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Eco-friendly solvent-free synthesis of thiazolylpyrazole derivatives

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Abstract Highly versatile ethyl 3-thiosemicarbazidobutanoate was ball-milled with phenacyl bromide to afford the corresponding ethyl 3-[(4-phenyl-2-thiazolyl)hydrazono]butanoate which underwent heterocyclization by heating in ethanolic sodium acetate to give thiazolylpyrazolone that coupled chemoselectively with aromatic diazonium salts to furnish arylhydrazonothiazolylpyrazoles. *Vilsmeier-Haack* reaction of ethyl 3-thiosemicarbazidobutanoate furnished selectively thiazolylpyrazole. A series of pyrazolylthiosemicarbazones were synthesized by solid-state technique which allowed waste-free production. The reaction of pyrazolylthiosemicarbazones with phenacyl bromide afforded the corresponding 2-(arylidenehydrazino)-4-phenylthiazoles in quantitative yields.

Keywords Thiazole; Pyrazole; Thiosemicarbazide; Ball-milling.

Introduction

The development of simple synthesis routes for widely used organic compounds from readily available reagents is one of the major tasks in organic synthesis. Compounds containing the thiazole ring system are known to possess pharmacological properties such as analgesic, antibacterial, anticonvulsant, antiparasitic, antiinflammatory, and herbicidal activity [1–8]. Some derivatives of thiazole are potent anti-HIV agents [9]. In view of the various physiological activities of thiazoles, several approaches for their synthesis have been described by our group in Refs. [10–12]. As part of our current studies on the development of new routes for the synthesis of thiazoles incorporating a pyrazole moiety [13–16], we report herein an efficient, solid-state synthesis of highly functionalized thiazolylpyrazoles *via* the reaction of ethyl 3-thiosemicarbazidobutanoate and/or a variety of pyrazolylthiosemicarbazones with phenacyl bromide.

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Results and discussion

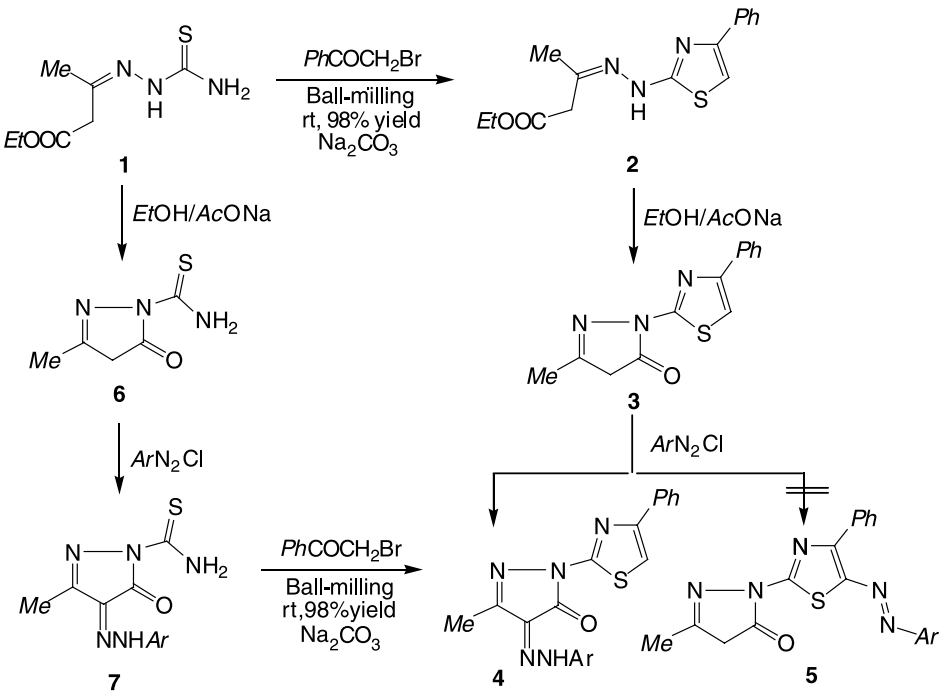
The reaction of ethyl acetoacetate with thiosemicarbazide has been reported to afford the highly versatile ethyl 3-thiosemicarbazidobutanoate (**1**) [17] which was used as a precursor for the synthesis of a variety of heterocycles. The ball-milling of the intermediate **1** with phenacyl bromide was carried out at room temperature to afford the corresponding thiazole derivative **2** in quantitative yield (98%). The chemical structure of **2** was established on the basis of spectral data. The IR spectrum confirmed the presence of NH, CO, and C=N stretching absorption bands at $\bar{\nu} = 3300$, 1720, and 1606 cm^{-1}. The ^1H NMR spectrum revealed a triplet signal at $\delta =$ 1.28 ppm and a quartet signal at $\delta = 4.20$ ppm due to the methyl and methylene protons of the ethoxy group, in addition to four singlets at $\delta = 2.10$, 3.38, 6.8, and 9.05 ppm assigned to methyl, methylene, thiazole H-5, and NH protons. The mass spectrum

showed a molecular ion peak (M^+) at $m/z = 303$, corresponding to the molecular weight of the molecular formula $C_{15}H_{17}N_3O_2S$.

