New one-pot synthesis of 2-ylidenehydrazono-thiazoles

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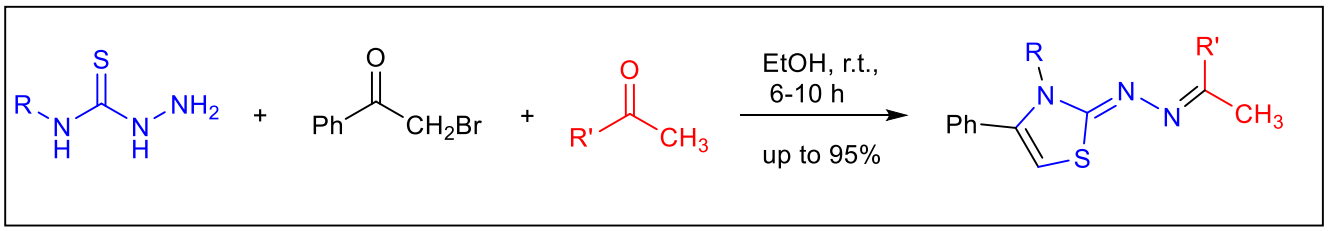
Abstract. A new one pot reaction of substituted thiosemicarbazides with 2-bromoacetophenone and carbonyl compounds gave 2-hydrazonothiazoles in good yields. The structures of the isolated compounds were corroborated by NMR, IR, mass spectra and elemental analyses in addition to X-ray structure



Keywords: Substituted thiosemicarbazides, 2-bromoacetophenone, carbonyl compounds, 2-ylidine-hydrazinothiazoles, NMR, X-ray.

1. Introduction

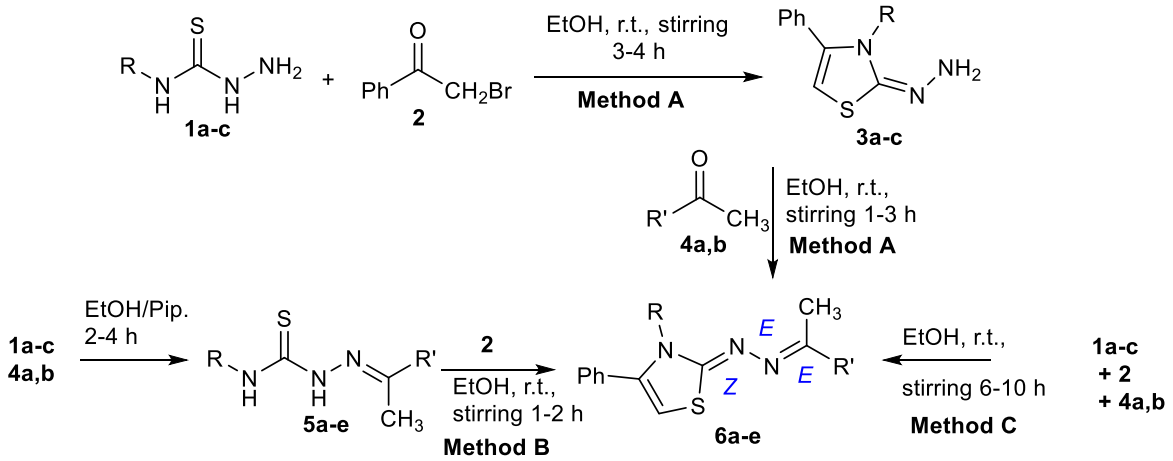
1,3-thiazole moiety is one of the most important scaffolds in heterocyclic chemistry and drug design and discovery [1]. It is widely found in diverse pharmacologically active substances and in some naturally-occurring compounds [1]. It was reported that substituted 2-hydrazino-1,3-thiazoles show an inhibitory activity (MIC of 16l µg/mL) against a resistant strain of *Candida krusei* [2]. Few other 2-hydrazino-1,3-thiazole analogues that exhibit significant antimicrobial activity have been recently reported in the literature [3]. Thiazoles bearing a bicyclic or heterocyclic ring on the hydrazone function and a phenyl at C-4 position of the thiazole nucleus are particularly active and present micromolar or submicromolar MIC against several

Candida spp. Strains (repeated) [1]. Thus, such scaffolds could be seen as a starting point for further optimization of novel antifungal agents.

