMSO-d_6.

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

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Data Availability Statement: The data presented in this study are available within the article or Supplementary Materials.

Conflicts of Interest: The authors declare no conflict of interest.

Sample Availability: Samples of the compounds are available from the corresponding author.

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