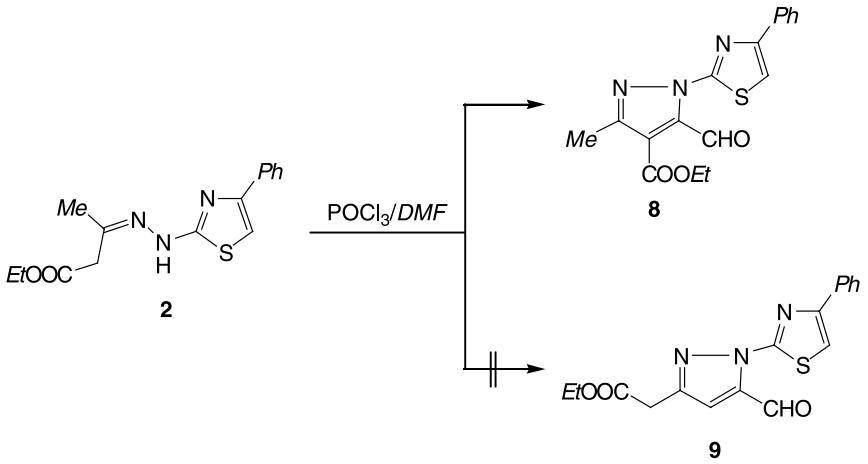
Heterocyclization of ethyl 3-[(4-phenyl-2-thiazolyl)hydrazono]butanoate (**2**) by refluxing in ethanolic sodium acetate solution afforded the corresponding thiazolyl-pyrazol-5-one **3**. The chemical structure of **3** was elucidated on the basis of spectral techniques. The IR spectrum displayed the characteristic absorption band for the amidic carbonyl at $\bar{\nu} = 1634\,cm^{-1}$. The ^1H NMR spectrum displayed three singlets at $\delta = 2.25$, 5.30, and 6.78 ppm due to methyl protons, pyrazolone H-4, and thiazole H-5, in addition to a multiplet signal of the aromatic protons at $\delta = 7.35$–8.00 ppm. Also the spectrum clearly indicated the absence of ethyl ester protons (triplet and quartet signals). The mass spectrum showed a molecular ion peak (M^+) at $m/z = 257$ (intensity 100%) corresponding to a molecular formula $C_{13}H_{11}N_3OS$.

The thiazolylpyrazol-5-one **3** couples with aromatic diazonium salts in pyridine at 0–5°C to afford the coupling product for which two isomeric structures **4** or **5** seemed possible. The ^1H NMR spectrum provided a firm support for structure **4** and ruled out the other possible isomer **5** by lack of the signal due to the methylene protons of the pyrazolone ring and the appearance of the signal due to the thiazole H-5 around 6.62 ppm. Also, the structure **4** was further confirmed by an independent synthesis *via* the cyclization of compound **1** by heating in ethanol containing sodium acetate to give the corresponding pyrazolone **6**, which underwent coupling with aromatic diazonium salts to produce the arylhydrazonopyrazolone **7** that cyclized with phenacyl bromide to afford the target compound **4**. The IR spectrum of **4a** (for example) showed an absorption band at $\bar{\nu} = 3212\,cm^{-1}$ due to the hydrazono NH function besides one amidic carbonyl absorption band at $\bar{\nu} = 1666\,cm^{-1}$. The mass spectrum of **4b** showed a molecular ion peak at $m/z = 375$ (intensity 7.8%) corresponding to the mass of the molecular formula $C_{20}H_{17}N_5OS$.