Thiazoles and their analogues serve also as precursors for the synthesis of biologically active compounds [4]. They were reported to possess antimicrobial [5-8], analgesic [9], anti-inflammatory [10], anticonvulsant [11], cardiotonic [12], anticancer [13-15], antitubercular [16] and anthelmintic [17] effects. (it is better to start with this paragraph) Several methods for the synthesis of thiazole derivatives have been developed [18-20], the most widely used is being the Hantzsch synthesis, which uses thioamides and α-halocarbonyl (or α-halo ester) compounds as starting materials [21].

It was previously shown that ylidenes of hydrazinothiazoles could be synthesized by two different methods: **a**) reaction of hydrazinothiazoles with the appropriate ketones or aldehydes or **b**) reaction between thiosemicarbazides and 2-bromoacetophenones. The yields of the methods described have been suffered from long time of reaction. Our recent publication includes the synthesis of versatile, hitherto thiazole derivatives resembling LY293111 [22]. Besides that, we reported on thiazole synthesis *via* donor-acceptor reactions [23-25]. To address these interesting biological and pharmaceutical properties and their synthetic utility, we aim to design a new facile method in order to prepare ylidenes of hydrazonothiazoles in a one pot reaction starting from substituted thiosemicarbazides, 2-bromoacetophenones and ketones.

2. Results and Discussion



1,3: a, R = Ph; **b**, R = CH_2=CH-CH_2; **c**, R = Et
4: a, R' = CH_3; **b**, R = Ph
5,6: a, R = Ph, R' = CH_3; **b**, R = R' = Ph; **c**, R = CH_2=CH-CH_2, R' = Ph; **d** = R = Et, R' = CH_3; **e**, R = Et, R' = Ph

Scheme 1. Synthesis of 2-ylidenes of hydrazonothiazoles **6a-e**

The compounds **3a-c** [26] were previously prepared on one hand by reaction of substituted thiosemicarbazides **1a-c** with 2-bromo-acetophenone (**2**) (Scheme 1, method **A**). On the other hand, reaction of **1a-c** with appropriate ketones **4a,b**, gave the corresponding thiosemihydrazones **5a-e** [27] and upon subjecting compounds **5a-e** with bromide **2**, the corresponding 2-ylidenes of hydrazinothiazoles **6a-e** were obtained in moderate yields (Scheme 1, method **B**). The yields of the products **6a-e** (i.e. preparation of compounds **6a-d** according to lit [28]) using the two aforesaid procedures were not optimal (Scheme 1).

We herein reported on one-pot method using a mixture of **1a-c**, **2** and **4a,b** (Scheme 1, method **C**). The yields of compounds **6a-e** using the method **C** are shown in Table 1. The distinctive carbons of the aforesaid compounds are shown in Figure 1. The structures of the isolated products were confirmed by mass, NMR, IR spectra in addition to elemental analyses. For example, the NMR spectroscopic data of compounds **6a** and **6b** are shown in Tables 2 and 3.

