



New Route for the Synthesis of Pyrazolone Derivatives

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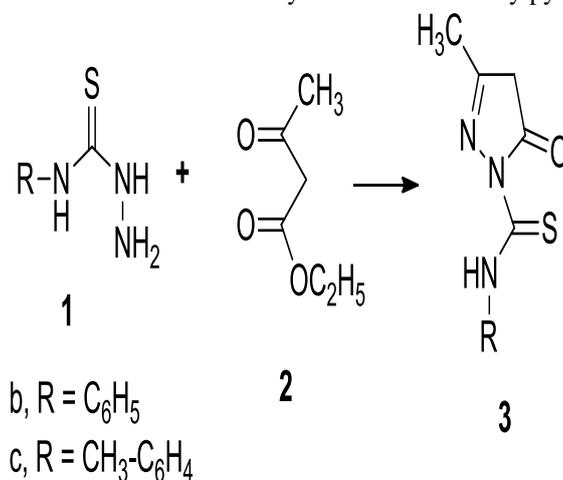
ABSTRACT

Condensation of ethyl acetoacetate 2 with thiosemicarbazide 1a gave hydrazone derivative 4 not pyrazolone 5. Pyrazolone 5 can be obtained by treatment of 4 with 5 % sodium hydroxide in ethanol. Reactions of 4 with phenyl bromide, aryl diazonium chloride, arylidene malononitrile afforded pyrazole derivatives 6, 7 and pyranopyrazole 8 respectively. Also, treatment of 4 with *N,N*-dimethylformamide dimethyl acetal (DMFDMA) gave compound 11 not 9 nor 10. Reactions of pyrazole derivatives 6 with arylidene malononitrile afforded condensed compound 15 which was obtained by reaction with aromatic aldehydes. While reaction of 6 with DMFDMA gave the corresponding enamine 16.

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Introduction

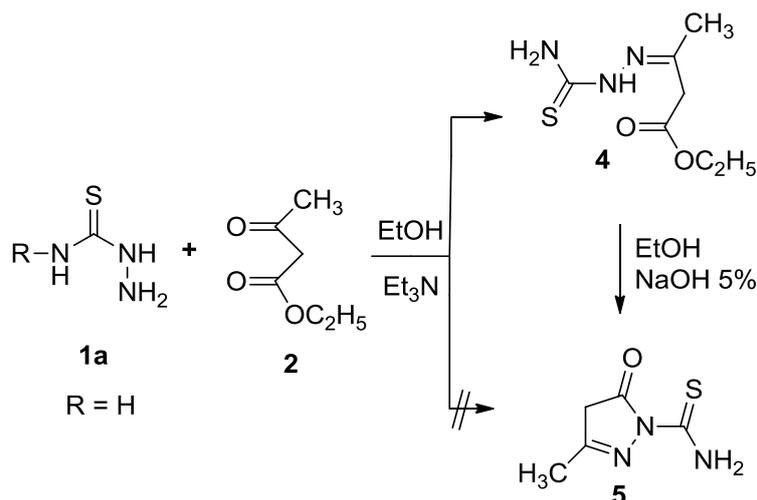
An intensive literature survey including the methods of synthesis for various pyrazolone derivatives has been carried out, as the derivatives of pyrazolone have been of interest to medicinal chemists for their wide range of biological activity [1]. Pyrazolones are important class of heterocyclic compounds that occur in many drugs and is a nonsteroidal anti-inflammatory agent used in the treatment of arthritis and other musculoskeletal and joint disorders. Pyrazolones are biologically important group of compounds having different activities like antibacterial, antifungal, anti-inflammatory, antidiabetic, analgesic, antipyretic, immunosuppressive agents, hypoglycemic, antiviral, antineoplastic activity and other biological activities [2]. The most widely method synthesis for pyrazol-5-one [3-5] is the condensation of dicarbonyl compounds with hydrazines [6,7]. The reaction of arylthiosemicarbazide 1b,c and ethyl acetoacetate 2 afforded 1-aryltioanilido-3-methylpyrazolone 3 [8]



Results and Discussion

The main purpose of the present study is to synthesize different derivatives with pyrazolone as basic heterocyclic nucleus. So that we treated ethyl acetoacetate with thiosemicarbazide in ethanol and triethylamine afforded the condensation product ethyl 3-(2-carbamothioylhydrazone)butanoate 4 not the cyclized form 5. The later compound 5 was obtained by the treatment of 4 with 5% sodium hydroxide in ethanol as shown in scheme 1.

