SYNTHESIS OF NEW 4-SUBSTITUTED-1-AROYL-THIOSEMICARBAZIDES AND THEIR CYCLIZATION TO MERCAPTOTRIAZOLES AND AMINOTHIADIAZOLES

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ABSTRACT

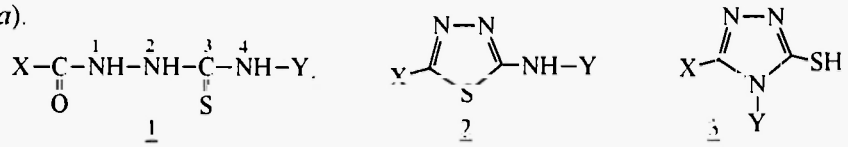
Nine new thiosemicarbazides bearing arylsulfonylbenzoyl groups at N^1 and β-phenylethyl, cyclohexyl or *n*-butyl groups at N^4 were synthesized using classical procedures. Cyclization of β-phenylethyl- and *n*-butyl-thiosemicarbazides in NaOH solutions afforded the corresponding mercaptotriazoles. Cyclization of β-phenylethyl thiosemicarbazides in concentrated H_2SO_4 gave rise to substituted aminothiadiazoles bearing an $-SO_3H$ group in the *para*- position of the side-chain phenyl ring whereas cyclization of *n*-butyl thiosemicarbazides conducted in a clean way to the expected substituted aminothiadiazoles. The thiosemicarbazides possessing cyclohexyl substituents proved reluctant to cyclization both in alkaline and acidic medium, most probably due to steric hindrances. All the new compounds–extensively characterised by IR, UV, ^{1}H-NMR and ^{13}C-NMR– will be biologically tested as tuberculostatics and carbonic anhydrase inhibitors.

INTRODUCTION

Cyclization of N^1-acyl thiosemicarbazides to five-membered ring heterocycles is a known procedure in the synthesis of biologically active compounds (1-3). Continuing our researches in the domain of biologically active heterocyclic compounds (4-6) we describe in this preliminary communication the syntheses of some new 1,4-disubstituted thiosemicarbazides with general formula 1 and their behavior in cyclization reactions aimed to afford aminothiadiazoles or mercaptotriazoles with general formulas 2 respectively 3.

The new compounds will be biologically screened in order to evaluate their activities as

tuberculostatics and carbonic anhydrase inhibitors taking into account the pharmacophoric effects of their structural moieties including the heterocyclic rings as well as the diarylsulfonic susbstituent X (*vide infra*).

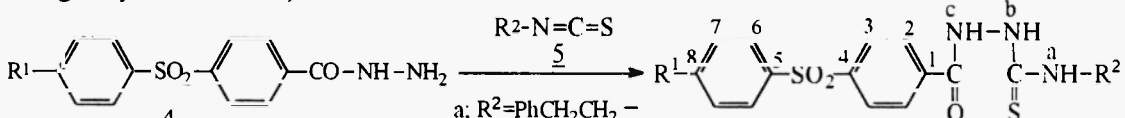


1 2 3

RESULTS

a) *Thiosemicarbazides*

The thiosemicarbazides 1 with specific structures 6 a-i were easily obtained from the corresponding acid hydrazides 4 a-c (7) and substituted isothiocyanates 5 a-c (6 hrs heating in boiling anhydrous ethanol).



4

a; R^1=H
b; R^1=Cl
c: R^1=Br

5

a: R^2=$PhCH_2CH_2$ –
b: R^2=C_6H_{11} –
c: R^2=*n*-Bu –

6

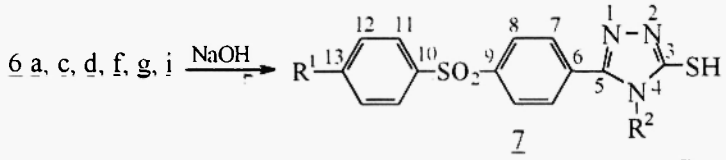
	m.p. (° C)
a: R^1=H; R^2=$PhCH_2CH_2$ –	215
b: R^1=H; R^2=C_6H_{11} –	198
c: R^1=H; R^2=*n*-Bu –	190
d: R^1=Cl; R^2=$PhCH_2CH_2$ –	208
e: R^1=Cl; R^2=C_6H_{11} –	206
f: R^1=Cl; R^2=*n*-Bu –	205
g: R^1=Br; R^2=$PhCH_2CH_2$ –	212
h: R^1=Br; R^2=C_6H_{11} –	204
i: R^1=Br; R^2=*n*-Bu –	215

