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SYNTHESIS OF SOME NOVEL FUSED AZOLE DERIVATIVES

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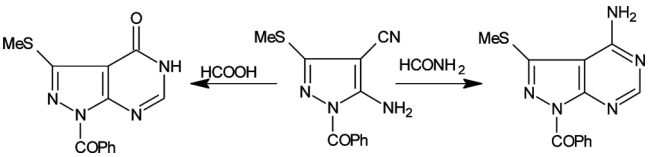
GRAPHICAL ABSTRACT



Abstract *A novel synthesis of pyrazolopyrimidine derivatives was reported wherein 5-amino-1-benzoyl-3-(methylthio)-1*H*-pyrazole-4-carbonitrile was treated with formic acid, formamide, thioacetamide, carbon disulfide, and phenylisocyanate and phenylisothiocyanate.*

Keywords Isocyanate; phenylisothiocyanate; pyrazolopyridine; pyrazolopyrimidine

INTRODUCTION

Pyrazole derivatives have attracted particular interest because they are used as the core structure in many drug substances covering a wide range of pharmacological applications,[1–6] such as antibacterials, antifungals, anticonvulsants,[6] hypertensives,[7] antidepressants,[8] analgesics, antiinflammatories,[9] and neuroprotectives.[10] Also, pyrazole derivatives are used as antianemic agents,[11] novel legands for estrogen receptor,[12] claimed and nitrification inhibitors with the use of fertilizers.[13] Pyrazolopyrimidines and related fused heterocycles are of interest as potential bioactive molecules. They are known to exhibit pharmacological activities such as CNS depressive,[14] neuroleptic,[15] and tuberculostatic[16] activities. In connection with our efforts directed toward the synthesis of heterocyclic ring systems,[14–19] our target in this study was the synthesis of some new heterocyclic compounds with an expected wide spectrum of potential applications.

RESULTS AND DISCUSSION

Our first attempts to prepare the key precursor 5-amino-1-benzoyl-3-(methylthio)-1*H*-pyrazole-4-carbonitrile **2**[20] led us to obtain a product that has a

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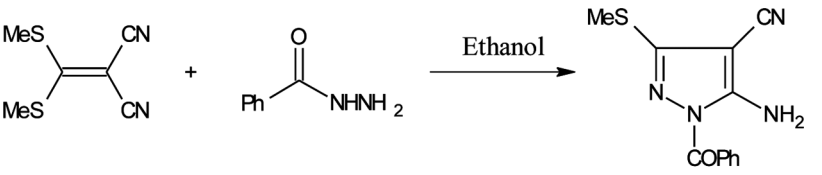
melting point of 220 °C, different from the melting point reported (290 °C). The lack of the reported analytical data prompted us to investigate this reaction. So,we prepared the compound **2** via either the previously reported procedure or by refluxing in ethanol. In both cases, we obtained the same product with melting point 218–220 °C. The structure of compound **2** was established through analytical data (IR, ^{1}H NMR, and mass spectra). IR: 3382, 3291 (NH_2), 3223 (NH), 2209 (CN), 1681 (CO) cm^{-1}; ^{1}HNMR: 8.2 (s, 2H, NH_2), 8.00–7.52(m, 5H, phenyl), 2.50(s, 3H, SCH_3); MS: m/z (100%): 258 (M^+, 10.5%); 105 (100%); 77 (73%). Compound **2** was reacted with formic acid to give 1-benzoyl-3-(methylthio)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one **4**. The formation of compound **4** was assumed to proceed via the amide formation, followed by an intramolecular cyclization with formic acid to furnish the desired product.[21]



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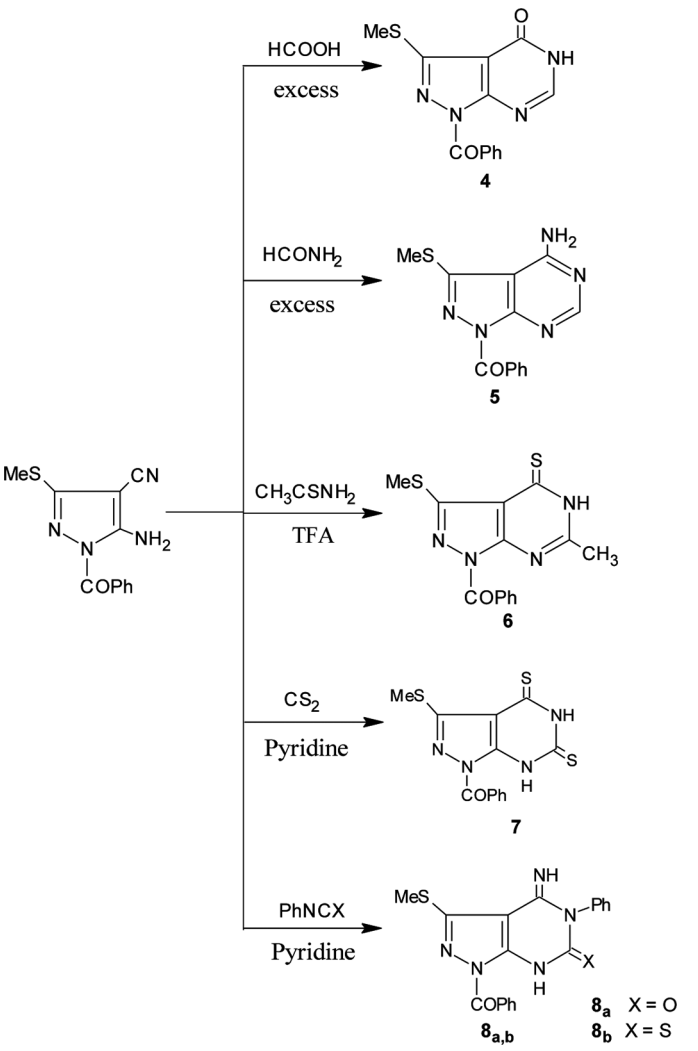
Also, compound **2** was cyclocondensed with formamide, thio-acetamide, carbon disulfide, and phenyl isocyanate or phenyl isothiocyanate to give 1-benzoyl-3-(methylthio)-1H-pyrazolo[3,4-d] pyrimidin-4-amine **5**, 1-benzoyl-6-methyl-3-(methyl thio)-1,5-dihydro-4H-pyrazolo[3,4-d] pyrimidine-4-thione **6**, 1-benzoyl-3-(methyl thio)-1H-pyrazolo[3,4-d]pyramidine-4,6-(5H,7H)-dithione **7**, 1-benzoyl-4-imino-3-(methylthio)-5-phenyl-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-d]pyrimidin-6-one **8$_a$**,1-benzoyl-4-imino-3-(methylthio)-5-phenyl-1,4,5,7-tetrahydro-6H-pyrazolo[3,4-d]pyrimidine-6-thione **8$_b$** respectively (Scheme 1).