Treatment of compound **2** with phosphorus oxychloride and *DMF* under *Vislmeier-Haack* reaction conditions afforded selectively the formylpyrazole **8** rather than **9** in good yield (Scheme 2). The chemical structure of **8** was inferred based on spectral data. The ^1H NMR spectrum displayed a new downfield singlet signal at $\delta = 9.84$ ppm assigned to the formyl proton, in addition to the absence of the activated methylene protons. The IR spectrum showed two



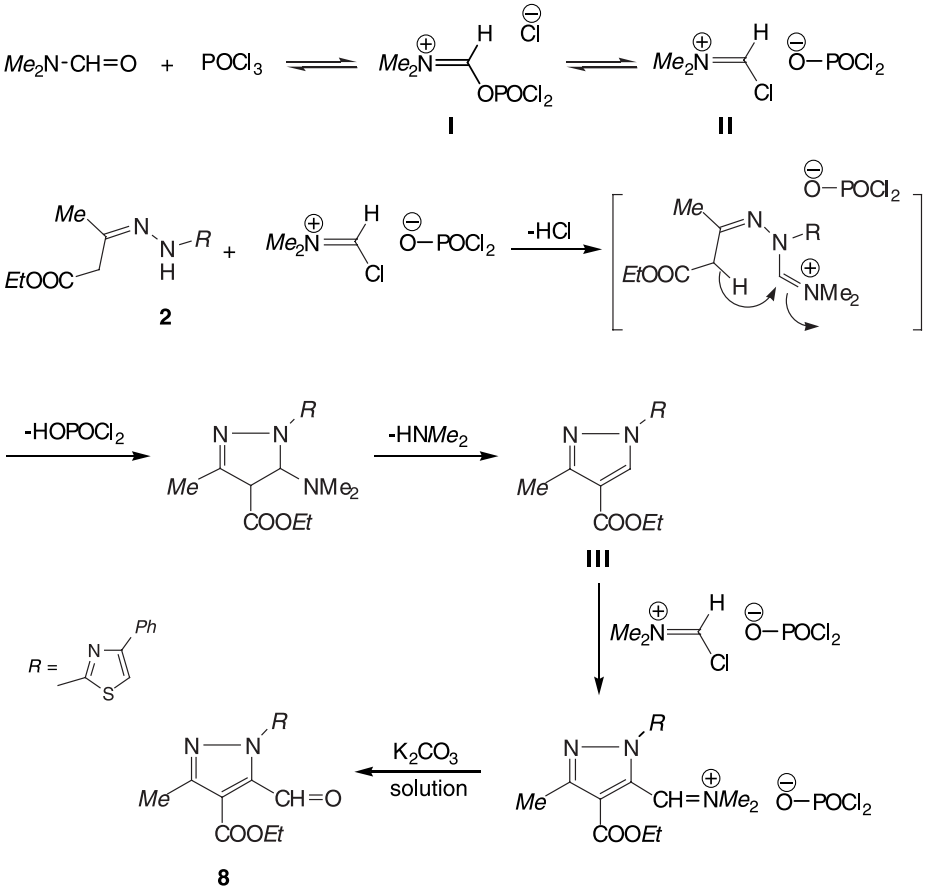
Scheme 1



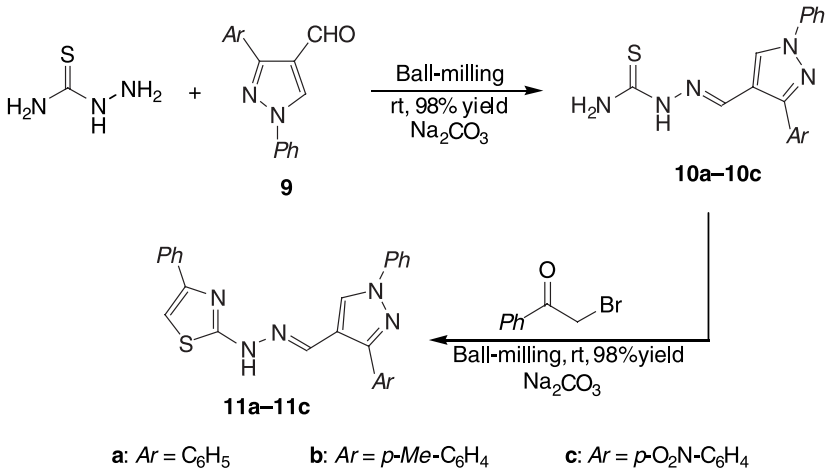
Scheme 2

strong absorption bands at $\bar{\nu} = 1704$ and $1695\,\mathrm{cm}^{-1}$ characteristic for the two carbonyl groups.