Spectral data fully confirm the structures 6 of the new thiosemicarbazides. Thus, in the IR spectra (FTS-135 Bio-Rad apparatus; KBr; cm^{-1}) the characteristic absorptions appeared at: 3321-3367 (ν_{NH}), 1673-1681 ($\nu_{C=O}$), 1297-1321 ($\nu^{as}_{SO_2}$), 1158-1160 ($\nu^{sym}_{SO_2}$), 575 (ν_{C-Br}), 767 (ν_{C-Cl}) along with the frequencies characteristic for hydrocarbon moieties. All the examined compounds 6 a-i afford very similar UV absorption spectra exhibiting only two maxima at 207 and 247-251.5 nm. The ^{1}H-NMR spectra (VARIAN GEMINI, 300 MHz; DMSO; δ ppm, JHz) exhibit distinct subspectra for the aromatic diarylsulfonyl moiety as well as for the remaining functional side-chain. The signals of rather equivalent protons H^2 and H^3 appear as wide singlets at about 8.10 ppm. On the contrary the non-equivalent protons H^6 and H^7 appear as AA'BB' systems between 7.63 and 8.02 ppm with the main coupling constant of 8.5-8.7 Hz. The chemical shift of H^8 in 6 a-c is 7.70 ppm (triplet of triplets). The ^{a}NH protons in the proximity of R^2 are the most shielded ones (7.55-8.22 ppm) being followed by ^{b}NH (9.26-9.45 ppm) and ^{c}NH (10.5-10.6 ppm). The R^2 groups

from 6 a-i gave rise to ^{1}H-NMR signals in agreement with their structures. In the ^{13}C-NMR spectra (VARIAN GEMINI, 75 MHz; DMSO; δ ppm) along with the aromatic carbons (whose attributions were made on the basis of 2D-HETCOR experiments) resonating between 127.4 and 143.7 ppm, the most deshielded carbons are the C=S ones (δ=180-182 ppm) followed by C=O ones (δ=164 ppm).

b) *Mercaptotriazoles*

The 4-substituted 1-aroylthiosemicarbazides 6 a-i were subjected to cyclization (6 hours reflux in 2N-NaOH solutions) which usually affords 4,5-disubstituted 3-mercapto-1,2,4-triazoles (8). Unexpectedly, from the thiosemicarbazides 6 only 6a, 6d, 6g (with R^2=$PhCH_2CH_2$) and 6c, 6f, 6i (with R^2=*n*-Bu) reacted in the above mentioned way affording mercaptotriazoles 7 a-f of the general type 3 whereas in the cases of 6b, 6e and 6h (with R^2=cyclohexyl) no cyclization occurred.



7

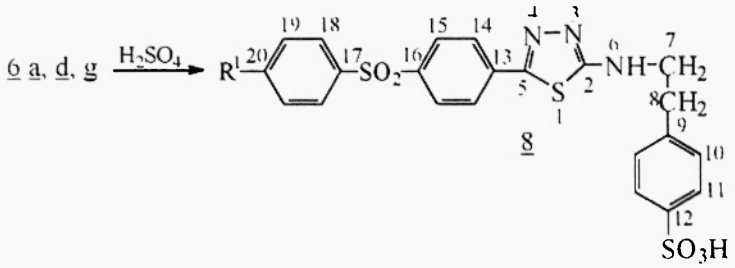
	m.p. (° C)
a: R^1=H; R^2=$PhCH_2CH_2$ –	248
b: R^1=H; R^2=*n*-Bu –	210
c: R^1=Cl; R^2=$PhCH_2CH_2$ –	220
d: R^1=Cl; R^2=*n*-Bu –	190
e: R^1=Br; R^2=$PhCH_2CH_2$ –	221
f: R^1=Br; R^2=*n*-Bu –	178

The IR-spectra proved the cyclization of 6 to 7 by the disappearance of $\nu_{C=O}$ and ν_{NH} frequencies and the occurrence of ν_{SH} bands at ~2550 cm^{-1}. In the ^{1}H-NMR spectra of 7 a-f the protons of the diarylsulfone (δ=7.53-8.04 ppm) and β-phenylethyl (2.89t; 4.25t; 6.76-7.02) or *n*-butyl (~0.85t; 1.23 sextet; 1.45 quintet; 3.40t) moieties present very similar patterns, chemical shifts and coupling constants with those of the starting materials 6. Moreover a new signal at about 3.31-3.33 ppm can be attributed to SH proton confirming also the existence of 7 in the mercaptotriazolic tautomeric form. In the ^{13}C-NMR spectrum of 7 the most characteristic signals are those of C^3 (δ=149.5-149.8 ppm) and C^5 (159.2-167.3 ppm).