Scheme 1. Synthesis of compound 4

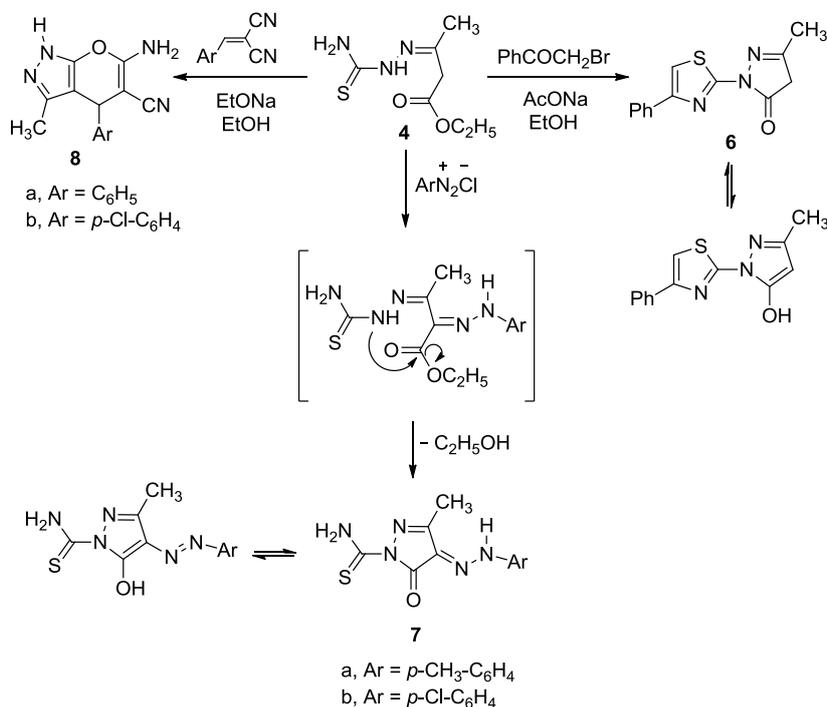


The structure of the isolated product was confirmed by elemental analysis as well as spectral analysis. IR spectrum of compound 4 shows carbonyl group at ν_{\max} 1725 cm^{-1} corresponding to ester group and ν_{\max} 3432, 3378 and 3279 cm^{-1} corresponding to NH₂ and NH groups. The mass spectrum of this compound shows the molecular ion peak at m/z 203 which corresponding to the molecular formula (C₇H₁₃N₃O₂S). The structure of compound 5 is confirmed by IR spectrum which shows the disappearance of carbonyl of ester and appearance of carbonyl of amide at ν_{\max} 1651 cm^{-1} . Also, the mass spectrum shows the molecular ion peak at m/z 157 which corresponding to the molecular formula (C₅H₇N₃OS).

The treatment of 4 with phenyl bromide in ethanol and fused sodium acetate afforded 3-methyl-1-(4-phenylthiazol-2-yl)-1H-pyrazol-5(4H)-one 6, scheme 2. The IR spectrum of compound 6 shows carbonyl group at ν_{\max} 1646 cm^{-1} and broad band at ν_{\max} 3445 cm^{-1} corresponding to (OH) group. Also, the ¹H NMR spectrum shows appearance of multiplet signal at δ_{H} 7.45-8.00 ppm corresponding to aromatic and thiazole protons while the mass spectrum shows the molecular ion peak at m/z 257 which corresponding to the molecular formula (C₁₃H₁₁N₃OS).

