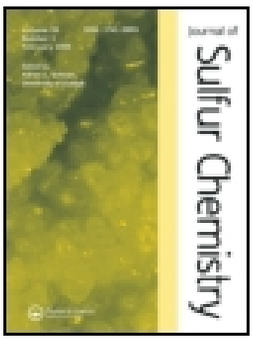

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New one-pot synthesis of 2-ylidenehydrazono-thiazoles

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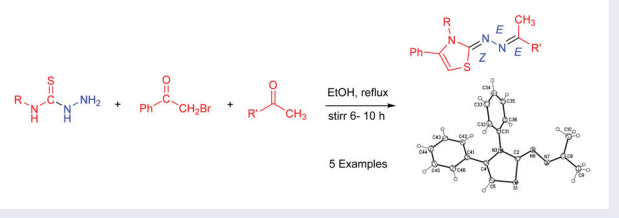
ABSTRACT

A new one pot reaction of substituted thiosemicarbazides with 2-bromoacetophenone and carbonyl compounds gave 2-hydrazono thiazoles 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 determination.



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Substituted thiosemicarbazides; 2-bromoacetophenone; carbonyl compounds; 2-ylidine-hydrazinothiazoles; NMR; X-ray

Introduction

The 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]. In recent years, many thiazole derivatives have been synthesized and subjected to various biological activity studies. Thiazoles and their analogues serve as precursors for the synthesis of biologically active compounds [2]. They were reported to possess antimicrobial [3–6], analgesic [7], anti-inflammatory [8], anticonvulsant [9], cardiotonic [10], anticancer [11–13], antitubercular [14] and anthelmintic [15] effects.

It was reported that substituted 2-hydrazino-1,3-thiazoles show an inhibitory activity (MIC of 16 l μg/mL) against a resistant strain of *Candida krusei* [16]. Only a few other 2-hydrazino-1,3-thiazole analogues that exhibit significant antimicrobial activity have recently been reported in the literature [17]. Thiazoles bearing a bicyclic or heterocyclic ring on a hydrazone functionality and a phenyl at the C-4 position of the thiazole

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nucleus are particularly active and present micromolar or submicromolar MIC activity against several *Candida spp.* Strains (repeated) [1]. Thus, such scaffolds are an interesting starting point for further optimization of novel antifungal agents.

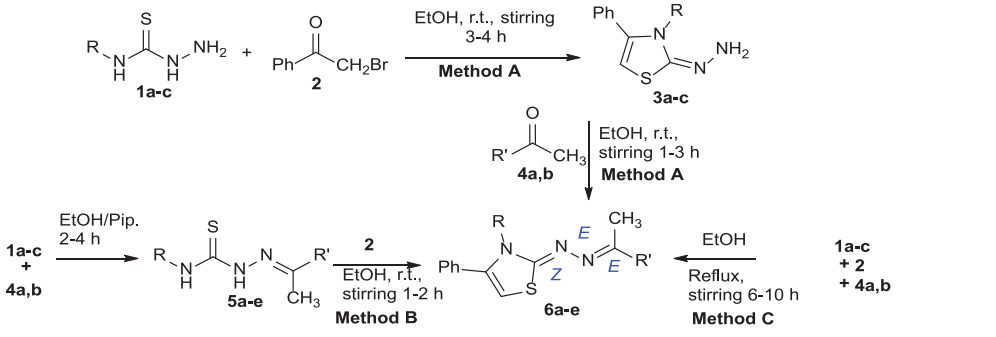
Several methods for the synthesis of thiazole derivatives have been developed [18–20], the most widely used is the Hantzsch synthesis, which uses thioamides and α-halocarbonyl (or α-halo ester) compounds as starting materials [21]. It was previously shown that ylidenes of hydrazinothiazoles could be 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 suffer from long reaction times. In this manuscript, we have designed a new facile method in order to prepare ylidenes of hydrazonothiazoles in a one pot reaction starting from substituted thiosemicarbazides, 2-bromoacetophenones and ketones.

Results and Discussion

The compounds **3a-c** [22,23] were previously prepared by reaction of substituted thiosemicarbazides **1a-c** with 2-bromoacetophenone (**2**) (Scheme 1, method **A**). On the other hand, reaction of **1a-c** with appropriate ketones **4a,b**, gave the corresponding thiosemihydrazones **5a-e** [24–28] and upon subjecting compounds **5a-e** to 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 the literature [29–31]) using the two aforesaid procedures were not optimal (Scheme 1).

