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Synthesis and Theoretical Characterization of Some New 4-Substituted-1,3-diphenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazoles with Potential Pharmacological Activity

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ABSTRACT: *Synthesis of some new triazoles fused to triazoles **5a–c** or thiadiazoles **6a–c** and the thiol-thione tautomeric equilibrium study of the title compounds are reported. The "rule of five" and complementary criteria of pharmacokinetic properties were determined to predict whether these compounds are orally bioavailable. Semiempirical parameterizations have been critically benchmarked for the thiol-thione tautomeric equilibrium against the DFT calculations. It was shown that unlike the AM1 and PM3 Hamiltonians, which erroneously predict higher stability of the thiol tautomer, the newly developed RM1 Hamiltonian, on the other hand, predicts energetics of this equilibrium in excellent agreement with the DFT results.* © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:713–718, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20499

INTRODUCTION

Sulfur-containing compounds, such as thiosemicarbazides, mercapto-1,2,4-triazoles, and 1,3,4-thiadiazoles, are known to be antibacterially, antivirostatically, and CNS active [1]. For this reason, they often appear as a building element in drug molecules [2]. The most common procedure for the synthesis of 1,3,4-trisubstituted-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazole consists of two steps: the first one is the intramolecular, dehydrative cyclization of 1-acyl-4-disubstituted thiosemicarbazide, and the second step is the substitution of the proton at N1 of the triazole ring. Herein, we present an alternative synthetic method, which uses N^1-phenyl benzamidrazone hydrochloride **1** as the starting compound. Obtained product, 4-ethoxycarbonylmethyl-1,3-diphenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazole **2**, by the transformation of the acetate residue located at N4 gives triazoles fused to triazoles or thiadiazoles (compounds composed of two 1,2,4-triazoles **5a–c** or 1,2,4-triazole and 1,3,4-thiadiazole **6a–c**, respectively). Compounds **4a–c**, **5a–c**, and **6a–c** are reasonable potential candidates as bioactive substances because they satisfy Lipinski's rule of five [3] and complementary criteria [4].

One of the interesting properties of mercapto-substituted triazoles is the existence of thiol and thione tautomeric forms. As tautomerization plays a significant role in several processes related to bioactivity, such as proton transfer and hydrogen

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bonding, we became interested in the thiol-thione tautomerism of the new title compounds. Therefore, part of our studies has been devoted to the tautomeric equilibrium. We have applied the DFT level in our previous studies [5–7] of this tautomeric equilibria because both AM1 and PM3 parameterizations lead to higher stability of the thiol form in disagreement with the DFT results and the experimental data [8]. Herein, we have tested the performance of the newly developed RM1 method [9] and have shown that it predicts relative stability of the tautomers in excellent agreement with the DFT results. Furthermore, calculations on oxo-analogues of the thio-tautomers allowed us to pinpoint the problems with AM1 and PM3 calculations to the parameterization of the sulfur atom.

RESULTS AND DISCUSSION

Chemistry

The synthesis pathway leading to the title compounds is given in Scheme 1. N^1-phenyl benzamidrazone hydrochloride, staring material **1**, 4-ethoxycarbonylmethyl-1,3-diphenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazole **2**, and 1,3-diphenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazole-4-acetic acid hydrazide **3** were synthesized according to the literature method [10]. The reaction of hydrazide **3** with aryl isothiocyanates afforded 4-aryl-1-[(1,3-diphenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-4-yl) acetyl]thiosemicarbazides **4a–c** with 86%–91% yields. Cyclization of **4a–c** using 2% NaOH gave 4-aryl-3-[(1,3-diphenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-4-yl)methyl]-4,5-dihydro-1*H*-1,2,4-triazol-5-thiones **5a–c** in 87%–89% yields. 2-Arylamino-5-[(1,3-diphenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-4-yl)methyl]-1,3,4-thiadiazoles **6a–c** were obtained with 52%–56% yields by cyclization of **4a–c** in concentrated H_2SO_4.