The plausible mechanism for the formation of formylpyrazole **8** maybe explained as follows: the *Vilsmeier-Haack* reagent (formylating agent), formed *in situ* from *DMF* and phosphorus oxychloride, is an equilibrium mixture of iminium salts **I** and **II** [18]. Two moles of the mixture of **I** and **II** were used in the reaction with the highly reactive methylene of the hydrazone form **2**. It is well known that the hydrogen



Scheme 3



Scheme 4

of the methylene group in our moiety possesses a partially positive charge due to hyperconjugation and hence the methylene carbon is readily attacked by a strong and reactive electrophile. In the first step, one mole of the reagent is responsible for the cyclization furnishing the pyrazole **III**. In the second step, the other mole of reagent reacts with pyrazole intermediate **III** to give the formyl pyrazole **8** after hydrolysis by alkaline solution. The reaction course is depicted in Scheme 3.

Waste-free environmentally benign solid-state reactions mean quantitative yield of one product without any necessity for purifying workup by recrystallization, chromatography, *etc*. Organic solid-state reactions in the gas-solid and stoichiometric solid–solid versions are highly promising new tools for solvent-free sustainable synthesis. More than thousand waste-free quantitative syntheses in organic solid-state chemistry are already known and have been reported in a review article that covers more than 25 reaction types [19–21]. These include solvent-free salt formations, complexations, condensations of amines, heterocyclic syntheses, *Knoevenagel* condensations, cascade reactions, halogen additions, stereo- and regio-specific protective reactions, and redox reactions. All of these may be of technical importance. Some of these involve now easily obtainable products that cannot be produced by solution reactions.

Thus, a series of thiosemicarbazone derivatives **10a–10c** were synthesized by solid-state technique which allowed waste-free production. Ball-milling of thiosemicarbazide with a series of 4-formylpyrazoles **9** [22] afforded the corresponding thiosemicarbazones **10a–10c**. The reaction proceeds at room temperature, yields are quantitative in all cases, and the products do not require purifying workup.

The technique of waste-free solid-state reaction could be also applied to prepare the 2-(arylidenehydrazino)-4-phenylthiazoles **11a–11c**. Stoichiometric runs by ball milling of phenacyl bromide with the arylidenethiosemicarbazone derivatives **10a–10c** afforded the corresponding iminium hydrobromide salts with 98% yield without the aid of basic catalysts and solvents. The water of the reaction can be removed by evaporation at 80°C in vacuum without loss by hydrolysis. Washings with aqueous Na_2CO_3 can easily liberate the free bases **11a–11c** (Scheme 4).

The chemical structure of **11a–11c** was elucidated on the basis of spectral techniques. The IR spectrum of **11c** (for example) showed the characteristic absorption bands for NH and C=N stretching at $\bar{\nu} = 3121$ and $1614\,cm^{-1}$. The ^1H NMR spectrum of **11c** displayed three singlets at $\delta = 6.62$, 8.36, and 8.63 ppm due to the thiazole H-5, azomethine proton (CH=N), and NH proton, in addition to a multiplet signal centered around the region 7.27–8.30 assigned to the aromatic and pyrazole-H-5 protons. The mass spectrum of **11c** showed a molecular ion peak at $m/z = 466$ (intensity 75.3%) corresponding to the molecular weight of the molecular formula $C_{25}H_{18}N_6O_2S$, in addition to other fragments at 344, 306, and 122.

Conclusion

In conclusion, several thiazolylpyrazole derivatives were prepared from the readily available ethyl 3-[(4-

phenyl-2-thiazolyl)hydrazono]butanoate either by heating in ethanol in the presence of a catalytic amount of sodium acetate or by treatment with *Vilsmeier-Haack* reagent. A number of 2-(arylidenehydrazino)thiazole derivatives **11a–11c** has been synthesized by a solid-state solvent-free technique which allowed waste-free production. These highly functionalized derivatives may be of interest for pharmaceutical purposes, yet to be explored.

Experimental

All melting points were measured on an electrothermal Gallenkamp melting apparatus. Elemental analyses were carried out at the Microanalytical Unit of the Faculty of Science, Cairo University, and all compounds gave satisfactory elemental analyses. IR spectra (KBr) were determined on a Mattson 5000 FTIR spectrometer (not all frequencies are reported). ^{1}H NMR (300 MHz) and ^{13}C NMR (75.5 MHz) spectra were measured on a Bruker WP 300 in $CDCl_3$ or *DMSO*-d_6 as solvents, using *TMS* as an internal standard, and chemical shifts are expressed as δ in ppm. Mass spectra were obtained on a Finnigan MAT 212 instrument by electron impact (EI) at 70 eV. The ball-mill was a Retsch MM 2000 swing mill with a 10-cm^3 stainless steel, double-walled beaker with fittings for circulating coolants. Two stainless steel balls of 12 mm diameter were used. Ball-milling was performed at 20225 Hz frequency, usually at room temperature (without circulating liquid the temperature did not rise above 30°C). Water or methanol of the appropriate temperature was circulated for heating or cooling. Ethyl 3-thiosemicarbazidobutanoate (**1**) [17], 4,5-dihydro-3-methyl-5-oxopyrazole-1-carbothioamide (**6**) [23], and 4-(2-arylhydrazono)-4,5-dihydro-3-methyl-5-oxopyrazole-1-carbothioamide (**7**) [24] were prepared according to the reported procedures.