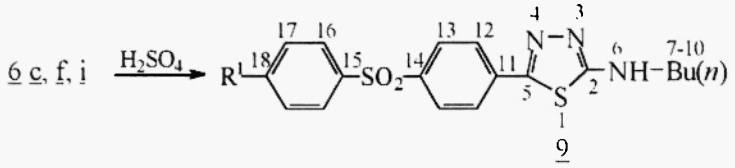
c) *Thiadiazoles*

Treatment of thiosemicarbazides 6 with concentrated H_2SO_4 usually produces the cyclization to 5-substituted amino-1,3,4-thiadiazoles (9). Unexpectedly, the thiosemicarbazides 6 behave differently on treatment with H_2SO_4: whereas the compounds 6b, 6e, 6h (with R^2=cyclohexyl) did not show any propensity to cyclize, the compounds 6a, 6d, 6g (with R^2=$PhCH_2CH_2$) afforded the unusual aminothiadiazoles 8 a-c possessing an additional -SO_3H group in the *para*-position of the side-chain phenyl ring and only the thiosemicarbazides 6c, 6f, 6i

(with R^2=*n*-butyl) gave rise to expected thiadiazoles 9 a-c.



	mp. (°C)
a: R^1= H	300 (dec.)
b: R^1= Cl	320 (dec.)
c: R^1= Br	310 (dec.)



	mp. (°C)
a: R^1= H	156
b: R^1= Cl	183
c: R^1= Br	197

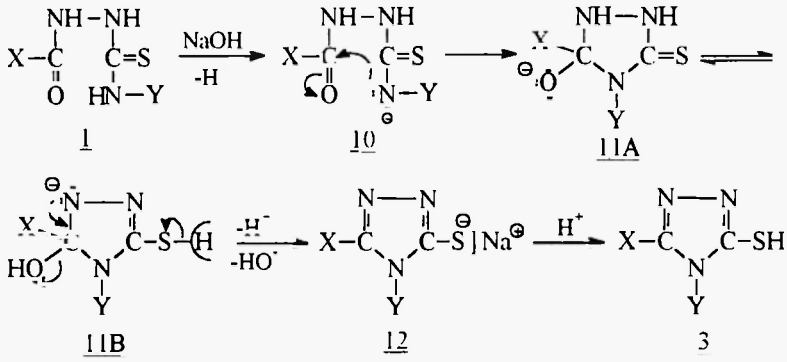
Proofs for the presence of *p*–SO_3H group in 8 a-c were brought by correct elemental analyses (e.g. for 8a, Found: C, 52.96; H, 4.03; S, 18.76%. Calcd for $C_{22}H_{19}N_3O_5S_3$: C, 52.68; H, 3.81; S, 19.18%), as well as by NMR data. The ^{1}H-NMR data of diarylsulfone moiety in 8 a-c are rather similar to that of 6 and 7 whereas in the second side-chain (*p*-HO_3S-C_6H_4-CH_2-CH_2) the proton H^7 (δ~3.58-3.60 ppm) is more shielded than the corresponding proton from 7a, c, e (δ=4.25 ppm) where the effect of the neighbouring aromatic triazole ring is easily recognisable. The protons H^8 from 8 a-c (δ=2.92 ppm) resonate at rather similar field with corresponding protons from 7 (δ=2.89-2.90 ppm). The higher chemical shifts observed for aromatic protons H^{10}, H^{11} in 8 a-c (δ=7.23 and 7.56 ppm respectively) in comparison with the corresponding aromatic protons from R^2 of compounds 7 (δ~6.79 and 6.90 ppm) is an effect of the *para*-sulfonic group in 8. Moreover, the chemical shifts of H^{10} and H^{11} from 8 can be favourable compared with those (δ=7.32 and 7.70 ppm) of the corresponding protons in *para*-toluenesulfonic acid and the ^{13}C-NMR signal of C^{12} (δ=146.1 ppm), similar with that of the corresponding C-atom from *para*-toluenesulfonic acid (δ=145.31 ppm) is very different from δ=126.4 ppm for the *para*-aromatic carbon from R^2=$C_6H_5CH_2CH_2$ in triazoles 7a, c, e.