The structures of all compounds were confirmed by the results of elemental analysis as well as by IR and ^{1}H NMR. The characterization and spectral data of original compounds **4b, 4c, 5b, 5c** and **6a–c**, are presented in Table 1 and Table 2, respectively. Characterization data of noted compounds **4a** and **5a** were reported earlier in [11].

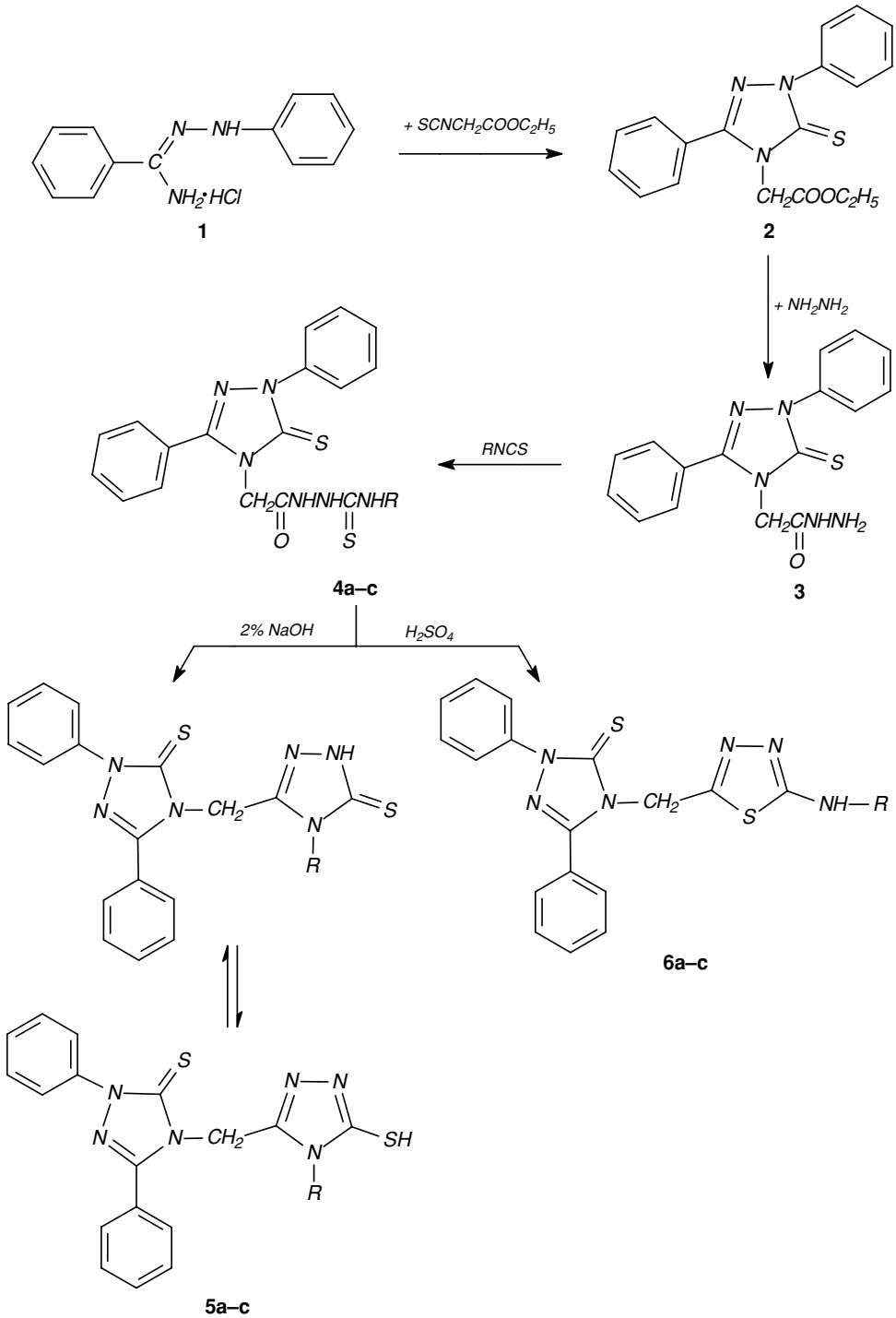
The ^{1}H NMR spectra of **5a–c** show a sharp singlet at 13.8–13.9 ppm, typical for the proton linked to N1, indicating the presence the thione tautomer. The domination of the thione form was observed also in the IR. The infrared spectra of **5a–c** showed an absorption in the region 3306–3356 cm^{-1}, attributed to NH and at 1308–1352 cm^{-1} attributed to C=S in agreement with our earlier calculations for both tautomers [6].