Ethyl 3-[(4-phenyl-2-thiazolyl)hydrazono]butanoate (**2**, $C_{15}H_{17}N_3O_2S$)

A mixture of 0.41 g ethyl 3-thiosemicarbazidobutanoate (2 mmol) and 398 mg phenacyl bromide (2 mmol) was ball-milled at room temperature for 1 h. A quantitative yield of thiazole · HBr **2** was obtained. The free base **2** was recovered by washing the fine powder of the thiazole · HBr salt with 5% aqueous Na_2CO_3 solution followed by H_2O and drying at 0.01 bar at 80°C in vacuum. Violet powder; yield 0.59 g (98%); mp 149–150°C; IR (KBr): $\bar{\nu} = 3300$ (NH), 1720 (C=O), 1606 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 1.28$ (t, $J = 7.0$ Hz, CH_3CH_2), 2.1 (s, CH_3), 3.38 (s, CH_2), 4.2 (q, $J = 7.0$ Hz, OCH_2CH_3), 6.80 (s, thiazole-H_5), 7.27–7.74 (m, 5*Ar*–H), 9.05 (s, NH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 13.1$ (CH_3), 16.9 (CH_3), 43.2 (CH_2), 61.5 (OCH_2), 105.2 (C_5-thiazole), 126.4 ($2CH_{Ar}$), 128.1 (CH_{Ar}), 128.8 ($2CH_{Ar}$), 135.5 (C_{Ar}), 153.7 (C_4-thiazole), 164.3 (C=N), 167.3 (C=O), 170.8 (C_2-thiazole) ppm; MS (EI, 70 eV): m/z (%) = 303 (M^+, 28.7), 257 (100), 216 (61.6), 134 (81.2).

3-Methyl-1-(4-phenylthiazol-2-yl)-1H-pyrazol-5(4H)-one (**3**, $C_{13}H_{11}N_3OS$)

A solution of 0.6 g **2** (2 mmol) in 20 cm^3 *Et*OH containing 25 mmol sodium acetate was refluxed for 2 h. The reaction mixture was allowed to cool, then poured into ice-H_2O. The formed precipitate was collected by filtration, dried, and recrystallized from a mixture of *Et*OH:*DMF* (2:1). Buff crystals; yield 0.36 g (70%); mp 188–189°C (Ref. [23] 190–191°C); IR (KBr): $\bar{\nu} = 1634$ (C=O), 1620 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 2.25$ (s, CH_3), 5.30 (s, CH_2), 6.78 (s, thiazole-H_5), 7.35–8.0 (m, 5*Ar*–H) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 16.2$ (CH_3), 42.1 (CH_2), 107.8 (C_5-thiazole), 126.2 ($2CH_{Ar}$), 128.1 (CH_{Ar}), 128.7 ($2CH_{Ar}$), 134.3 (C_{Ar}), 139.2 (C_3-pyrazole), 155.9 (C_4-thiazole), 164.3 (C=O), 166.3 (C_2-thiazole) ppm; MS (EI, 70 eV): m/z (%) = 257 (M^+, 100), 176 (16.4), 134 (41.8), 102 (31.1), 69 (28.3).

Synthesis of 4-(2-arylhydrazono)-3-methyl-1-(4-phenylthiazol-2-yl)-1H-pyrazol-5(4H)-ones ***4a–4c***

Method A: A mixture of 2 mmol **7** and 398 mg phenacyl bromide (2 mmol) was ball-milled at room temperature for 1 h. The solid powders were washed with 5% Na_2CO_3 solution, followed by H_2O, and drying at 0.01 bar at 80°C in vacuum to liberate the free arylhydrazonothiazolylpyrazoles **4a–4c**.

Method B: A well stirred solution of an aromatic amine (5 mmol) in 1.5 cm^3 concentrated HCl and 3 cm^3 H_2O was cooled in an ice-bath at 0–5°C and diazotized with a solution of 0.35 g $NaNO_2$ in 5 cm^3 H_2O. Then, the above cold diazonium solution was added dropwise to a well stirred cold solution of 0.51 g **3** (5 mmol) in 25 cm^3 pyridine. The reaction mixture was stirred for 2 h until complete coupling reaction was achieved. The solid product was collected by filtration, washed with cold water, and recrystallized from a mixture of *Et*OH:*DMF* (1:1) to give **4a–4c**.

