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Synthesis of new polysubstituted (pyrazoles, pyrimidines and quinolines) five and six-membered heterocycles: reaction of α,α-dioxoketene dithioacetals with nucleophiles

M. A. Ebraheem [a,*], K. M. Lokanatha Rai [a], N. U. Kudva.N [a], A. S. Bahjat [b]

[a] Department of Chemistry, University of Mysore, Manasagangotri, Mysore 570 006, India
[b] Department of Chemistry, University of Basrah, Basrah, Iraq

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ABSTRACT

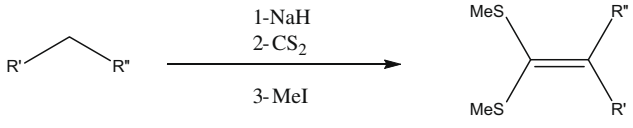
A novel synthesis of polysubstituted pyrazoles **3a–d**, pyrimidines **4a–f** and quinolines **5a–c** via the reaction of α,α-oxoketene dithioacetals **2a–c** with hydrazine hydrate, malonohydrazide, urea, thiourea and aniline is reported and the synthetic potential of the method is demonstrated. The structure of the new compounds was established upon their elemental analysis, IR, ^{1}H NMR and ^{13}C NMR.

1. Introduction

Five- and six-membered hetrocycles compounds such as substituted pyrazoles, pyrimidines and quinolines have been investigated intensively for the last several years because of their biological and pharmaceutical activities, for example, many natural and synthetic products containing pyrazoles were reported to possess varied biological and pharmacological activities.[1–11] On the other hand, pyrimidines and quinolines are known as one of the most important classes of organic compounds some of which show significant biological and pharmaceutical activities.[11–28] A number of synthetic pharmacophores based upon the pyrimidyl and quinolyl structures exhibit antilishmanial, antiparasitic, antibacterial, antimicrobial, anticancer, anti-HIV-1 and antirubella virus activities.[13–22] One of the reported useful methods employed for the synthesis of substituted pyrazoles and pyrimidines involves the cyclocondensation of α-oxoketene dithioacetals as 1,3-bielectrophilic synthon with nucleophiles such as hydrazine hydrate, urea and thiourea.[29,30] On the other hand, one method for the preparation of quinolinecarboxylic acid derivatives is reported.[31] The effort made towards the development of newer synthetic routes for synthesis of new type of polysubstituted pyrazoles, pyrimidines and quinolines via α,α-oxoketene dithioacetals **2a–f** is still unreported. It is clear in these systems that there is a highly polarized push (dialkylthio)—pull (dicarbonyl) interaction on the C–C double bond Scheme 1, therefore we became interested in investigating the reactivity of this system towards nucleophiles. We report herein the novel and very convenient synthetic routes for some new polysubstituted pyrazoles, pyrimidines and quinolines by cyclocondensation of the nucleophiles such as hydrazine hydrate, malonohydrazide, urea, thiourea and aniline with α,α-oxoketene dithioacetals **2a–c** as 1,3-bielectrophilic synthon.

2. Results and discussion

The desired α,α-dioxoketene dithioacetals **2a–c** were prepared in high yield by reacting the corresponding active methylene compounds with carbon disulfide in the presence of sodium hydride as a base in benzene followed by alkylation with methyl iodide in one-pot reaction[32] Scheme 1. The reaction of the α,α-oxoketene dithioacetals **2a–f** with hydrazine hydrate and malonohydrazide in refluxing ethanol gave the respective pyrazoles derivatives **3a–d** in 69–87% yields as shown in Scheme 2.



1 **1a**, R' = R" = COMe; **1b**, R' = COMe, R" = CO_2Et; **1c**, R' = R" = CO_2Et **2**

Scheme 1.

* Corresponding author. Tel.: +91 9972165994; fax: +91 0821 2421263.
E-mail address: alhashmi.ibrahim@yahoo.com (M.A. Ebraheem).