The pharmacokinetic properties of 4-substituted-1,3-diphenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazoles **5a–c** and **6a–c** were established for determining whether the compounds will be orally bioavailable. All compounds obey Lipinski's "rule of five" and complementary criteria as shown in Table 3.

Computational Part

The title compounds are considerably large for theoretical calculations especially when a routine calculation is desired to evaluate a priori pharmacokinetic parameters at the quantum level. Our previous experience with fast semiempirical calculations was, however, discouraging because the two most robust parameterizations (AM1 and PM3) proved inadequate in describing tautomeric equilibria of the class of compounds studied here. Thus far we have, therefore, used DFT hybrid functionals. In the present study, we have explored the performance of the newly developed RM1 parameterization that is supposed to outperform both AM1 and PM3 by fixing their major deficiencies. As presented in Table 4, our calculations support this claim in the case of compounds studied here. The data collected in this table refer to 4-methyl-1,2,4-triazoline-5-thione (X = S) and 4-methyl-1,2,4-triazoline-5-one (X = O) for which DFT calculations were partly available [7]. Although AM1 and PM3 erroneously predict higher stability of the thiol tautomer, RM1 yields this energetics correctly, with very good agreement with the results obtained at the DFT level. A comparison of the results obtained for thio- with oxo-compounds indicates that the RM1 method is an improvement over the older parameterizations. Furthermore, it allows us to point to parameters of the sulfur atom as the source of the error because all three semiempirical methods that were tested predicted higher stability of the NH tautomeric form for X = O.

In conclusion, we have presented an alternative synthetic route for 1,3,4-trisubstituted-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazole. Based on the calculated parameters described by Lipinski and Veber, it was found that compounds **4a–c, 5a–c**, and **6a–c** are reasonable potential candidates as bioactive substances. In addition, we have shown that the new semiempirical method RM1 is capable of efficiently providing energetic and geometrical information about this class of compounds.



SCHEME 1 Synthesis of the 4-aryl-1-[(1,3-diphenyl-5-thioxo-3,4-dihydro-1*H*-1,2,4-triazol-4-yl)acetyl]thiosemicarbazide **4a–c**, 4-aryl-3-[(1,3-diphenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-4-yl)methyl]-4,5-dihydro-1*H*-1,2,4-triazol-5-thiones **5a–c**, and 2-arylamino-5-[(1,3-diphenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-4-yl)methyl]-1,3,4-thiadiazoles **6a–c**.

TABLE 1 Characterization Data of Compounds **4b, 4c, 5b, 5c**, and **6a–c**

				Percent Carbonyl		*Percent Hydrogen*		*Percent Nitrogen*	
Compound No.	*R*	*Yield (%)*	*MP (°C)*	*Calcd*	*Found*	*Calcd*	*Found*	*Calcd*	*Found*
4b	4-$CH_3C_6H_4$	86	196–168	60.74	60.55	4.67	4.62	17.71	17.56
4c	4-$OCH_3C_6H_4$	91	223–225	58.76	58.51	4.52	4.44	17.13	16.96
5b	4-$CH_3C_6H_4$	87	251–253	63.13	63.22	4.42	4.56	18.41	18.26
5c	4-$OCH_3C_6H_4$	89	233–235	61.00	60.69	4.27	4.26	17.78	17.93
6a	C_6H_5	52	220–222	62.42	62.62	4.10	3.89	18.99	19.20
6b	4-$CH_3C_6H_4$	55	170–172	63.13	63.22	4.42	4.44	18.41	18.53
6c	4-$OCH_3C_6H_4$	56	253–255	61.00	60.69	4.27	4.30	17.78	17.52