Table 1. Yields of compounds **6a-e** using method **C**

Compound	Yield (%)
6a	92
6b	95
6c	93
6d	78
6e	94

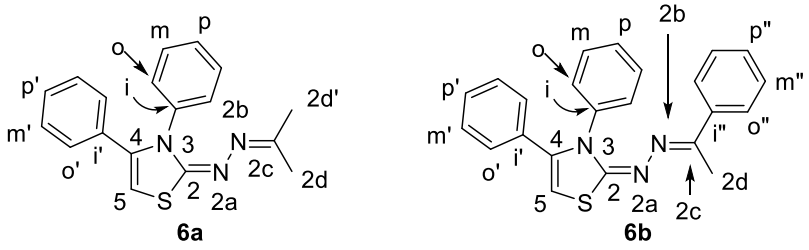


Figure 1. Distinctive carbons of compounds **6a** and **6b**

Table 2. NMR spectroscopy of 6a

^{1}H NMR:	**COSY:**	**Assignment**
7.33 ("t", *J* = 7.5; 2H)	7.22, *7.15*	H-*m*
7.22 (m; 6H)	7.33, 7.15	H-*o, m', p, p'*
7.15 (m; 2H)	*7.33*, 7.22	H-*o'*
6.51 (s; 1H)		H-5
1.91 (s; 3H)		H-2d/2d'
1.79 (s; 3H)		H-2d'/2d

^{13}C NMR:	**HSQC:**	**HMBC:**	**Assignment:**
165.94		6.51, *1.91*, *1.79*	C-2
158.86		1.91, 1.79	C-2c
139.08, 138.06		7.33, 7.22, 7.15, 6.51	C-*i*, 4

131.05		7.22, 7.15, 6.51	C-*i'*
128.52	7.33	7.33, 7.22, 7.15, 6.51	C-*m*
128.32, 128.19	7.22	7.33, 7.22, 7.15, 6.51	C-*o, m'*
128.14	7.22	7.33, 7.22, 7.15, 6.51	C-*p/p'*
127.89	7.15	7.33, 7.22, 7.15, 6.51	C-*o'*
127.23	7.22	7.33, 7.22, 7.15, 6.51	C-*p'/p*
100.95	6.51		C-5
24.30	1.91	1.79	C-2d/2d'
18.17	1.79	1.91	C-2d'/2d

^{15}N NMR:	**HSQC:**	**HMBC:**	**Assignment:**
344.5		1.91, 1.79	N-2b
138.5		7.22, 6.51	N-3

Table 3. NMR spectroscopy of compound 6b

^{1}H NMR:	**COSY:**	**Assignment:**
7.81 (dd, *J* = 8.0, 1.5; 2H)	7.37	H-*o"*
7.37 (m; 5H)	7.81, 7.30, 7.26	H-*m, m", p"*
7.30 (m; 3H)	7.37, 7.26, *7.19*	H-*o, p/p'*
7.26 (m; 3H)	7.37, 7.30, 7.19	H-*m', p'/p*
7.19 (m; 2H)	*7.30*, 7.26	H-*o'*
6.66 (s; 1H)		H-5
2.20 (s; 3H)		H-2d

^{15}N NMR:	**HSQC:**	**HMBC:**	**Assignment:**
354.1	2.20		N-2b
142.6	6.66		N-3

^{13}C NMR:	**HSQC:**	**HMBC:**	**Assignment:**
168.90		6.66, *2.20*	C-2
155.80		7.81, 2.20	C-2c
139.57		*7.26*, 7.19, 6.66	C-4
138.25, 137.71		7.37, 7.30, 2.20	C-*i, i"*
130.77		7.26, 6.66	C-*i'*
128.88	7.37	7.81, 7.37, 7.30, 7.26, 7.19, *6.66*	C-*p"*
128.69	7.37		C-*m*
128.40	7.30		C-*o'*
128.33	7.26		C-*p/p'*
128.25	7.37		C-*m'*
128.22	7.37		C-*m"*
128.09	7.19		C-*o'*
127.64	7.30		C-*p'/p*
125.90	7.81	7.81, 7.37	C-*o"*
102.02	6.66		C-5
14.40	2.20		C-2d

The X-ray structure analysis confirmed the structure of **6a** as shown in Figure 2. The stereochemistry of compound **6a** was determined with a *Z, s-trans (transoid)* configuration for the CNN moiety and the

compound was identified finally as (*Z,s-trans*)-3,4-diphenyl-propan-2-ylidenehydrazono-2,3-dihydro-thiazole.