Compound **2** was treated with ethyl cyanoacetate, 2,5-dimethoxy- tetrahydrofuran or Lawesson's reagent (LR) to give 4-amino-1-benzoyl-3-(methylthio)-6-oxo-6, 7-dihydro-1H-pyrazolo [3,4-b] pyridine-5-carbonitrile **9**, 1-benzoyl-3-(methylthio)-5-(1H-pyrrol-1-yl)-1H-pyrazole-4-carbonitrile **10**, and 2-(4-methoxyphenyl)-5-(methyllthio)-7-[(phenyl-λ^4-sulf-anylidyne)methyl]-1,2,3,7-tetra-hydro-4H-pyrazolo[3,4-d] [1,3,2]diazaphosphinine-4-thione 2-sulfide **11** respectively (Scheme 2).

When compound **2** was allowed to react with hydrazine, only the substitution reaction occurred, and the replacement of 3-methoxythio group with hydrazine led to 5-amino-1-benzoyl-3-hydrazino-1*H*-pyrazole-4-carbonitrile **12** and did not give the cyclic compound as we expected. We tried to interpret why the attachment hydrazine group did not add to the cyano group by studying this reaction through minimized energy structure of compound **12** by MM2 and AM1, and we noticed that the hydrazo group is out of plane with the cyano group (Fig. 1).

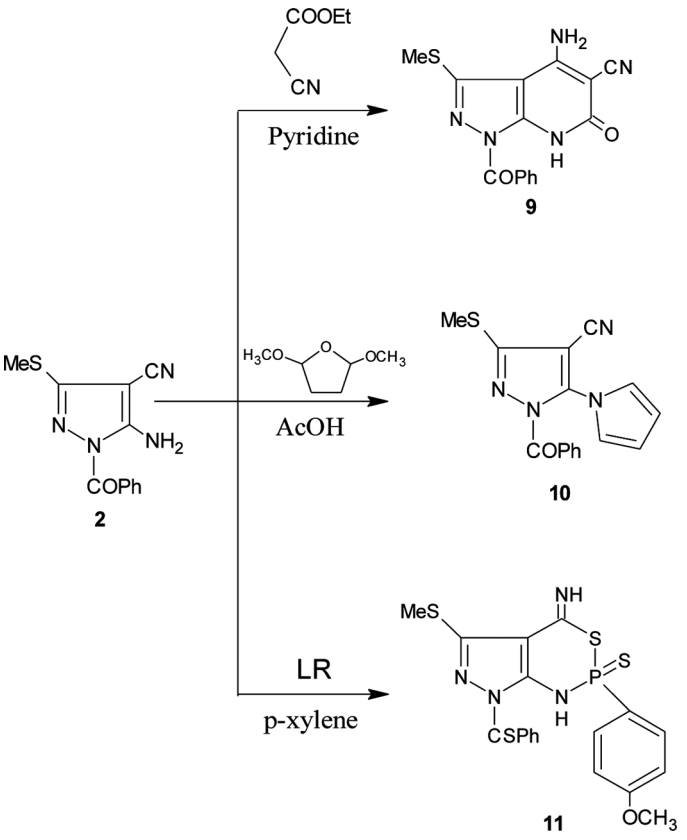
N-[1-Benzoyl-4-cyano-3-(methylthio)-1*H*-pyrazol-5-yl]-3-oxo-3-phenyl propanamid **13** was yielded on treating compound **2** with ethyl benzoylacetate in either pyridine, dimethylformamide (DMF), or fusion and did not give the expected cyclized product even when the isolated compound **13** was refluxed in ethanol with sodium ethoxid as a catalyst for 6 h. Compound **2** was easily acylated with acetic anhydride or acetyl chloride to give *N*-[1-benzoyl-4-cyano-3-(methylthio)-1*H*-pyrazol-5-yl]



Scheme 1. Synthesis of pyrazolopyrimidine derivatives (**2–8**).

acetamide **14** and also with triethylorthoformate to give ethyl[1-benzoyl-4-cyano-3-(methylthio)-1*H*-pyrazol-5-yl] imidoformate **15**. Compound **15** was allowed to react with hydrazine or phenylhydrazine and gave the starting compound **2** (Scheme 3). For the same reason mentioned previously when we studied this reaction through the minimized energy structure of compound **15** with hydrazine or phenylhydrazine by MM2 and AM1, we deduced that the imidoformate group is out of plane with the cyano group (Fig. 2).

Ethyl 5-amino-1-*benzoyl*-3-(methylthio)-1*H*-pyrazole-4-carboxylate **3**[20] was treated with malononitril to give 6-amino-1-benzoyl-4-hydroxy-3-(methylthio)-1*H*-pyrazo-lo[3,4-*b*]pyridine-5-carbonitrile **16**. On the other hand, when compound **3** was treated with formamide it gave the same compound **4** and this confirmed the



Scheme 2. Preparation of pyrazole derivatives (**9–11**).