4-(2-Phenylhydrazono)-3-methyl-1-(4-phenylthiazol-2-yl)-1H-pyrazol-5(4H)-one (**4a**, $C_{19}H_{15}N_5OS$)

Brown crystals; yield 1.30 g (72%); mp 214–215°C; IR (KBr): $\bar{\nu} = 3212$ (NH), 1666 (C=O), 1595 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 2.32$ (s, CH_3), 6.62 (s, thiazole-H_5), 7.00–7.48 (m, 10*Ar*–H), 13.32 (s, NH) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 11.4$ (CH_3), 106.9 (C_5-thiazole), 119.8 ($2CH_{Ar}$), 125.6 (CH_{Ar}), 126.1 ($2CH_{Ar}$), 127.8 (CH_{Ar}), 128.8 ($2CH_{Ar}$), 129.5 ($2CH_{Ar}$), 131.9 (C_3-pyrazole), 134.6 (C_{Ar}), 142.2 (C_{Ar}), 150.4 (C_4-pyrazole), 156.1 (C_4-thiazole), 159.6 (C=O), 165.4 (C_2-thiazole) ppm.

4-(2-p-Tolylhydrazono)-3-methyl-1-(4-phenylthiazol-2-yl)-1H-pyrazol-5(4H)-one (**4b**, $C_{20}H_{17}N_5OS$)

Reddish brown crystals; yield 1.54 g (82%); mp 195–196°C; IR (KBr): $\bar{\nu} = 3175$ (NH), 1660 (C=O), 1594 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 2.38$ (s, CH_3), 2.46 (s, CH_3-pyrazole), 7.23–7.38 (m, 5*Ar*–H and thiazole-H_5), 7.80–7.82 (d, $J = 7.5$ Hz, 4-CH_3–C_6H_4), 7.96–7.98 (d, $J = 7.5$ Hz, 4-CH_3–C_6H_4), 13.3 (s, NH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 11.7$ (CH_3), 21.2 (CH_3), 105.8 (C_5-thiazole), 120.9 ($2CH_{Ar}$), 126.3 ($2CH_{Ar}$), 128.1 (CH_{Ar}), 128.8 ($2CH_{Ar}$), 129.8 ($2CH_{Ar}$), 132.6 (C_3-pyrazole), 134.8 (C_{Ar}), 136.9 (C_{Ar}), 140.2 (C_{Ar}),

150.7 (C_4-pyrazole), 156.9 (C_4-thiazole), 162.1 (C=O), 165.8 (C_2-thiazole) ppm; MS (EI, 70 eV): m/z (%) = 375 (M^+, 7.8), 317 (9.3), 269 (5.8), 202 (9.3), 97 (26), 57 (100), 69 (69.6).

4-(2-(4-Methoxyphenyl)hydrazono)-3-methyl-1-(4-phenylthiazol-2-yl)-1H-pyrazol-5(4H)-one (**4c**, $C_{20}H_{17}N_5O_2S$)
Reddish brown crystals; yield 1.66 g (85%); mp 184–185°C; IR (KBr): $\bar{\nu}$ = 3167 (NH), 1656 (C=O), 1604 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): δ = 2.3 (s, CH_3), 3.76 (s, OCH_3), 7.00–7.62 (m, 5*Ar*–H, thiazole-H_5), 7.78–7.80 (d, J = 7.5 Hz, 4-CH_3O–C_6H_4), 7.93–7.95 (d, J = 7.5 Hz, 4-CH_3O–C_6H_4), 13.3 (s, NH) ppm; ^{13}C NMR (*DMSO*-d_6): δ = 11.9 (CH_3), 51.8 (OCH_3), 107.2 (C_5-thiazole), 119.7 ($2CH_{Ar}$), 127.1 ($2CH_{Ar}$), 128.0 (CH_{Ar}), 128.9 ($2CH_{Ar}$), 130.3 ($2CH_{Ar}$), 133.8 (C_3-pyrazole), 134.9 (C_{Ar}), 137.4 (C_{Ar}), 140.6 (C_{Ar}), 151.3 (C_4-pyrazole), 155.8 (C_4-thiazole), 164.2 (C=O), 166.7 (C_2-thiazole) ppm.