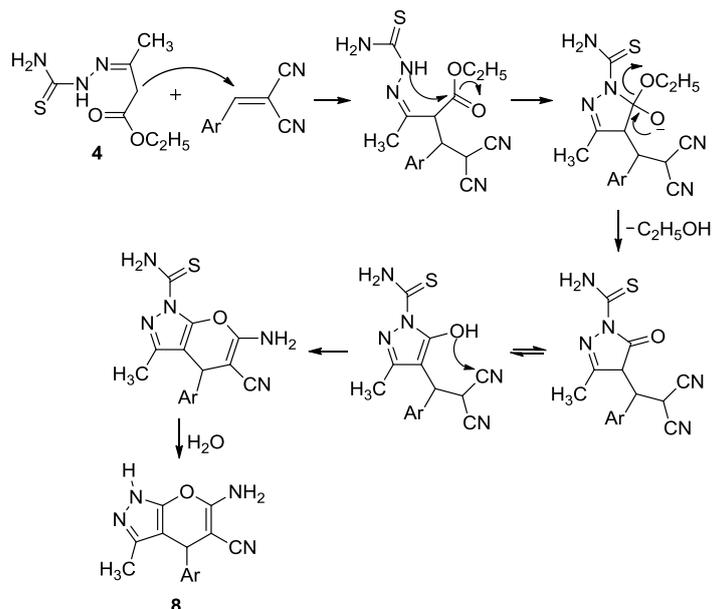
Coupling of 4 with aryl diazonium chloride gave pyrazolone 7, scheme 2, the reaction was carried out on the active methylene group followed by cyclization to give 7. The IR spectrum of compound 7a shows carbonyl group at ν_{\max} 1690 cm^{-1} , amino group at ν_{\max} 3262, 3159 cm^{-1} and hydroxyl group at ν_{\max} 3432 cm^{-1} . Also, the ¹H NMR spectrum shows two signals at δ_{H} 8.9 ppm and δ_{H} 9.4 ppm for OH and NH groups respectively beside aromatic protons at δ_{H} 7.21-7.55 ppm while the mass spectrum shows the molecular ion peak at m/z 275 which corresponding to the molecular formula (C₁₂H₁₃N₃OS). For further reaction of 4 we treated it with arylidene malononitrile to afford pyranopyrazole 8, scheme 2.

Scheme 2. Synthetic pathways for compounds 6-8



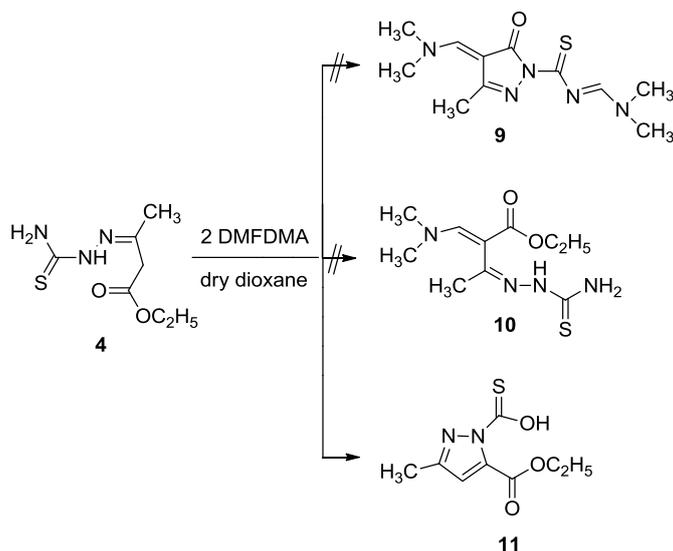
The formation of compound **8** proceeds *via* Michael addition followed by cyclization as in scheme 3. The IR spectrum of compound **8a** shows the appearance of cyano group while the mass spectrum shows the molecular ion peak at m/z 252 corresponding to $(C_{14}H_{12}N_4O)$.