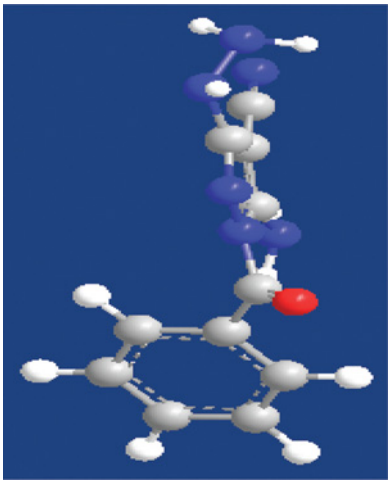
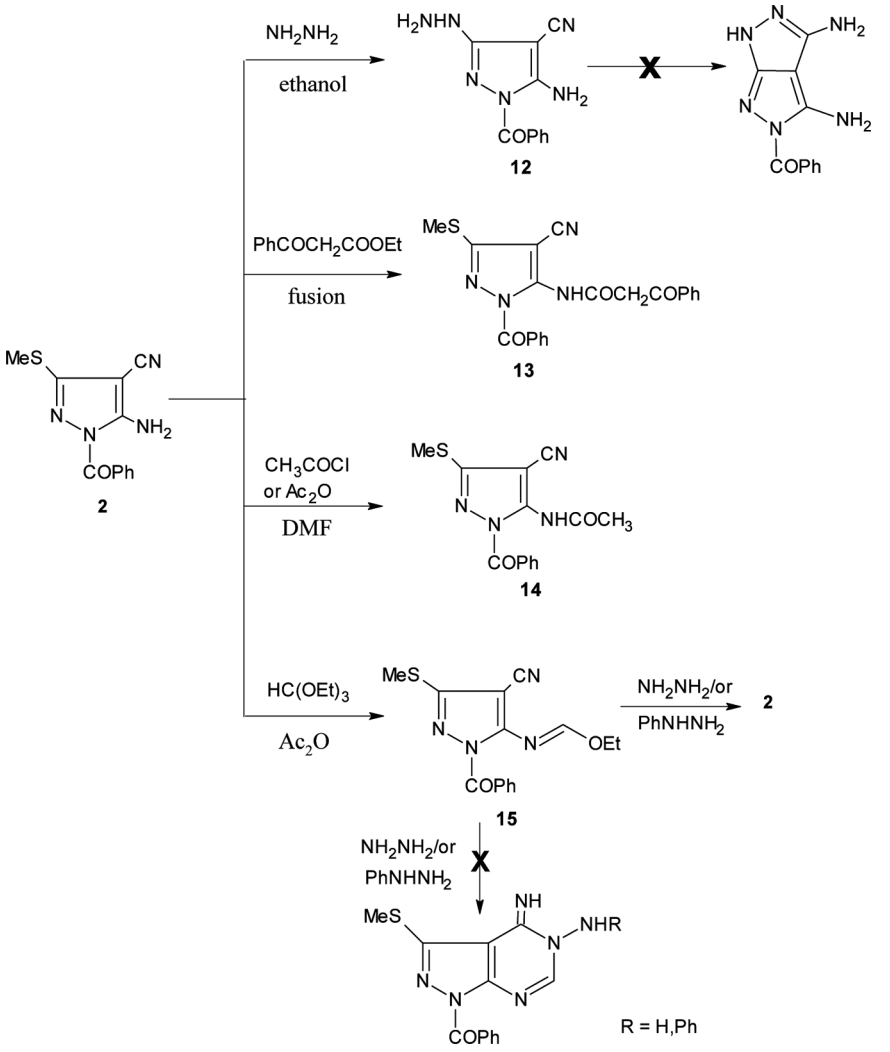


Figure 1. Minimized energy structure of 12 by MM2 and AM1. Optimization was done using semiempirical calculation with MM2 and AM1 force fields. The optimization done for 50,000 steps. Calculations were performed using ChemOffice software developed by Cambridge Soft. (Figure is provided in color online.)

reaction pathway, which was assumed to proceed via hydrolysis of the cyano group.[21]

Also, 1-benzoyl-3-(methylthio)-5-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4,6 (5*H*, 7*H*) dione **17** was obtained via treatment of compound **3** with phenylisocyanate (Scheme 4).

When compound **3** was treated with phenylisothiocyanate under the same reaction conditions, the reaction gave the open product identified on the basis of microanalysis and spectral data as ethyl-1-benzoyl-3-(methylthio)-5-[(phenylcarbamothioyl)amino]-1*H*-pyrazole-4-carboxylate **18**, ^{1}H-NMR spectrum showed clear two beaks at δ4.2 (q, 2H, CH_2) and δ 1.22 (t, 3H, CH_3) corresponding to the ethyl group. The reaction of compound **3** with ethyl cyanoacetate, ethyl



Scheme 3. Synthesis of unexpected open chain products (**12–15**).

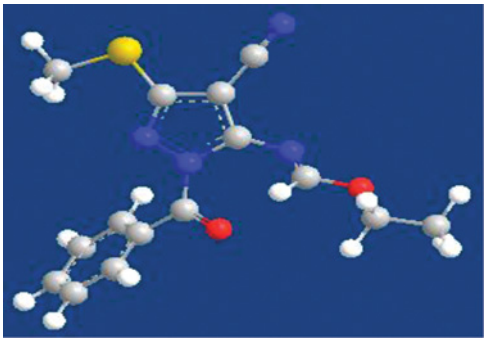
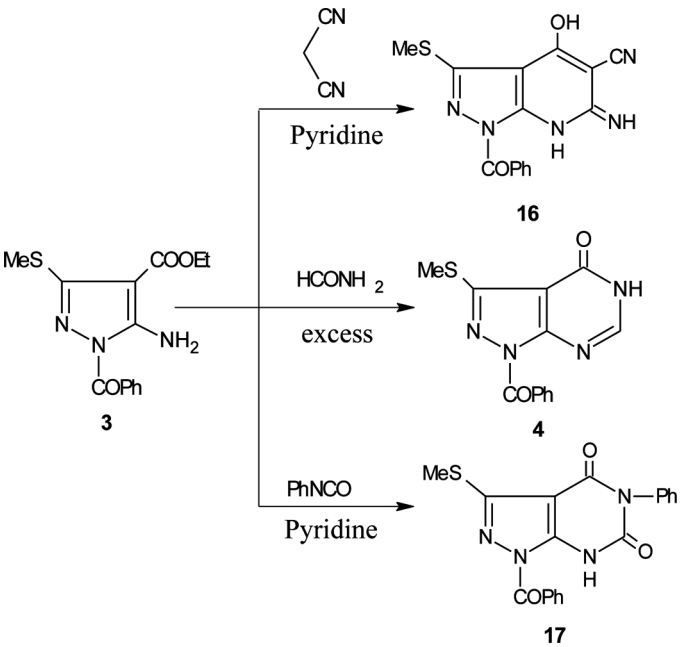