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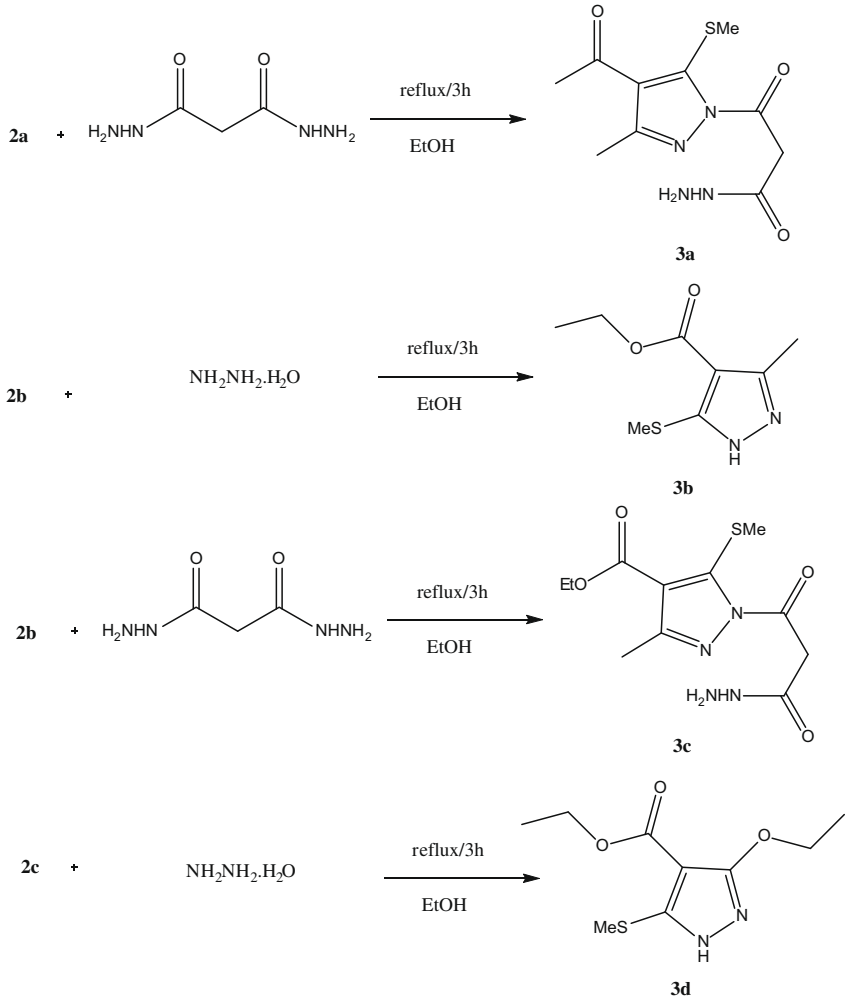
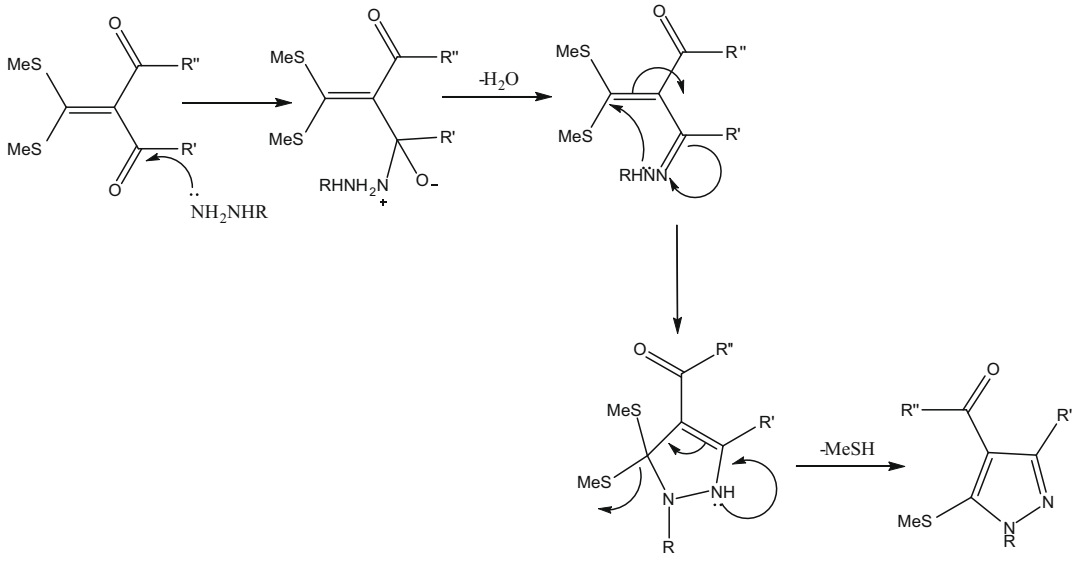