TABLE 2 Spectral Data of Compounds **4b, 4c, 5b, 5c**, and **6a–c**

Compound No.	*Spectral Data*
4b	IR (KBr, ν in cm^{-1}): 3356 (—NH), 2990, 1570, 807 (ArH), 2839, 1454 (Aliph.), 1686 (—C═O), 1262 (—C═S), 751 (C—S—C); ^{1}H NMR δ: 2.3 (s, 3H, CH_3), 4.9 (s, 2H, CH_2), 7.1–8.0 (m, 14H, ArH), 9.5, 9.8, 10.6 (3s, 3H, 3NH, D_2O exchangeable)
4c	IR (KBr, ν in cm^{-1}): 3342 (—NH), 2996, 1568, 824 (ArH), 2830, 1460 (Aliph.), 1679 (—C═O), 1259 (—C═S), 801 (C—S—C); ^{1}H NMR δ: 3.8 (s, 3H, OCH_3), 4.9 (s, 2H, CH_2), 6.9–8.3 (m, 14H, ArH), 9.4, 9.8, 10.6 (3s, 3H, 3NH, D_2O exchangeable)
5b	IR (KBr, ν in cm^{-1}): 3306 (—NH), 3040, 1567, 818 (ArH), 2831, 1467 (Aliph.), 1594 (—C═N), 1352, 1276 (—C═S); ^{1}H NMR δ: 2.4 (s, 3H, CH_3), 5.2 (s, 2H, CH_2), 7.3–8.0 (m, 14H, ArH), 13.9 (s, 1H, NH, D_2O exchangeable)
5c	IR (KBr, ν in cm^{-1}): 3356 (—NH), 3022, 1571, 826 (ArH), 2840, 1465 (Aliph.), 1590 (—C═N), 1308, 1261 (—C═S); ^{1}H NMR δ: 3.8 (s, 3H, OCH_3), 5.1 (s, 2H, CH_2), 7.1–8.3 (m, 14H, ArH), 13.8 (s, 1H, NH, D_2O exchangeable)
6a	IR (KBr, ν in cm^{-1}): 3298 (—NH), 2931, 1586, 759 (ArH), 2825, 1451 (Aliph.), 1624 (—C═N), 1343, 1260 (—C═S), 790 (C—S—C); ^{1}H NMR δ: 5.6 (s, 2H, CH_2), 7.0–8.1 (m, 15H, ArH), 10.4 (s, 1H, NH, D_2O exchangeable)
6b	IR (KBr, ν in cm^{-1}): 3283 (—NH), 3020, 1578, 845 (ArH), 2822, 1450 (Aliph.), 1621 (—C═N), 1212, 1145 (—C═S), 798 (C—S—C); ^{1}H NMR δ: 2.3 (s, 3H, CH_3), 5.6 (s, 2H, CH_2), 7.1–8.1 (m, 14H, ArH), 10.3 (s, 1H, NH, D_2O exchangeable)
6c	IR (KBr, ν in cm^{-1}): 3294 (—NH), 2995, 1564, 864 (ArH), 2819, 1455 (Aliph.), 1615 (—C═N), 1293, 1156 (—C═S), 801 (C—S—C); ^{1}H NMR δ: 3.8 (s, 3H, OCH_3), 5.6 (s, 2H, CH_2), 6.9–8.1 (m, 14H, ArH), 10.2 (s, 1H, NH, D_2O exchangeable)

EXPERIMENTAL

Chemistry

Melting points were determined in a Fischer–Johns block and are uncorrected. IR spectra (ν, cm^{-1}) were recorded in KBr using a Specord IR-75 spectrophotometer. ^{1}H NMR spectra (δ, ppm) were recorded on a Bruker Avance 300 in DMSO-d_6 with TMS as an internal standard.