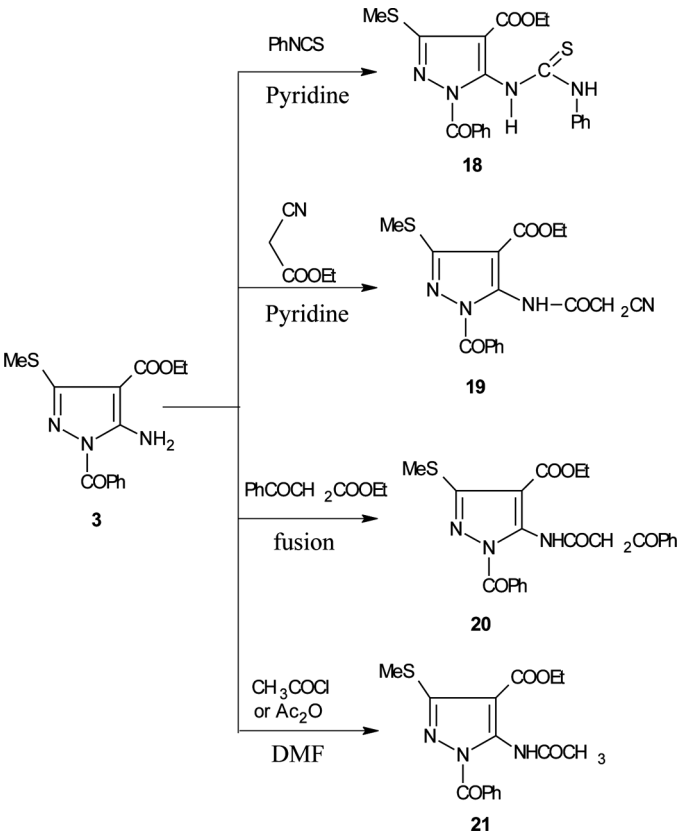
Figure 2. Minimized energy structure of 15 by MM2 and AM1. (Figure is provided in color online.)

benzoylacetate, acetyl chloride, or acetic anhydride occurred on the amino function to give the open products, namely ethyl 1-benzoyl-5-[(cyanoacetyl)amino]-3-(methylthio)-1*H*-pyrazole-4-carboxy-late **19**, ethyl 5-(3-oxo-3-phenyl-propanamido)-1-benzoyl-3-(methylthio)-1*H*-pyrazole-4-carboxylate **20**, and ethyl 5-acetamido-1-benzoyl-3-(methylthio)-1*H*-pyraz-ole-4-carboxylate **21** respectively (Scheme 5).

The only substitution reaction occurred via the replacement of 3-methylthio with hydrazine when compound **3** was refluxed with hydrazine to give ethyl 5-amino-1-benzoyl-3-hydrazino-1*H*-pyrazole-4-carboxylate **22**, and this was confirmed by the spectral studies. Also, when we studied this reaction through minimized energy



Scheme 4. Preparation of pyrazolopyridine and pyrazolopyrimidine derivatives (**16,17**).



Scheme 5. Synthesis of *N*-substituted pyrazole derivatives (**18–21**).

structure of compound **22** by MM2 and AM1, we noticed that the hydrazo group is out of plane with the ester group as in compound **22** (Fig. 3).

Ethyl-1-benzoyl-3-(methylthio)-5-(1*H*-pyrrol-1-yl)-1*H*-pyra-zole-4-carboxylate **23** was yielded when compound **3** was reacted with 2,5-dimethoxytetrahydrofuran. When ethyl 1-benzoyl-5-{[(1*E*)-ethoxymethylene]amino}-3-(methylthio)-1*H*-pyrazole-4-carboxylate **24**, which was yielded from the reaction of triethylorthoformat with compound **3**, was reacted with hydrazine or phenylhydrazine, it underwent the same behavior as the previous reactions of compound **2** with hydrazine or phenyl-hydrazine, and we also separated the starting compound **3** (Scheme 6).

The third case was the same as we deduced, that the imidoformate lies out of plan, with the ester group (Fig. 4).

EXPERIMENTAL

Pyrazolopyrimidine Derivatives 4 and 5

Compound **2** (0.004 mol, 1 g) and excess formic acid or formamide (10 ml) were heated under reflux for 10 h. The mixture was left to cool and poured onto

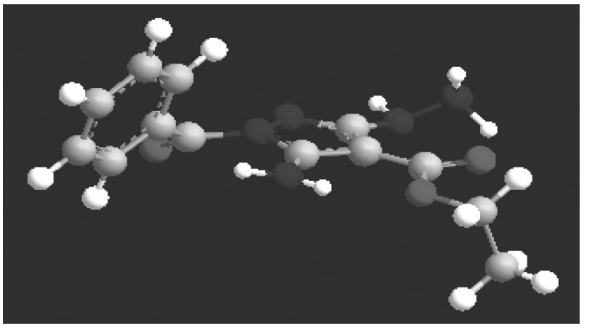
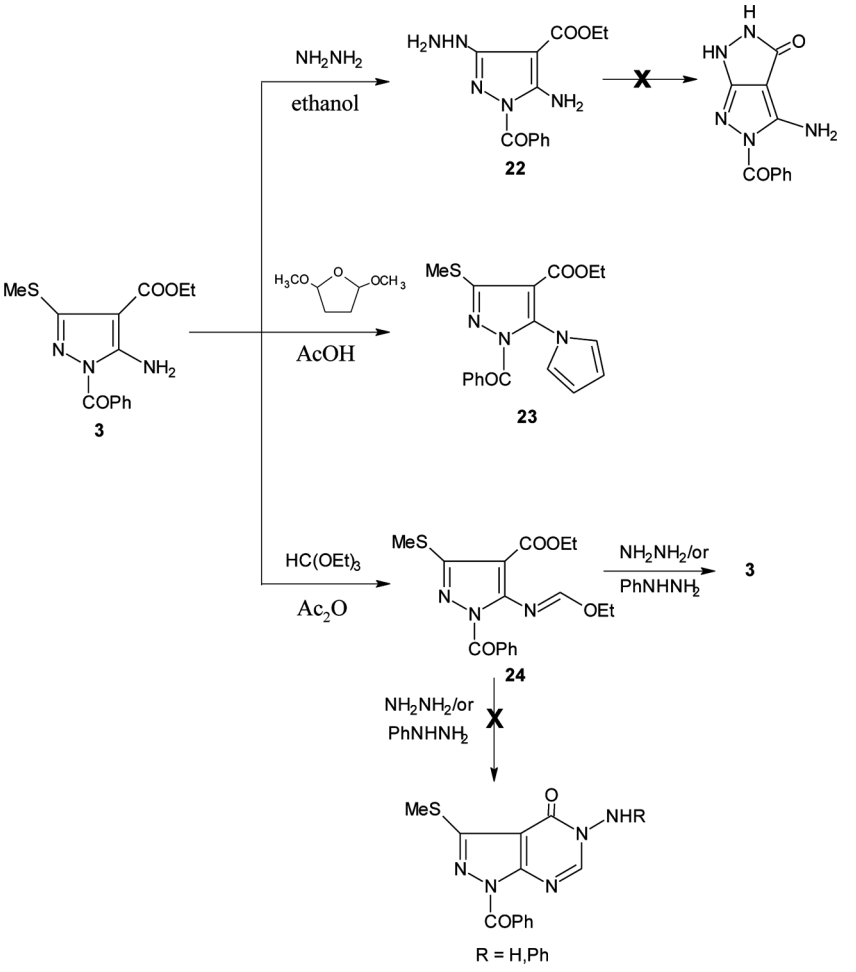


Figure 3. Minimized energy structure of 22 by MM2 and AM1. (Figure is provided in color online.)