Ethyl 5-formyl-3-methyl-1-(4-phenylthiazol-2-yl)-1H-pyrazole-4-carboxylate (**8**, $C_{17}H_{15}N_5S$)
In a 50 cm^3 round bottom flask 0.6 cm^3 phosphourous oxychloride (4 mmol) were gradually added to well cooled (0–5°C) 20 cm^3 *DMF* with stirring for 30 min, then 0.6 g **2** (2 mmol) were added in one portion. The reaction mixture was allowed to rise at room temperature for 5 min, then refluxed on a water bath at 75°C for 2 h. The reaction mixture was cooled, poured into crushed ice; the solid product that formed was filtered off, dried, and recrystallized from *Et*OH to give **8**. Yellow crystals; yield 0.40 g (58%); mp 140–141°C; IR (KBr): $\bar{\nu}$ = 1704, 1695 (2C=O), 1600 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.40 (t, J = 7.5 Hz, CH_3), 2.57 (s, CH_3), 4.36 (q, J = 7.5 Hz, OCH_2), 7.27–7.93 (m, 5*Ar*–H, thiazole-H_5), 9.84 (s, CHO) ppm; ^{13}C NMR ($CDCl_3$): δ = 13.1 (CH_3), 13.8 (CH_3), 62.1 (OCH_2), 105.1 (C_5-thiazole), 112.6 (C_4-pyrazole), 126.3 ($2CH_{Ar}$), 128.1 (CH_{Ar}), 128.5 ($2CH_{Ar}$), 136.3 (C_{Ar}), 137.8 (C_3-pyrazole), 146.2 (C_5-pyrazole), 156.3 (C_4-thiazole), 165.5 (C=O), 167.6 (C_2-thiazole), 178.8 (HC=O) ppm.

Preparation of thiosemicarbazones derivatives ***10a–10c***
A mixture of 273 mg thiosemicarbazide (3 mmol) and the appropriate aldehydes **9** (3 mmol) was ball-milled at room temperature for 1 h. The solid products that formed were collected and dried at 0.01 bar at 80°C in vacuum.

1-((1,3-Diphenyl-1H-pyrazol-4-yl)methylene)thiosemicarbazide (**10a**, $C_{17}H_{15}N_5S$)
Buff powder; yield 0.94 g (98%); mp 228–230°C (Ref. [25] 230°C); IR (KBr): $\bar{\nu}$ = 3255–3322 (NH_2), 3139 (NH), 1616 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): δ = 7.4–7.92 (m, 10*Ar*–H, pyrazole-H_5), 8.3 (s, NH_2), 9.2 (s, CH=N), 11.3 (s, NH) ppm.

1-((1-Phenyl-3-p-tolyl-1H-pyrazol-4-yl)methylene)thiosemicarbazide (**10b**, $C_{18}H_{17}N_5S$)
White powder; yield 0.98 g (98%); mp 198–200°C; IR (KBr): $\bar{\nu}$ = 3253–3393 (NH_2), 3139 (NH), 1595 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 2.43 (s, CH_3), 7.3–7.8 (m, 9*Ar*–H, pyrazole-H_5), 8.23 (s, NH_2), 8.34 (s, CH=N), 9.6 (s, NH) ppm; ^{13}C NMR ($CDCl_3$): δ = 21.0 (CH_3), 113.2 (C_4-pyrazole), 119.6 ($2CH_{Ar}$), 125.2 ($2CH_{Ar}$), 126.9 ($2CH_{Ar}$), 128.1 (CH_{Ar}), 129.3 ($2CH_{Ar}$), 134.8 (C_{Ar}), 137.8 (C_3-pyrazole), 138.7 (C_{Ar}), 140.5 (C_{Ar}), 144.3 (C_5-pyrazole), 149.6 (CH=N), 177.4 (C=S) ppm.

1-((3-(4-Nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)-thiosemicarbazide (**10c**, $C_{17}H_{14}N_6O_2S$)
Deep yellow powder; yield 1.10 g (98%); mp 294–295°C; IR (KBr): $\bar{\nu}$ = 3174–3360 (NH_2), 3136 (NH), 1597 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): δ = 7.42–8.0 (m, 9*Ar*–H, pyrazole-H_5), 8.42 (s, NH_2), 9.23 (s, CH=N), 11.34 (s, NH) ppm; ^{13}C NMR (*DMSO*-d_6): δ = 115.2 (C_4-pyrazole), 120.1 ($2CH_{Ar}$), 125.0 (CH_{Ar}), 127.8 ($2CH_{Ar}$), 129.1 ($2CH_{Ar}$), 129.4 ($2CH_{Ar}$), 135.8 (C_{Ar}), 137.8 (C_3-pyrazole), 138.9 (C_{Ar}), 140.5 (C_{Ar}), 144.3 (C_5-pyrazole), 150.6 (CH=N), 178.4 (C=S) ppm.