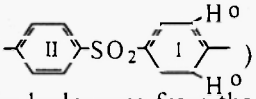
The spectral data of thiadiazoles 9a, b, c (with *n*-butylamino side chain) are in perfect agreement with the proposed structures. Both the diarylsulfone protons (δ=7.63-8.04 ppm) and *n*-butyl protons of 9a, b, c (0.89t; 1.35sextet; 1.56m; 3.31td) indicated good similarities with the signals of the corresponding protons from 6c, f, i and 7b, d, f (R^2=*n*-butyl). The signals of C^5 (169.5 ppm) and C^2 (153.5 ppm) from 9 a-c are also of the same order of magnitude with those of C^5 and C^3 from related mercaptotriazoles 7 (R^2=*n*-butyl).

DISCUSSION

Cyclization of thiosemicarbazides to mercaptotriazoles could be explained, as in other related cases (8) by the mechanism depicted in Scheme 1 where the essential intermediate is the tautomeric anion 11:

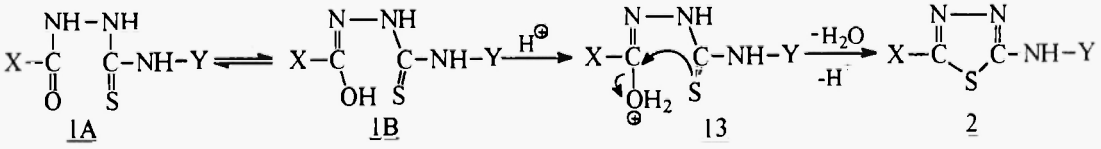
Scheme 1



In the case of thiosemicarbazides bearing a bulky cyclohexyl group ($Y=C_6H_{11}$) the inspection of Dreiding stereomodels of the anion 10 revealed strong hindrances between the $-\overset{\ominus}{\underset{\cdot\cdot}{N}}-$ atom and the neighbouring aromatic ring I from X, a fact which could prevent the cyclization to 11. Moreover the Dreiding models of triazoles 3 (with $Y=C_6H_{11}$ and X= ) indicated also strong hindrances between cyclohexyl group and the two *ortho*-hydrogens from the neighbouring benzenic ring I. These facts may render impossible the formation of triazoles with general formula 3 with $Y=C_6H_{11}$. On the contrary, the above mentioned effects are inoperative when $Y=PhCH_2CH_2$ (with a removed bulky phenyl group) or when Y=*n*-Bu (with no bulky group).

Cyclization of thiosemicarbazides to aminothiadiazoles in acidic medium can be easily explained by the intervention of enolic tautomers, protonation and water elimination/cyclization (Scheme 2):

Scheme 2



The failure of cyclization of thiosemicarbazides with bulky C_6H_{11} groups can be also attributed - at least in part - to steric hindrance. The rather strange behavior of thiosemicarbazides with Y= $PhCH_2CH_2$ which suffer electrophilic sulfonation even at low temperatures (0→20°C) seems to be due to increased reactivity of β-phenyl group from the side-chain. Performing the same reaction with the thiosemicarbazides bearing Y=*n*-butyl simultaneously eliminate the both above

mentioned "unfavourable" factors (bulkiness and propensity to sulfonation) allowing the normal cyclization to proceed either to mercaptotriazoles or to aminothiadiazoles.

CONCLUSIONS

- Nine new thiosemicarbazides possessing arylsulfonylbenzoyl groups at N^1 and β-phenylethyl, cyclohexyl and *n*-butyl groups at N^4 were synthesised and spectrally characterised.
- Attempted cyclization of cyclohexyl-thiosemicarbazides both in alkaline and acidic medium failed probably due to steric hindrance.
- Cyclization of β-phenylethyl-thiosemicarbazides in NaOH solution afforded the corresponding mercaptotriazoles whereas cyclization in concentrated H_2SO_4 gave rise to substituted amino-thiadiazoles bearing an $-SO_3H$ group in the *para*-position of the removed phenyl group.
- Cyclization of *n*-butyl-thiosemicarbazides (devoid of steric hindrance and of propensity to sulfonation) conducted to normal products, mercaptotriazoles in alkaline solution and substituted aminothiadiazoles in acidic medium.

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