Scheme 6. Preparation of pyrazole derivatives (**22–24**).

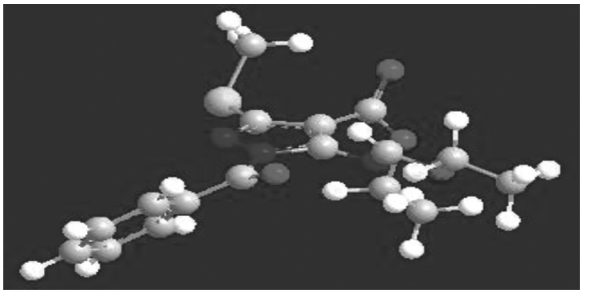


Figure 4. Minimized energy structure of 24 by MM2 and AM1. (Figure is provided in color online.)

ice-cold water. The obtained solid product was filtered off, washed with water, and crystallized from ethanol.

1-Benzoyl-3-(methylthio)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (4).

Method A. Yield 2.2 g, 77%, Buff, mp 305 °C; IR: cm^{-1} 3161 (NH), 1680 (2CO); ^{1}H NMR: δ 10.50 (s, 1H, NH), 8.25 (s, 1H, CH pyrimidine), 7.94–7.55 (m, 5H, arom), 2.50 (s, 3H, SCH_3); ^{13}C NMR (DMSO-d), TMS, δ (ppm) 161.97, 151.20, 150.57, 142.12, 134.48, 130.57, 129.64, 110.08, 12.02. Anal. calc. for $C_{13}H_{10}N_4O_2S$ (286.31): C, 54.54; H, 3.52; N, 19.57; S, 11.20. Found: C, 54.12; H, 3.15; N, 19.92; S, 11.01.

Method B. Compound **3** (0.003 mol, 1 g) and excess formamide (10 ml) were heated under reflux for 10 h. The mixture was left to cool and poured onto ice-cold water. The obtained solid product was filtered, washed with water, and crystallized from ethanol.

1-Benzoyl-3-(methylthio)-1*H*-pyrazolo[3,4-*d*]pyrimidin -4-amine (5). Yield 2.1 g, 74%, pale yellow, mp 250 °C; IR: cm^{-1} 3217, 3105 (NH_2), 1662 (CO); ^{1}H NMR: 8.11 (s, 1H, CH pyrimidine), 7.83–7.55 (m, 5H, arom), 6.43 (s, 2H, NH_2), 2.50 (s, 3H, SCH_3); ^{13}C NMR (DMSO-d), TMS, δ (ppm) 161.76, 154.94, 154.63, 154.13, 146.87, 134.06, 129.34, 128.88, 102.34, 12.34. Anal. calc. for $C_{13}H_{11}N_5OS$ (285.32): C, 54.72; H, 3.89; N, 24.55; S, 11.24. Found: C, 54.44; H, 3.65; N, 24.92; S, 11.46.

1-Benzoyl-6-methyl-3-(methylthio)-1,5-dihydro-4*H*-pyrazolo [3,4-*d*]pyrimidine-4-thione (6)

Compound **2** (0.004 mol, 1 g) and thioacetamide (0.004 mol, 0.4 g) in trifluoroacetic acid (5 ml) were heated under reflux for 24 h. The mixture was left to cool and poured onto ice-cold water. The obtained solid product was filtered, washed with water and crystallized from ethanol. Yield 2.8 g, 88%, brown, mp 245 °C; IR: cm^{-1} 3172 (NH), 1660 (CO); ^{1}H NMR: δ 11.50 (s, 1H, NH), 7.95–7.50 (m, 5H, arom), 2.50 (s, 3H, SCH_3), 2.48 (s, 3H, CH_3); ^{13}C NMR (DMSO-d), TMS, δ (ppm) 193.23, 164.52, 158.83, 157. 31, 146.13, 134.48, 131.08, 129.36, 115.03, 20.35, 10.47. Anal.

calc. for C_{14} $H_{12}N_4O$ S_2 (316.40): C, 53.14; H, 3.82; N, 17.71; S, 20.27. Found: C, 53.44; H, 3.55; N, 17.42; S, 20.45.

Pyrazolopyrimidine and Pyridine Derivatives 7–$8_{a,b}$

Compound **2** (0.004 mol, 1 g) and carbon disulfide, phenyl isocyanate, phenylisothiocyanate, or ethyl cyanoacetate (0.004 mol) in pyridine (15 ml) were heated under reflux for 12 h. The mixture was left to cool and poured onto ice cold water. The obtained solid product was filtered, washed with water, and crystallized from ethanol.

1-Benzoyl-3-(methylthio)-1*H*-pyrazolo[3,4-*d*]pyramid-dine-4,6(*5H,7H*)-dithione (7). Yield 3 g, 90%, yellowish white, mp 320 °C; IR: cm^{-1} 3223 (2NH), 1662 (CO); ^{1}H NMR: δ 11.19 (s, 1H, NH), 8.19 (s, 1H, NH), 8.01–7.52 (m, 5H, arom), 2.51 (s, 3H, SCH_3); ^{13}C NMR (DMSO-d), TMS, δ (ppm) 197. 32, 167.50, 163.38, 153.31, 150.27, 134.85, 134.48, 129.32, 127.98, 112.14, 10.37. Anal. calc. For $C_{13}H_{10}$ N_4OS_3 (334.44): C, 46.69; H, 3.01; N, 16.75; S, 28.76. Found: C, 46.34; H, 3.45; N, 16.42; S, 28.43.

1-Benzoyl-4-imino-3-(methylthio)-5-phenyl-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*d*]pyrimidin-6-one (8_a). Yield 2.9 g 77%, Yellowish white, mp 140 °C; IR: cm^{-1} 3351, (2NH), 1668 (2CO); ^{1}H NMR: δ 13.90 (s, 1H, NH), 10.24 (s, 1H, NH), 7.97–7.10 (m, 10H, arom), 2.50 (s,3H, SCH_3); ^{13}C NMR (DMSO-d), TMS, δ (ppm)) 164.59, 150.34, 143.83, 142. 61, 134.13, 130.80, 130.08, 128.98, 125.03, 95.15, 10.68. Anal. calc. for $C_{19}H_{15}N_5O_2S$ (377.42): C, 60.46; H, 4.01; N, 18.56; S, 8.50. Found: C, 60.13; H, 3.75; N, 18.86; S, 8.23.