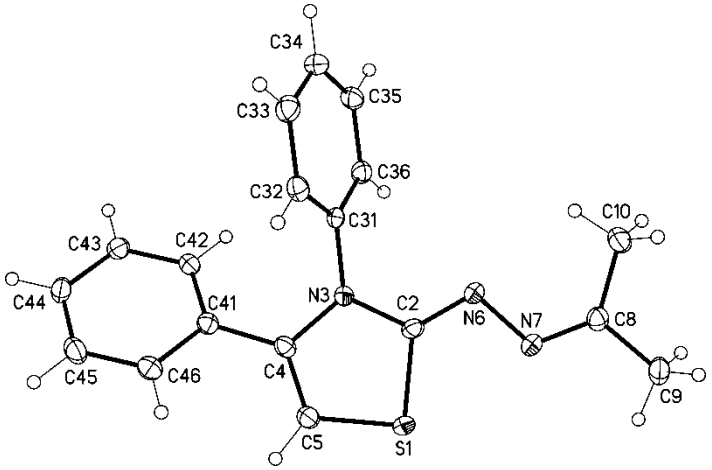


Figure 1. Molecular structure of **6a** (displacement parameters are drawn at 50% probability level)

3. Experimental Part

3.1. General

Melting points were determined using an APP Digital ST 15 melting point apparatus and uncorrected. TLC analyses were performed using analytical Merck 9385 silica aluminum sheets (Kieselgel 60) with PF_{254} indicator. The IR spectra were recorded as KBr disks on Shimadzu-408 infrared spectrophotometer, Faculty of Science, Minia University. The NMR spectra were measured using a Bruker AV-400 spectrometer at the Karlsruher Institut für Technologie (KIT), Institute of Organic Chemistry, Karlsruhe, Germany. Chemical shifts were expressed as δ (ppm) with tetramethylsilane as internal reference. The samples were dissolved in DMSO-d_6, s = singlet, d = doublet, dd = doublet of doublet and t = triplet. Mass spectrometry were recorded on a Varian MAT 312 instrument in EI mode (70 eV), at the Karlsruhe Institut für Technologie (KIT), Institute of Organic Chemistry, Karlsruhe, Germany. Elemental analyses were carried out using Varian Elementary device in National Research Center, Giza, Egypt.

3.2. Crystal Structure Determination of 6a

The single-crystal X-ray diffraction study was carried out on a Bruker D8 Venture diffractometer with Photon100 detector at 123(2) K using Cu-Kα radiation (λ = 1.54178 Å). Dual space methods (SHELXT) [29] were used for structure solution and refinement was carried out using SHELXL-2014 (full-matrix least-

squares on F^2) [29]. Hydrogen atoms were refined using a riding model. A semi-empirical absorption correction and an extinction correction were applied.

6a: Yellow crystals, $C_{18}H_{17}N_3S$, M_r = 307.40, crystal size 0.20 × 0.08 × 0.04 mm, monoclinic, space group $P2_1/c$ (No. 14), a = 5.8645(2) Å, b = 14.0488(5) Å, c = 18.7533(7) Å, β = 97.003(2)°, V = 1533.11(10) Å^3, Z = 4, ρ = 1.332 Mg/m^{-3}, μ(Cu-K$_\alpha$) = 1.857 mm^{-1}, F(000) = 648, $2\theta_{max}$ = 144.4°, 16566 reflections, of which 3015 were independent (R_{int} = 0.025), 202 parameters, R_1 = 0.029 (for 2856 I > 2σ(I)), wR_2 = 0.072 (all data), S = 1.04, largest diff. peak / hole = 0.255 / -0.240 e Å^{-3}.

CCDC 1896104 (**6a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

3.3. Starting materials

Compounds **3a-c** and **5a-e** were prepared according to literature [26] and [27], respectively (see their corresponding references). Compounds **6a-d** were prepared for comparison according to literature [28].

3.4. General procedure describes preparation of compounds 6a-e

A mixture of **1a-c**, **2** and **4a,b** (1 mmol) in absolute ethanol (EtOH, 150 mL), was stirred at room temperature for 6-10 h (the reaction was monitored by TLC). The reaction mixture was allowed to stand overnight. The formed products were recrystallized from the stated solvents.