Scheme 3. Mechanism of formation of compound **8**



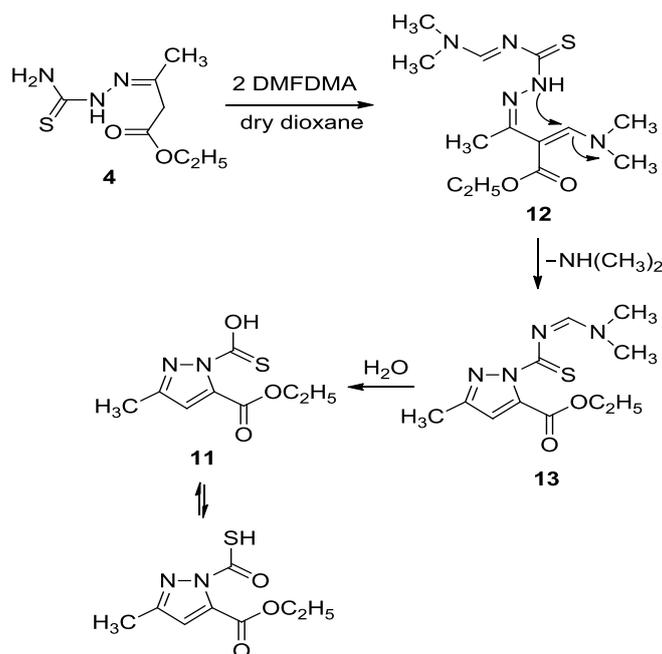
The reaction of compound **4** with *N,N*-dimethylformamide dimethyl acetal was a very interesting reaction because we thought that it will give compound **9** or **10**, but the reaction proceeds *via* different pathways. This reaction afforded **11** instead of **9** and **10** as shown in scheme 4.

Scheme 4. Synthesis of compound **11**



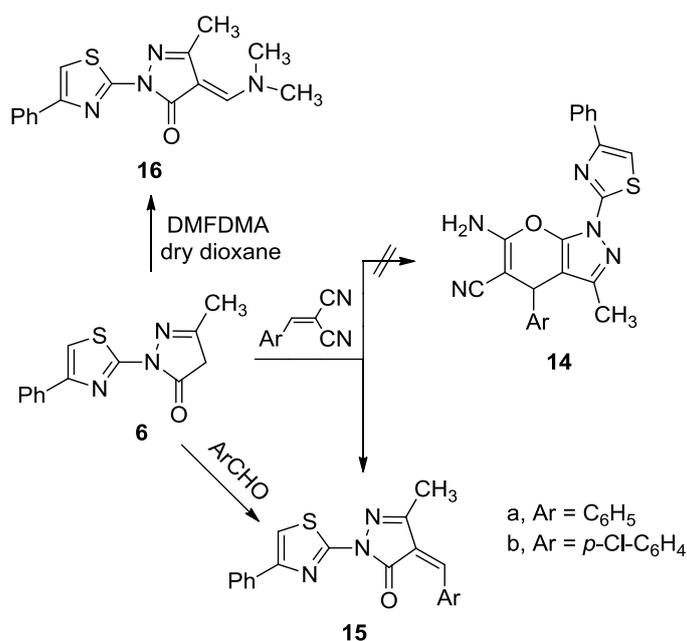
The structure of isolated product was confirmed by elemental analysis as well as spectral analysis. IR spectrum of compound **11** shows SH group at ν_{\max} 2610 cm^{-1} and two carbonyl groups at ν_{\max} 1707 and 1656 cm^{-1} . Also, the ^1H NMR spectrum shows triplet signal at δ_{H} 1.21 ppm and quartet signal at δ_{H} 4.16 ppm corresponding to ethyl moiety and signals at δ_{H} 2.48, 6.46 and 9.1 ppm corresponding to CH_3 of pyrazole, CH of pyrazole and OH or SH of thiocarboxyl group respectively. The mass spectrum of this compound shows the molecular ion peak at m/z 214 which corresponding to the molecular formula $(C_8H_{10}N_2O_3S)$. The mechanism for this reaction is shown in scheme 5, the first step is the reaction of DMFDMA with both active methylene and amino group of thiamide group to give **12**, and the second step is the cyclization of **12** and finally by hydrolysis of **13** gave the target product **11**.

Scheme 5. Mechanism of formation of compound 11



The reaction of N-(2-thiazolyl)pyrazolone derivative **6** with arylidene malononitrile, we thought that the reaction proceeds through Michael addition to give **14**, but the isolated product is **15**. The latter one is confirmed by the reaction of **6** with aromatic aldehyde, as shown in scheme 6. IR spectrum of compounds **15a,b** not appear to groups of cyano nor amino. Also, mass spectra of compounds **15a,b** show molecular ion peaks at m/z 345 and m/z 379.5 respectively. Finally, reaction of compound **6** with DMFDMA afforded enaminone **16**. Mass spectrum of compound **16** shows the molecular ion peak at m/z 312 which corresponding to the molecular formula ($C_{16}H_{16}N_4OS$).