1-Benzoyl-4-imino-3-(methylthio)-5-phenyl-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*d*]pyrimidine-6-thione (8_b). Yield 3.2 g 81%, yellowish white, mp 250 °C; IR: cm^{-1} 3206 (2NH), 1687 (CO); ^{1}H NMR: δ 13.80 (s, 1H, NH), 8.56 (s, 1H, NH), 7.72–7.01 (m,10H, arom), 2.51 (s,3H, SCH_3); Anal. calc. for C_{19} $H_{15}N_5OS_2$ (393.48): C, 58.00; H, 3.84; N, 17.80; S, 16.30. Found: C, 58.44; H, 3.55; N, 17.42; S, 16.54.

4-Amino-1-benzoyl-3-(methylthio)-6-oxo-6,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (9)

Yield 2.5 g, 77%, yellowish white, mp 230 °C; IR: cm^{-1} 3384, 3286, 3228 (NH, NH_2), 2223 (CN), 1667 (2CO); ^{1}H NMR:δ 9.76 (s, 1H, NH), 7.83 (s, 2H, NH_2), 7.67–7.43 (m, 5H, arom), 2.50 (s, 3H, SCH_3); ^{13}C NMR (DMSO-d), TMS, δ (ppm) 167.47, 165.44, 154.24, 149. 53, 139.01, 134.48, 130.01, 128.98, 128.43, 89.18, 77.58, 10.73. Anal. calc. for C_{15} $H_{11}N_5O_2S$ (325.34): C, 55.38; H, 3.41; N, 21.53; S, 9.86. Found: C, 55.54; H, 3.75; N, 21.85; S, 9.55.

1-Benzoyl-3-(methylthio)-5-(1*H*-pyrrol-1-yl)-1*H*-pyrazole-4-carbonitrile (10)

An equimolar ratio of compound **2** (0.004 mol, 1 g) and 2,5-dimethoxytetrahydro-furan (0.7 ml) in 15 ml of glacial acetic acid were heated under reflux for 1 h, left to cool, and then poured onto ice-cold water. The precipitated solid was filtered off,

washed well with water, dried, and crystallized from ethanol. Yield 2.7 g, 87%, brown, mp 250 °C; IR: cm^{-1} 2220 (CN), 1669 (CO); ^1H NMR: δ 8.25–7.58 (br, 7H, arom + pyrrolyl), 7.37 (d, 2H, pyrrolyl); 2.50 (s, 3H, SCH_3); MS m/z (%): M^+ 308 (21.2), 258 (7.3), 105 (100), 77 (833); ^{13}C NMR (DMSO-d), TMS, δ (ppm) 163.59, 148.04, 143.73, 135. 61, 134.43, 130.60, 128.28, 120.89, 116.93, 113.15, 79.08, 11.78. Anal. calc. for $C_{16}H_{12}N_4OS$ (308.36): C, 62.32; H, 3.92; N, 18.17; S, 10.40. Found: C, 62.00; H, 3.65; N, 18.52; S, 10.64.

2-(4-Methoxyphenyl)-5-(methylthio)-7-[(phenyl-λ^4-sulfanylidyne) methyl]-1,2,3,7-tetrahydro-4*H*-pyrazolo[3,4-*d*][1,3,2] diazaphosphinine-4-thione 2-sulfide (11)

A mixture of compound **2** (0.004 mol, 1 g) and Lawesson's reagent (0.004 mol, 1.3 g) in dry p-xylene (20 ml) was heated under reflux for 6 h. The solvent was removed under reduced pressure, and the obtained residue was triturated with cold methanol (20 ml). The precipitate was filtered off and crystallized from dioxane. Yield 3.4 g, 71%, Reddish brown, mp 120°C; IR: cm^{-1} 3435, 3287 (2NH); ^1H NMR: δ 10.50 (s, 2H, 2NH), 7.67–6.26 (m, 9H, arom), 3.78 (s, 3H, OCH_3), 2.50 (s, 3H, SCH_3); ^{13}C NMR (DMSO-d), TMS, δ (ppm) 188.90, 188.54, 161.63, 161. 51, 152.16, 143.62, 140.40, 140.08, 139.88, 132.00, 131.77, 128.15, 127.71, 126.58, 103.97, 103.77, 55.30, 10.88. Anal. calc. for C_{19} $H_{17}N_4OPS_4$ (476.60): C, 47.88; H, 3.60; N, 11.76; S, 26.91. Found: C, 47.44; H, 3.25; N, 12.10; S, 26.77.

5-Amino-1-benzoyl-3-hydrazino-1*H*-pyraz-ole-4-carbonitrile (12)

Compound **2** (0.004 mol, 1 g) and excess of hydrazine hydrate (5 ml) in absolute ethanol (15 ml) were heated under reflux for 7 h. The reaction mixture was concentrated and left to cool. The obtained solid filtered and crystallized from ethanol. Yield 1.8 g, 74%, brown, mp 110 °C; IR: cm^{-1} 3386, 3285, 3210, 3135 (NH, $2NH_2$), 2219 (CN), 1664 (CO); ^1H NMR: δ 9.76 (s, 1H, NH), 8.25 (s, 2H, NH_2), 7.83–7.43 (m, 5H, arom), 6.43 (s, 2H, NH_2); ^{13}C NMR (DMSO-d), TMS, δ (ppm) 163.09, 154.54, 149.83, 134. 48, 132.43, 130.55, 128.58, 118.18, 77.03. Anal. calc. for $C_{11}H_{10}N_6O$ (242.24): C, 54.54; H, 4.16; N, 34.69. Found: C, 54.84; H,3.85; N, 34.92.

N-[1-Benzoyl-4-cyano-3-(Methylthio)-1*H*-pyrazol-5-yl]-3-oxo-3-phenylpropanamide (13)

Compound **2** (0.004 mol, 1 g) and excess ethyl benzoylacetate (10 ml) were heated at 200 °C. solid products began to form after 15–20 min. The heating was continued for 1 h. The solid products was filtered, washed with ethanol and crystallized from ethanol. Yield 3.1 g, 77%, yellow, mp 270 °C; IR: cm^{-1} 3280 (NH), 2228 (CN), 1694–1673 (3CO); ^1H NMR: δ 10.24(s, 1H, NH), 7.97–7.10, 7.10 (m, 10H, arom), 4.10 (s, 2H, CH_2) 2.50 (s, 3H, SCH_3); Anal. calc. for $C_{21}H_{16}N_4O_3S$ (404.44): C, 62.36; H, 3.99; N, 13.85; S, 7.93. Found: C, 62.02; H, 3.65; N, 13.45; S, 7.73.