We herein reported a new one-pot method using a mixture of **1a-c**, **2** and **4a,b** (Scheme 1, method **C**). The yields of this one-pot method are far superior to those obtained by methods **A** and **C**. The X-ray structure confirmed the identity of **6a** as shown in Figure 1. It further established the stereochemistry of the CNN moiety as *Z, s-trans (transoid)* conclusively establishing its structure as (*Z,s-trans*)-3,4-diphenyl-propan-2-ylidenehydrazono-2,3-dihydrothiazole.

The yields of compounds **6a-e** using the **Method C** are shown in Table 1. In comparison, as examples, the yields of compound **6a,c** with those reported by **Method B**, we can find



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

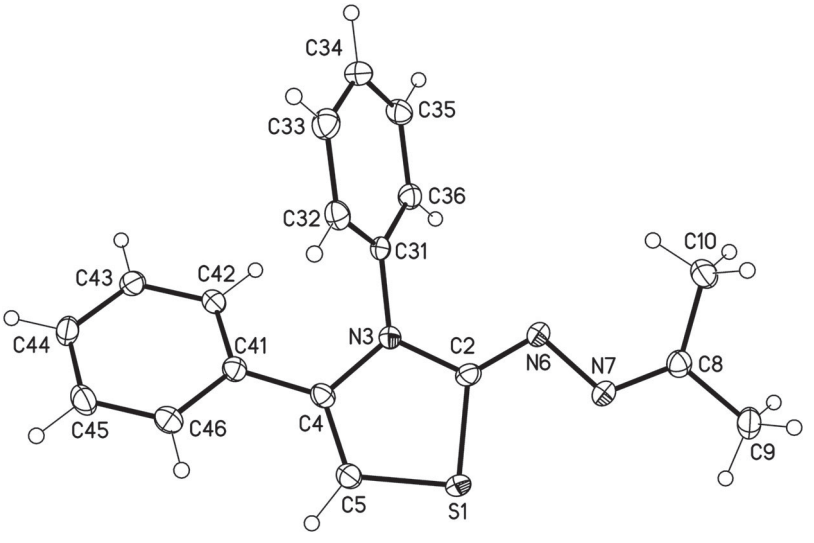


Figure 1. Molecular structure of **6a** (displacement parameters are drawn at 50% probability level).

Table 1. Yields of compounds **6a-e** using methods **C** and those reported by **B**.

Compound	Yield (%) from Method C	Yield (%) from Method B
6a	92	88 [24]
6b	95	
6c	93	70 [25]
6d	78	
6e	94	

out the advantages of our procedure. In addition time and chemicals were conserved by our new method.

Conclusion

In this paper, we have illustrated a new method of synthesizing hydrazonothiazoles by a one-pot reaction consisting of substituted thiosemicarbazides, 2-bromoacetophenones and ketones. The advantages of our new method are; a) high yields of the products, b) facile one pot method and c) the absence of any additives.

Experimental

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 Florida Institute of Technology, Melbourne, FL, USA. Chemical shifts were expressed as δ (ppm) with tetramethylsilane as internal reference. The samples were dissolved in $CDCl_3$ and 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.

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) [32] were used for structure solution and refinement was carried out using SHELXL-2014 (full-matrix least-squares on F^2) [33]. 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.

Starting materials

Compounds **3a-c** and **5a-e** were prepared according to literature [22] and [23], respectively (see their corresponding references). Compounds **6a-d** were prepared for comparison according to the literature [24]. The NMR assignments were made with a combination of COSY, HSQC, and HMBC experiments.