Scheme 6. Synthesis of compounds 15,16



Experimental

All melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 17,100 FTIR spectrometer as KBr disks. NMR spectra were recorded on a Varian Gemini (400 MHz) spectrometer for solutions in $CDCl_3$ or $DMSO-d_6$ with tetramethylsilane (TMS) as an internal standard unless otherwise. Mass spectra were obtained on Finnigan 4500 (low resolution) spectrometers using electron impact (EI) at Micro-analytical Center Cairo University Giza Egypt.

Ethyl 3-(2-carbamothioylhydrazino)butanoate (**4**)

A mixture of thiosemicarbazide **1a** (0.91g, 0.01 mol) and ethyl acetoacetate **2** (1.3 g, 0.01 mol) was taken in 30 mL absolute ethanol containing 0.5 mL of triethylamine. The mixture was heated under reflux for 2 h. The white precipitate that formed after cooling, washed with ethyl alcohol, and recrystallized from ethyl alcohol to give **4**, as white crystalline solid, 2.15 g (96.8%), mp 98-100 °C; IR (KBr, ν_{max} , cm^{-1}) 3432, 3378 (NH_2), 3279 (NH), 2994 (CH-aliph.), 1725 (CO); MS: m/z 203 (M^+). Anal. Calcd. for $C_7H_{13}N_3O_2S$: C, 41.36; H, 6.45; N, 20.67. Found: C, 44.18; H, 6.29; N, 20.45.

3-Methyl-5-oxo-4,5-dihydro-1H-pyrazole-1-carbothioamide (5)

Compound **4** (2.03 g, 0.01 mol) was dissolved in 20 mL ethanol (95%) in the presence of sodium hydroxide (5%). The reaction mixture was left to stand for ½ h. Yellow precipitate that formed after diluted with water, filtered off, dried, and recrystallized from ethyl alcohol to give **5**, as yellowish crystalline solid, 0.65 g (84.41%), mp 175-177 °C; IR (KBr, ν_{\max} , cm^{-1}) 3268, 3109 (NH_2), 1651 (CO); MS: m/z 157 (M^+). *Anal.* Calcd. for $\text{C}_5\text{H}_7\text{N}_3\text{OS}$: C, 38.20; H, 4.49; N, 26.73. Found: C, 38.01; H, 4.38; N, 26.5.

3-Methyl-1-(4-phenylthiazol-2-yl)-1H-pyrazol-5(4H)-one (6)

A mixture of compound **4** (2.03 g, 0.01 mol) and phenacyl bromide (1.99 g, 0.01 mol) was taken in ethanol 30 mL containing of fused sodium acetate (0.82 g, 0.01 mol). The mixture was refluxed for 5 h, after cooling and the reaction mixture was poured onto acidified cold water. The precipitate that formed filtered off, dried, and recrystallized from ethyl alcohol to give **6**, as violet crystalline solid, 1.15 g (91.2 %), mp 182-184 °C; IR (KBr, ν_{\max} , cm^{-1}) 3445 (enolic OH), 1646 (CO); ^1H NMR (DMSO, δ , ppm): 2.09 (s, 3H, CH_3), 5.28 (s, 1H, CH-pyrazole), 7.45-8.00 (m, 6H, Ar-H and CH-thiazol), 12.35 (s, 1H, OH); MS: m/z 257 (M^+). *Anal.* Calcd. for $\text{C}_{13}\text{H}_{11}\text{N}_3\text{OS}$: C, 60.68; H, 4.31; N, 16.33. Found: C, 60.46; H, 4.14; N, 16.17

General procedure for the preparation of compounds (7a,b)

Compound **4** (2.03 g, 0.01 mol) and sodium acetate in ethanol (30 mL) was cooled in ice water. Aryl diazonium chloride (0.01 mol) cool in ice water, then add to cold **4** dropwise with stirring at 0 °C. The product which formed was left to stand, then filtered off and purified with the proper solvent

3-Methyl-5-oxo-4-(2-(p-tolyl)hydrazono)-4,5-dihydro-1H-pyrazole-1-carbothioamide (7a)