N-[1-Benzoyl-4-cyano-3-(methylthio)-1*H*-pyrazol-5-yl]acetamide (14)

Compound **2** (0.004 mol, 1 g) in DMF (15 ml) and acetyl chloride (0.004 mol, 0.3 ml) or acetic anhydride (10 ml) were stirred at room temperature for 30 min and then heated under reflux for 3 h. The reaction mixture was allowed to cool. The precipitated solid was filtered and crystallized from ethanol. Yield 2.5 g, 83%, yellowish white, mp 265 °C; IR: cm^{-1} 3290 (NH), 2225,(CN), 1687 (2CO); ^{1}H NMR: δ 10.20 (s, 1H, NH), 7.96–7.50 (m, 5H, arom), 2.50 (s, 3H, SCH_3), 2.30 (s, 3H, CH_3); Anal. calc. for $C_{14}H_{12}N_4O_2S$ (300.34): C, 55.99; H, 4.03; N, 18.65; S, 10.68. Found: C, 55.59; H, 3.75; N, 18.92; S, 10.87.

Ethyl [1-Benzoyl-4-cyano-3-(methylthio)-1*H*-pyrazol-5-yl]imidoformate (15)

A mixture of compound **2** (0.004 mol, 1 g), triethyl orthoformate (3 ml), and acetic anhydride (10 ml) was heated under reflux for 6 h. The reaction mixture was concentrated and poured onto ice-cold water. The separated solid was filtered and crystallized from ethanol. Yield 2.5 g, 80%, yellowish white, mp 170 °C; IR: cm^{-1} 2225 (CN), 1694 (CO); ^{1}H NMR: δ 7.82–7.33 (m, 5H, arom), 7.22 (s, 1H, CH), 3.33 (q, 2H, CH_2), 2.50 (s, 3H, SCH_3), 1.80 (t, 3H, CH_3); ^{13}C NMR (DMSO-d), TMS, δ (ppm)) 166.24, 164.64, 149.77, 134.47, 132.83, 132.19, 129.88, 112.95, 95.35, 61.70, 14.28, 10.37. Anal. calc. for $C_{15}H_{14}N_4O_2S$ (314.36): C, 57.31; H, 4.49; N, 17.82; S, 10.20. Found: C, 57.02; H, 4.12; N, 17.50; S, 10.41.

1-Benzoyl-4-hydroxy-6-imino-3-(methyl-thio)-6,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbo-nitrile (16)

Compound **3** (0.003 mol, 1 g) and malononitrile (0.003 mol) in pyridine (15 ml) were heated under reflux for 12 h. The mixture was left to cool and poured onto ice-cold water. The obtained solid product was filtered, washed with water, and crystallized from ethanol. Yield 2.2 g, 74%, buff, mp 240 °C; IR: cm^{-1} 3447 (OH), 3323, 3187 (2NH), 2213 (CN), 1671 (CO); ^{1}H NMR: δ 10.50 (s, 1H, OH), 9.76 (s, 2H, 2NH), 7.95–7.50 (m, 5H, arom), 2.5 (s, 3H, SCH_3); ^{13}C NMR (DMSO-d), TMS, δ (ppm) 165.61, 163.14, 155.46, 151. 37, 141.97, 134.50, 134.44, 128.88, 127.78, 121.65, 101.87, 59.61, 10.72. Anal. calc. for C_{15} $H_{11}N_5O_2S$ (325.34): C, 55.38; H, 3.41; N, 21.53; S, 9.86. Found: C, 55.69; H, 3.05; N, 21.93; S, 9.64.

1-Benzoyl-3-(methylthio)-5-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (17)

Compound **3** (0.003 mol, 1 g) and phenylisocyanate (0.003 mol) in pyridine (15 ml) were heated under reflux for 12 h. The mixture was left to cool and poured onto ice-cold water. The obtained solid product was filtered, washed with water and crystallized from ethanol. Yield 3.0 g, 79%, white, mp 160 °C; IR: cm^{-1} 3335 (NH), 1682-1660 (3CO); ^{1}H NMR: δ 10.34 (s, 1H, NH), 8.07–7.05 (m, 10H, arom), 2.59 (s, 3H, SCH_3); MS *m*/*z* (%): M^+ 378 (34), 197 (11.1), 105 (96.5), 77 (100). Anal. calc. for $C_{19}H_{14}N_4O_3S$ (378.40): C, 60.31; H, 3.73; N, 14.81; S, 8.47. Found: C, 60.64; H, 3.38; N, 14.42; S, 8.69.

Ethyl 1-Benzoyl-3-(methylthio)-5-[(phenyl-carbamothioyl)amino]-1*H*-pyrazole-4-carboxylate (18)

Compound **3** (0.003 mol, 1 g) and phenylisothiocyanate (0.003 mol) in pyridine (15 ml) were heated under reflux for 12 h. The mixture was left to cool and poured onto ice-cold water. The obtained solid product was filtered, washed with water, and crystallized from ethanol. Yield 3.6 g, 82%, white, mp 190 °C; IR: cm^{-1} 3279 (2NH), 1666 (2CO); ^{1}H NMR: δ 10.43 (s, 1H, NH), 10.23 (s, 1H, NH), 7.97–6.65 (m, 10H, arom), 4.16 (q, 2H, CH_2), 2.50 (s, 3H, SCH_3), 1.24 (t, 3H, CH_3). Anal. calc. for $C_{21}H_{20}N_4O_3S_2$ (440.54): C, 57.25; H, 4.58; N, 12.72; S, 14.56. Found: C, 57.66; H, 4.18; N, 13.03; S, 14.39.