Synthesis of 2-(arylidenehydrazino)-4-phenylthiazoles ***11a–11c***
A mixture of thiosemicarbazone **9** (2 mmol) and 398 mg phenacyl bromide (2 mmol) was ball-milled at room temperature for 60 min. After drying at 0.01 bar at 80°C, a quantitative yield of thiazole · HBr **11a–11c** was obtained. The free base **11a–11c** was recovered by washing the fine powder of the HBr salt with 5% aqueous Na_2CO_3 solution followed by H_2O and drying in vacuum.

2-((1,3-Diphenyl-1H-pyrazol-4-yl)methylene)-1-(4-phenylthiazol-2-yl)-hydrazine (**11a**, $C_{25}H_{19}N_5S$)
Brown powder; yield 0.82 (98%); mp 163–164°C (Ref. [25] 162°C); IR (KBr): $\bar{\nu}$ = 3113 (NH), 1623 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 6.72 (s, thiazole-H_5), 7.12–7.89 (m, 15*Ar*–H), 7.98 (s, pyrazole-H_5), 8.3 (s, CH=N), 9.6 (s, NH) ppm.

2-((1-Phenyl-3-p-tolyl-1H-pyrazol-4-yl)methylene)-1-(4-phenylthiazol-2-yl)-hydrazine (**11b**, $C_{26}H_{21}N_5S$)
Brown powder; yield 0.85 g (98%); mp 150–151°C; IR (KBr): $\bar{\nu}$ = 3112 (NH), 1622 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): δ = 2.45 (s, CH_3), 6.76 (s, thiazole-H_5), 7.12–7.80 (m, 14*Ar*–H, pyrazole-H_5), 8.43 (s, CH=N), 9.65 (s, NH) ppm; ^{13}C NMR (*DMSO*-d_6): δ = 19.8 (CH_3), 105.2 (C_5-thiazole), 115.0 (C_4-pyrazole), 119.9 ($2CH_{Ar}$), 124.6 (CH_{Ar}), 125.5 (CH_{Ar}), 126.5 ($2CH_{Ar}$), 127.8 ($2CH_{Ar}$), 128.1 ($2CH_{Ar}$), 129.7 ($2CH_{Ar}$), 129.9 ($2CH_{Ar}$), 134.0 (C_{Ar}), 134.5 (C_{Ar}), 137.1 (C_3-pyrazole), 138.3 (C_{Ar}), 140.1 (C_{Ar}), 145.0 (C_5-pyrazole), 148.6 (CH=N), 154.2 (C_4-thiazole), 168.7 (C_2-thiazole) ppm; MS (EI, 70 eV): m/z (%) = 468 ($M^+ + 2$, 3.8), 466 (M^+, 75.3), 344 (15.8), 306 (29.3), 264 (45.8), 122 (100), 69 (67.6).

2-((3-(4-Nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)-1-(4-phenylthiazol-2-yl)-hydrazine (**11c**, $C_{25}H_{18}N_6O_2S$)
Yellow powder; yield 0.91 g (98%); mp 230–231°C; IR (KBr): $\bar{\nu}$ = 3121 (NH), 1614 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): δ = 6.62 (s, thiazole-H_5), 7.23–8.30 (m, 14*Ar*–

H, pyrazole-H_5), 8.36 (s, CH=N), 8.63 (s, NH) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 104.9$ (C_5-thiazole), 114.8 (C_4-pyrazole), 119.8 ($2CH_{Ar}$), 124.8 (CH_{Ar}), 125.7 (CH_{Ar}), 126.4 ($2CH_{Ar}$), 127.4 ($2CH_{Ar}$), 128.3 ($2CH_{Ar}$), 129.5 ($2CH_{Ar}$), 129.9 ($2CH_{Ar}$), 134.5 (C_{Ar}), 134.9 (C_{Ar}), 137.4 (C_3-pyrazole), 139.1 (C_{Ar}), 141.4 (C_{Ar}), 144.8 (C_5-pyrazole), 149.7 (CH=N), 154.7 (C_4-thiazole), 169.8 (C_2-thiazole) ppm; MS (EI, 70 eV): m/z (%) = 468 ($M^+ + 2$, 3.8), 466 (M^+, 75.3), 344 (15.8), 306 (29.3), 264 (45.8), 122 (100), 69 (67.6).

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