This compound was obtained as yellow crystalline solid (ethyl alcohol) 2.3 g (83.6%), by the method described above using *p*-tolyl diazonium chloride (0.01 mol), mp 215-217 °C; IR (KBr, ν_{\max} , cm^{-1}) 3432 (OH), 3262, 3159 (NH_2), 2990 (CH, aliph), 1690 (CO); ^1H NMR (DMSO, δ , ppm): 2.25 (s, 3H, CH_3), 2.31 (s, 3H, CH_3 -Ar), 4.15 (s, 2H, NH_2), 7.21-7.55 (m, 4H, Ar-AB), 8.9 (s, 1H, OH), 9.4 (s, 1H, NH, exch., OH); ms: m/z 275 (M^+). *Anal.* Calcd. for $\text{C}_{12}\text{H}_{13}\text{N}_5\text{OS}$: C, 52.35; H, 4.76; N, 25.44. Found: C, 52.08; H, 4.53; N, 25.27

4-(2-(4-Chlorophenyl)hydrazono)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazole-1-carbothioamide (7b)

This compound was obtained as yellow crystalline solid (ethyl alcohol) 2.2 g (74.5%), by the method described above using *p*-chlorobenzenediazonium chloride (0.01 mol), mp 200-202 °C; IR (KBr, ν_{\max} , cm^{-1}) 3405 (OH), 3279, 3185 (NH_2), 2974 (CH, aliph), 1685 (CO); MS: m/z 295.5 (M^+). *Anal.* Calcd. for $\text{C}_{11}\text{H}_{10}\text{ClN}_5\text{OS}$: C, 44.67; H, 3.41; N, 23.68. Found: C, 44.41; H, 3.26; N, 23.45.

General procedure for the preparation of compounds (8a,b)

Compound **4** (2.03 g, 0.01 mol) was dissolved in 20 mL sodium ethoxide (sodium metal 0.23g, 0.01 mol), then add arylidene malononitrile (0.01 mol). The reaction mixture was left under reflux for 6h, after cooling and the reaction mixture was poured onto acidified cold water. The precipitate that formed filtered off, dried, and recrystallized from the proper solvent.

6-Amino-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (8a)

This compound was obtained as yellowish crystalline solid (ethyl alcohol) 0.9 g (72.58%), by the method described above using 2-benzylidene malononitrile (1.54 g, 0.01 mol), mp 240-242 °C; IR (KBr, ν_{\max} , cm^{-1}) 3373, 3171 (NH_2 , NH), 3050 (CH, Ar), 2923 (CH, aliph), 2192 ($\text{C}\equiv\text{N}$), 1640 ($\text{C}=\text{N}$); MS: m/z 252 (M^+). *Anal.* Calcd. for $\text{C}_{14}\text{H}_{12}\text{N}_4\text{O}$: C, 66.66; H, 4.79; N, 22.21. Found: C, 66.39; H, 4.61; N, 22.03.

6-Amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (8b)

This compound was obtained as yellowish crystalline solid (ethyl alcohol) 2.2 g (76.78%), by the method described above using 2-(4-Chloro-benzylidene) malononitrile (1.88 g, 0.01 mol), mp 235-237 °C; IR (KBr, ν_{\max} , cm^{-1}) 3372, 3171 (NH_2 , NH), 2923 (CH, aliph.), 2187 ($\text{C}\equiv\text{N}$), 1640 ($\text{C}=\text{N}$); MS: m/z 286.5 (M^+). *Anal.* Calcd. for $\text{C}_{14}\text{H}_{11}\text{ClN}_4\text{O}$: C, 58.65; H, 3.87; N, 19.54. Found: C, 58.44.; H, 3.60; N, 19.33.

5-(Ethoxycarbonyl)-3-methyl-1H-pyrazole-1-carbothioic O-acid (11)

In a dry flask a mixture of compound **4** (2.03 g, 0.01 mol) and *N,N*-dimethylformamide dimethyl acetal (1.19 g, 0.01 mol) was taken in a dry dioxane 20 mL. The reaction mixture was heated under reflux for 2h, after cooling, the precipitate that formed filtered off, washed with ethyl alcohol, dried, and recrystallized from ethyl alcohol as white crystalline solid, 0.9 g, (86.5%), mp 176-178 °C; IR (KBr, ν_{\max} , cm^{-1}) 2610 (SH), 2902 (CH, aliph.), 1707, 1656 (CO); ^1H NMR (DMSO, δ , ppm): 1.21 (t, 3H, CH_3), 2.48 (s, 3H, CH_3 -pyrazol), 4.16 (q, 2H, CH_2), 6.46 (s, 1H, CH), 9.1 (s, 1H, OH); MS: m/z 214 (M^+). *Anal.* Calcd. for $\text{C}_8\text{H}_{10}\text{N}_2\text{O}_3\text{S}$: C, 44.85; H, 4.70; N, 13.08. Found: C, 44.62; H, 4.56; N, 12.90.