*Synthesis of 4-Aryl-1-[(1,3-diphenyl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-4-yl)acetyl]thiosemicarbazides (**4a–c**).* 1,3-Diphenyl-5-thioxo-4,5-dihydro-1H-1,2,4-triazole-4-acetic acid hydrazide **3** (0.01 mol) and appropriate isothiocyanate (0.01 mol) were heated in an oil bath at 70°C for 12 h. The formed product was washed with diethyl ether, later with hot water, dried, and crystallized from ethanol.

*Synthesis of 4-Aryl-3-[(1,3-diphenyl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-4-yl)methyl]-4,5-dihydro-1H-1,2,4-triazol-5-thiones (**5a–c**).* The thiosemicarbazide derivative **4a–c** (0.01 mol) was dissolved in 2% NaOH (10 mL) and refluxed for 2 h. The reaction mixture was cooled and acidified with 3M HCl, whereupon a solid was separated. The formed solid was filtered, dried, and crystallized from ethanol.

*Synthesis of 2-Arylamino-5-[(1,3-diphenyl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-4-yl)methyl]-1,3,4-thiadiazoles (**6a–c**).* The thiosemicarbazide derivative **4a–c** (0.01 mol) was dissolved in concentrated H_2SO_4 (10 mL). The solution was kept at room temperature for 2 h and then poured into crushed ice to precipitate a crude solid. The product was then filtered, dried, and crystallized from ethanol.

TABLE 3 Pharmacokinetic and QSAR Properties[a] of **4a–c, 5a–c**, and **6a–c**

Compound No.	*Mw* *Log P*	*Hydratation Energy* *Volume*	$\Delta H_{SH\text{-}NH}$ *HOF*	*H-bond donors* *H-bond acceptors*	*Polarizability* *Rotable bonds*	*Surface area* *Polar surface area*	*Molar refractivity* *Dipole moment*
4a	460.6	−14.7	–	3	52.4	686.1	133.6
	3.02	1224.0	1275.1	7	8	75.9	6.6
4b	474.6	−13.5	–	3	54.3	713.5	138.7
	3.47	1275.3	1301.0	7	8	75.9	6.5
4c	490.6	−16.3	–	3	54.9	726.8	140.1
	3.08	1298.3	1362.2	8	9	85.1	5.3
5a	442.6	−10.9	11.2	1	51.2	627.1	128.4
	3.39	1136.3	1269.2	6	5	56.4	7.4
5b	456.6	−9.9	8.7	1	53.0	650.4	133.4
	3.84	1184.3	1295.0	6	5	56.4	7.5
5c	472.6	−12.4	8.8	1	53.6	667.3	134.8
	3.44	1213.5	1356.0	7	6	65.6	6.5
6a	442.6	−12.0	–	1	50.6	695.9	129.9
	4.94	1190.5	1271.2	6	6	60.6	6.7
6b	456.6	−10.7	–	1	52.4	724.9	134.9
	5.39	1242.0	1297.9	6	6	60.6	6.8
6c	472.6	−13.5	–	1	53.1	740.5	136.3
	4.99	1267.2	1359.8	7	7	69.8	7.4

[a]Energies in kcal/mol, surfaces in Å^2, and volumes in Å^3.

TABLE 4 Calculated Enthalpy differences (see text)

Theory Level	*X*	$\Delta H_{SH\text{-}NH}$ *(kcal/mol)*
AM1	S	−1.3
	O	9.5
PM3	S	−3.9
	O	12.0
RM1	S	13.4
	O	15.4
B3PW91/6-31G(d)	S	14.8
	O	18.0

Computational Methods

Calculations at the DFT level were carried out using the hybrid B3PW91 functional [12] and the 6-31G(d) basis set [13] as implemented in Gaussian [14]. Semiempirical calculations were performed using AM1, PM3, and RM1 parameterizations as implemented in HyperChem [15]. Molecular geometries were fully optimized in the gas phase to gradients of 0.3 kcal/(mol Å) for DFT and 0.01 kcal/(mol Å) for semiempirical levels, respectively. Vibrational analysis was carried out to confirm identity of the stationary points (3n-6 real vibrations). QSAR parameters were obtained using HyperChem and Interactive Polar Surface Area calculator [16].

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