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 refluxed with 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), yield: 0.283 g (92%), R_f = 0.6 (Toluene: AcOEt; 10:1), m.p. 165–167°C (m.p. [24] 165°C). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.33 (t, 2H, J = 7.5 Hz, Ar-H-*m*), 7.25–7.22 (m, 6H, Ar-H-*o, m', p, p'*), 7.17–7.15 (m, 2H, Ar-H-*o'*), 6.51 (s, 1H, H-5), 1.91 (s, 3H, CH_3), 1.79 (s, 3H, CH_3); ^{13}C NMR (400 MHz, DMSO-d_6): δ = 165.9 (C-2), 158.9,

139.1, 138.1, 131.1 (Ar-C), 128.5 (Ar-2CH-*m*), 128.3, 128.2 (Ar-2CH-*o*,*m*'), 128.1 (Ar-CH-*p*,*p*'), 127.9 (Ar-2CH-*o*'), 127.2 (Ar-CH-*p*, *p*'), 101.0 (thiazole-C-5), 24.3, 18.7 (CH_3). ^{15}N (NMR, DMSO-d_6): $\delta = 344.5$ (azomethine-*N*), 138.5 (thiazole-*N*). 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), yield: 0.350 g (95%), $R_f = 0.4$ (Toluene: AcOEt; 10:1), m.p. 310–312°C (m.p. [25] 310–312°C). ^1H NMR (400 MHz, DMSO-d_6): $\delta = 7.81$ (dd, 2H, $J = 8.0$, 1.50 Hz, Ar-H-*o*), 7.38–7.36 (m, 5H, Ar-H-*m, m*",*p*"), 7.32–7.29 (m, 3H, Ar-H-*o*,*p*/*p*'), 7.27–7.25 (m, 3H, Ar-H- H-*m*', *p*'/*p*), 7.21–7.20 (m, 2H, Ar-H- H-*o*'), 6.66 (s, 1H, H-5), 2.20 (s, 3H, CH_3), ^{13}C NMR (400 MHz, DMSO-d_6): $\delta = 168.9$ (C-2), 155.8, 139.6, 138.3, 137.7, 130.8 (Ar-C), 128.9 (Ar-CH-*p*"), 128.7, 128.4 (Ar-2CH-*o*'), 128.3 (Ar-CH-*p*,*p*'), 128.2 (Ar-2CH-*m*'), 128.1 (Ar-2CH-*m*"), 128.0 (Ar-2CH-*o*'), 127.6 (Ar-CH-*p*,*p*'), 125.9 (Ar-2CH-*o*'), 102.0 (thiazole-C-5), 14.4 (CH_3). ^{15}N (NMR, DMSO-d_6): $\delta = 354.1$ (azomethine-*N*), 142.6 (thiazole-*N*). 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), yield: 0.310 g (93%), $R_f = 0.45$ (Toluene: AcOEt; 10:1), m.p. 247–249°C (m.p. [25] 246–248°C). 1 H NMR (400 MHz, DMSO-d_6): $\delta = 7.54$–7.44 (m, 4H, Ar-CH), 7.34–7.21 (m, 6H, Ar-CH), 7.12 (s, 1H, H-5), 5.65–5.63 (m, 1H, allyl-CH), 5.28–5.24 (m, 2H, allyl-CH_2-), 4.49 (br, 2H, allyl-CH_2N), 2.31 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 163.0$ (thiazole-C), 158.9, 142.2, 137.9, 141.5 (Ar-C), 135.7 (Allyl-CH), 130.2, 129.2, 128.9, 128.2, 127.8, 126.7 (Ar-CH), 116.7 (Ally-CH_2), 106.2 (thiazole-CH-5), 45.8 (Allyl-CH_2N), 14.44 (CH_3); 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), yield: 0.202 g (78%), m.p. =97–98°C (lit [25] 96°C). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.78$–7.76 (m, 2H, Ph-H), 7.50-.46 (m, 3H, Ph-H), 7.10 (s, 1H, thiazole-5), 4.00 (q, 2H, $J = 7.0$ Hz, CH_2-ethyl), 2.40 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 1.20 (t, 3H, $J = 7.0$ Hz, CH_3-ethyl). ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 168.0$, 158.0 (C = N), 139.4 (C-4-thiazole), 136.5 (Ph-C), 128.6, 127.0 (Ph-2CH), 126.0 (Ph-CH), 103.0 (thiazole-CH-5), 39.4 (CH_2-ethyl), 22.4, 21.0 (CH_3), 13.0 (CH_3-ethyl). 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), yield: 0.302 g (94%), $R_f = 0.3$ (Toluene: AcOEt; 10:1), m.p. = 212–214 °C. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.80$–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, $CDCl_3$): $\delta = 164.0$, 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, 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.

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Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

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