Ethyl 1-Benzoyl-5-[(cyanoacetyl)amino]-3-(methylthio)-1*H*-pyrazole-4-carboxylate (19)

Compound **3** (0.003 mol, 1 g) and ethyl cyanoacetate (0.003 mol) in pyridine (15 ml) were heated under reflux for 12 h. The mixture was left to cool and poured onto ice-cold water. The obtained solid product was filtered, washed with water and crystallized from ethanol. Yield 2.8 g, 75%, yellowish green, mp 140 °C; IR: cm^{-1} 3203 (NH), 2222 (CN), 1687–1663 (3CO); ^{1}H NMR: δ 7.90 (s, 1H, NH), 7.60–7.00 (m, 5H, arom), 4.20 (q, 2H, CH_2), 3.80 (s, 2H, CH_2) 2.50 (s, 3H, SCH_3), 1.20 (t, 3H, CH_3). Anal. calc. for $C_{17}H_{16}N_4O_4S$ (372.40): C, 54.83; H, 4.33; N, 15.04; S, 8.61. Found: C, 54.44; H, 4.00; N, 15.42; S, 8.85.

Ethyl 5-(3-Oxo-3-phenylpropanamido)-1-benzoyl-3-(methylthio)-1*H*-pyrazole-4-carboxylate (20)

Compound **3** (0.003 mol, 1 g) and excess ethyl benzoylacetate (10 ml) were heated at 200 °C; solid products were began formed after 15–20 min. The heating was continued for 1 h. The solid products were filtered, and washed with ethanol. Yield 3.4 g 75%, pale yellow, mp 260 °C; IR: cm^{-1} 3234, (NH), 1689–1659 (4CO); ^{1}HNMR: δ 7.90 (s, 1H, NH), 7.67–7.00 (m,10H, arom), 4.16 (q, 2H, CH_2), 3.95 (s, 2H, CH_2), 2.50 (s, 3H, SCH_3), 1.24 (t, 3H, CH_3). Anal. calc. for C_{23} $H_{21}N_3O_5S$ (451.50): C, 61.18; H, 4.69; N, 9.31; S, 7.10. Found: C, 61.51; H, 4.25; N, 9.72; S, 7.23.

Ethyl 5-Acetamido-1-benzoyl-3-(methylthio)-1*H*-pyrazole-4-carboxylate (21)

Compound **3** (0.003 mol, 1 g) in DMF (15 ml) and acetyl chloride (0.003 mol, 0.3 ml) or acetic anhydride (10 ml) were stirred at room temperature for 30 min and then heated under reflux for 3 h. The reaction mixture was allowed to cool. The precipitated solid was filtered and crystallized from ethanol. Yield 2.7 g, 78%, white, mp 120 °C; IR: cm^{-1} 3329 (NH), 1696–1678 (3CO); ^{1}H NMR: δ 8.76 (s, 1H, NH), 7.87–7.00 (m, 5H, arom), 4.10 (q, 2H, CH_2), 2.50 (s, 3H, SCH_3), 2.30 (s, 3H, CH_3), 1.20 (t, 3H, CH_3). Anal. calc. for $C_{16}H_{17}N_3$ O_4S (347.39): C, 55.32; H, 4.93; N, 12.10; S, 9.23. Found: C, 55.73; H, 4.55; N, 12.54; S, 9.01.

Ethyl 5-Amino-1-benzoyl-3-hydrazino-1*H*-pyrazole-4-carboxylate (22)

Compound **3** (0.003 mol, 1 g) and excess hydrazine hydrate (5 ml) in absolute ethanol (15 ml) was heated under reflux for 7 h. The reaction mixture was left to cool and the obtained solid was filtered and crystallized from ethanol. Yield 2.2 g, 76%, buff, mp 150 °C; IR: cm^{-1} 3485, 3389, 3331 (NH, $2NH_2$), 1682 (2CO); ^1H NMR: δ 9.76 (s, 1H, NH), 7.83–7.40 (m, 5H, arom), 6.00 (s, 4H, $2NH_2$), 4.16 (q, 2H, CH_2), 1.23 (t, 3H, CH_3); ^{13}C NMR (DMSO-d), TMS, δ (ppm) 167.59, 164.94, 154.43, 150.61, 134.43, 132.30, 129.08, 128.88, 97. 30, 58.75, 14.18. Anal. calc. for $C_{13}H_{15}N_5O_3$ (289.30): C, 53.97; H, 5.23; N, 24.21. Found: C, 53.54; H, 4.85; N, 24.62.

Ethyl 1-Benzoyl-3-(methylthio)-5-(1*H*-pyrrol-1-yl)-1*H*-pyrazole-4-carboxylate (23)

An equimolar ratio of compound **3** (0.003 mol, 1 g) and 2,5-dimethoxytetrahydrofuran (0.6 ml) in 15 ml of glacial acetic acid was heated under reflux for 1 h, left to cool and then poured onto ice-cold water. The precipitated solid was filtered off, washed well with water, dried, and crystallized from ethanol. Yield 3.0 g, 85%, brown, mp 163 °C; IR: cm^{-1} 1695 (2CO); ^1H NMR: δ 8.10–7.40 (m, 5H, arom), 7.00 (d, 2H, pyrrolyl) 6.61 (d, 2H, pyrrolyl), 4.20 (q, 2H, CH_2), 2.50 (s, 3H, SCH_3), 1.20 (t, 3H, CH_3). Anal. calc. for $C_{18}H_{17}N_3O_3S$ (355.41): C, 60.83; H, 4.82; N, 11.82; S, 9.02. Found: C, 60.42; H, 4.55; N, 11.41; S, 9.22.

Ethyl 1-Benzoyl-5-{[(1*E*)-ethoxymethylene]amino}-3-(Methylthio)-1*H*-pyrazole-4-carboxylate (24)

A mixture of compound **3** (0.003 mol, 1 g), triethyl orthoformate (3 ml), and acetic anhydride (10 ml) was heated under reflux for 6 h. The reaction mixture was concentrated and poured onto ice-cold water. The solid product was filtered and crystallized from ethanol. Yield 3.0 g, 83%, White, mp 118–120 °C; IR: cm^{-1} 1701–1690 (2CO); ^1H NMR: δ 7.80–7.35 (m, 5H, arom), 7.19 (s, 1H, CH), 4.20 (q, 4H, $2CH_2$), 2.50 (s, 3H, SCH_3), 1.20 (t, 6H, $2CH_3$); ^{13}C NMR (DMSO-d), TMS, δ (ppm) 164.39, 160.74, 160.40, 157. 19, 149.63, 134.47, 132.78, 130.40, 129.63, 110.65, 61.70, 58.73, 14.20, 14.18, 10.36. Anal. calc. for $C_{17}H_{19}N_3O_4S$ (361.42): C, 56.50; H, 5.30; N, 11.63; S, 8.87. Found: C, 56.22; H, 4.93; N, 11.98; S, 8.65.

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