General procedure for the preparation of compounds (15a,b)

A solution of compound **6** (2.57 g, 0.01 mol) and arylidene malononitrile (0.01 mol) or aromatic aldehyde (0.01 mol) in ethanol 30 mL containing 0.5 mL of triethylamine was refluxed for 2 h. The obtained product was collected by filtration, washed with water, and recrystallized from the proper solvent.

4-Benzylidene-3-methyl-1-(4-phenylthiazol-2-yl)-1H-pyrazol-5(4H)-one (15a)

This compound was obtained by the method described above as brown crystalline solid (ethyl alcohol) using 2-benzylidenemalononitrile (1.54 g, 0.01 mol) or benzaldehyde (1.06 g, 0.01 mol), yield 2.57 g (74.5%) or 2.33 g (67.5%) respectively, mp 265-267 °C; IR (KBr, ν_{\max} , cm^{-1}) 2920 (CH, aliph), 1622 (CO); ^1H NMR (DMSO, δ , ppm): 2.08 (s, 3H, CH_3), 7.21-8.01 (m, 12H, CH- Ar + CH- thiazole + CH-methine); MS: m/z 345 (M^+). *Anal.* Calcd. for $\text{C}_{20}\text{H}_{15}\text{N}_3\text{OS}$: C, 69.54; H, 4.38; N, 12.16. Found: C, 69.31; H, 4.18; N, 11.94.

4-(4-Chlorobenzylidene)-3-methyl-1-(4-phenylthiazol-2-yl)-1H-pyrazol-5(4H)-one (15b)

This compound was obtained by the method described above as brown crystalline solid (ethyl alcohol) using 2-(4-chlorobenzylidene)malononitrile (1.88 g, 0.01 mol) or *p*-chlorobenzaldehyde (1.40 g, 0.01 mol), yield 2.85 g (75.2%) or 2.76 g

(72.8%) respectively, mp 275-277 °C; IR (KBr, ν_{\max} , cm^{-1}) 2919 (CH, aliph.), 1619 (CO); MS: m/z 379.5 (M^+). Anal. Calcd. for $\text{C}_{20}\text{H}_{14}\text{ClN}_3\text{OS}$: C, 63.24; H, 3.71; N, 11.06. Found: C, 62.95; H, 3.57; N, 10.89.

4-((Dimethylamino)methylene)-3-methyl-1-(4-phenylthiazol-2-yl)-1H-pyrazol-5(4H)-one(16)

In a dry flask a mixture of compound **6** (2.57 g, 0.01 mol) and *N,N*-dimethylformamide dimethyl acetal (1.19 g, 0.01 mol) was taken in dry dioxane 20 mL. The reaction mixture was refluxed for 2 h, after cooling, the precipitate that formed filtered off, washed with ethyl alcohol, dried, and recrystallized from ethyl alcohol as yellow powder, 2.1 g, (86.7%), mp > 300 °C; IR (KBr, ν_{\max} , cm^{-1}) 3050 (CH, Ar), 2917 (CH, aliph.), 1672 (CO); MS: m/z 312 (M^+). Anal. Calcd. for $\text{C}_{16}\text{H}_{16}\text{N}_4\text{OS}$: C, 61.52; H, 5.16; N, 17.93. Found: C, 61.38; H, 5.01; N, 17.78.

Conclusion

The utility of ethyl 3-(2-carbamothioylhydrazino)butanoate **4** with simple reagents such as phenyl bromide, arylidenes, aldehydes, diazonium compounds and *N,N*-dimethylformamide dimethyl acetal in the synthesis of pyrazole derivatives, thiazolylpyrazole and pyranopyrazole.

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