(Z)-3,4-Diphenyl-2-(propan-2-ylidenehydrazono)-2,3-dihydrothiazole (6a). Pale yellow crystals (EtOH), R_f = 0.5 (Toluene: Ethyl acetate: 10:1), yield 0.283 g (92%), m.p. 165-167 °C (m.p. [28a] 165 °C). NMR ($CDCl_3$): see Table 2. Anal. Calcd. For $C_{18}H_{17}N_3S$ (307.42): C, 70.33; H, 5.57; N, 13.67. Found: C, 70.22; H, 5.45; N, 13.55.

(Z)-3,4-Diphenyl-2-((E)-1-phenylethylidene)hydrazono)-2,3-dihydrothiazole (6b). Pale yellow crystals (EtOH), R_f = 0.4 (Toluene: Ethyl acetate: 10:1), yield 0.350 g (95%), m.p. 310-312 °C (m.p. [28b] 310-312 °C). NMR ($CDCl_3$): see Table 3. Anal. calcd. for $C_{23}H_{19}N_3S$ (369.49): C, 74.77; H, 5.18; N, 11.37. Found: C, 74.62; H, 5.00; N, 11.25.

(Z)-3-Allyl-4-phenyl-2-(E)-1-phenylethylidene)hydrazono)-2,3-dihydrothiazole (6c). Pale yellow crystals (CH_3CN), R_f = 0.7 (Toluene: Ethyl acetate: 10:1), yield 0.310 g (93%), m.p. 247-249 ^oC (m.p. [28b] 246-248 °C). Anal. calcd. for $C_{20}H_{19}N_3S$ (333.45): C, 72.04; H, 5.74; N, 12.60. Found: C, 72.16; H, 5.80; N, 12.46.

(Z)-3-Ethyl-4-phenyl-2-propan-2-ylidene)hydrazono)-2,3-dihydrothiazole (6d). Pale yellow crystals (CH_3OH), R_f = 0.75 (Toluene: Ethyl acetate: 10:1), yield 0.202 g (78%), m.p. =97-98 ^oC (lit [28b] 96 °C). Anal. calcd. for $C_{14}H_{17}N_3S$ (259.37): C, 64.83; H, 6.61; N, 16.20. Found: C, 64.70; H, 6.81; N, 16.36.

(Z)-3-Ethyl-4-phenyl-2-(E)-1-phenylethylidene)hydrazono)-2,3-dihydrothiazole (6e). Pale yellow crystals (CH_3OH), R_f = 0.8 (Toluene: Ethyl acetate: 10:1), yield 0.302 g (94%), m.p. = 212-214 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.80-7.78 (m, 2H, Ph-H), 7.60-7.40 (m, 4H, Ph-H), 6.92 (s, 1H, thiazole-5), 6.86-6.82 (m, 4H, Ph-H), 4.00 (q, 2H, *J* = 7.0 Hz, CH_2-ethyl), 2.40 (s, 3H, CH_3), 1.20 (t, 3H, *J* = 7.0 Hz, CH_3-ethyl). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 164.0, 155.0 (C=N), 139.0 (C-4-thiazole), 137.0 (Ph-2C), 132.0, 131.0, 130.6, 130.0 (Ph-2CH), 127.0, 126.2 (Ph-CH), 102.0 (Thiazole-CH-5), 38.9 (CH_2-ethyl), 21.0 (CH_3), 13.0 (CH_3). Anal. calcd. for $C_{19}H_{19}N_3S$ (321.44): C, 71,00; H, 5.96; N, 13.07. Found: C, 71.10; H, 6.00; N, 13.12.

4. Conclusion

In this paper, we illustrate a new method of synthesizing hydrazonothiazoles by one-pot reaction of substituted thiosemicarbazides, 2-bromoacetophenones and ketones. The advantages of our new method are; a) high yield percentages of the products, b) facile one pot method (at room temperature) and c) the illustrated method does not involve any additives.

5. Acknowledgements

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6. Disclosure statement

No potential conflict of interest was reported by the authors.

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