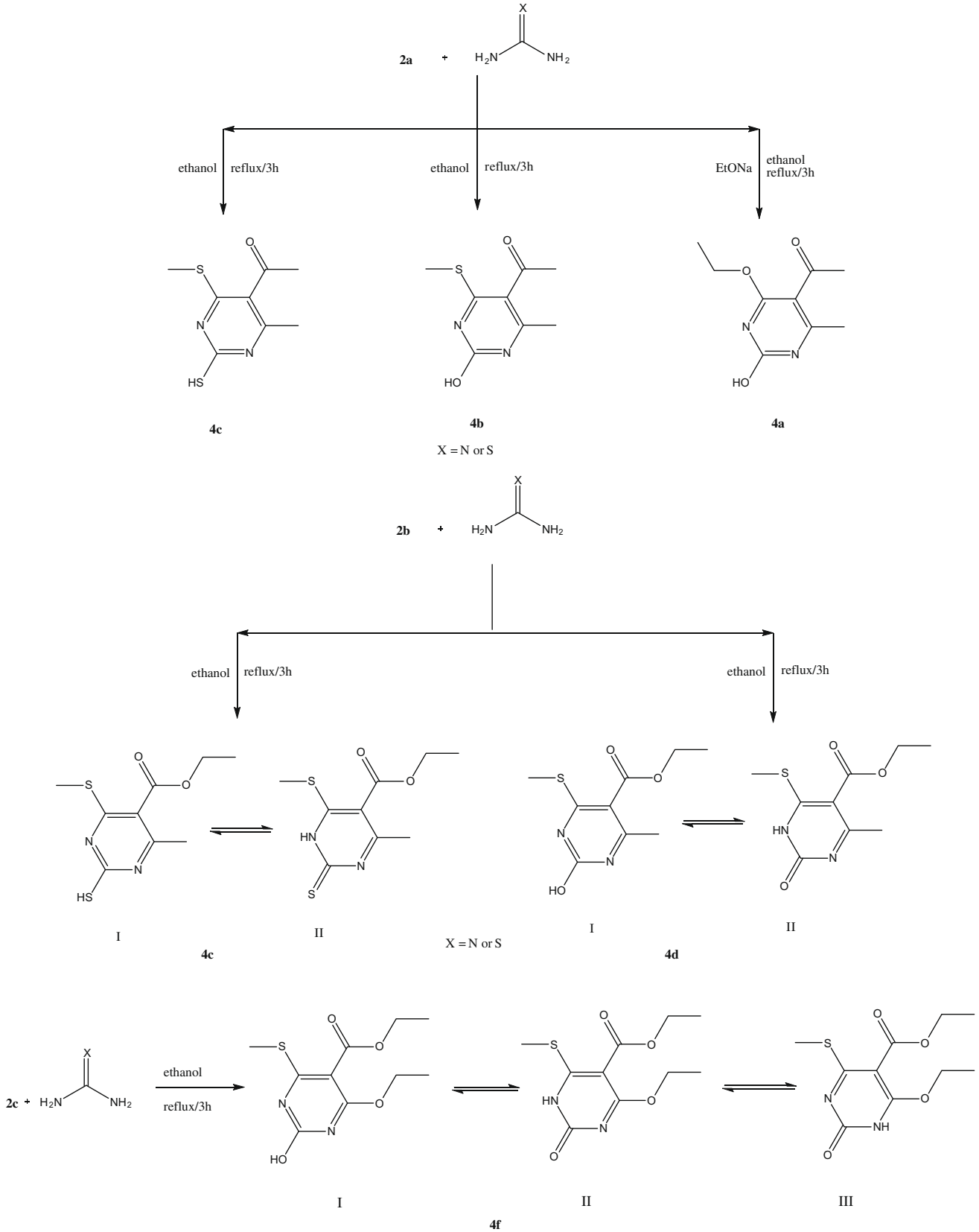
Scheme 2.

On the basis of analyses of the ^{1}H NMR and ^{13}C NMR spectra (DMSO-d_6) of isolated products, the structures of **3a–d** have been assigned. Therefore the probable mechanism for the formation of the products involves the attack of the $-NH_2$ of hydrazine hydrate on carbonyl carbon to give intermediate adduct (Scheme 3). Similarly in the case of malonohydrazide, the more basic nitrogen $-NH_2$



Scheme 3.

attacks carbonyl carbon to give intermediate adduct. In both cases, the intermediate adduct passes intramolecular cyclization in order to afford products **3a–d** rather than the regioisomeric (-3-methylthio-pyrazoles). In the presence of acid the nucleophile will attack the more electrophilic C-3 of protonated dithioacetal to yield exclusively the regioisomeric (-3-methylthio-pyrazoles).[29]



Scheme 4.

The α,α-dioxoketene dithioacetals **2a**–**c** were next reacted with urea and thiourea under refluxing ethanol to afford the products **4a**–**f** in 66–85% yields as shown in Scheme 4. In the case of treatment of the α,α-oxoketene dithioacetal **2a** with urea in the presence of sodium ethoxide in refluxing ethanol, the product isolated was characterized as 1-(4-ethoxy-2-hydroxy-6-methylpyrimidin-5-yl)-ethanone **4a** in which the methylthio group was replaced by the ethoxy group. The treatment of the α,α-dioxoketene dithioacetal **2a** with sodium ethoxide prior to reaction with urea afforded the product **4a** via the intermediate α-oxoketene *O*,*S*-acetals.

In general the probable mechanism for the formation of products **4a**–**f** is as we discussed above in Scheme 4. Here the products **4a**–**f** have been isolated as apparently pure, but on the basis of their spectral ^{1}H NMR and ^{13}C NMR (DMSO-d_6) analyses, it is indicated there are two or three components, for example, the ^{1}H NMR spectra of the product **4d** indicated two kinds of protons as singlet signal near δ 13.28 and 12.26 ppm assignable to –NH and –SH protons, respectively. For the product **4c**, the ^{1}H NMR spectra revealed two characteristic singlet signals near δ 13.26 and 13.01 ppm assignable to –NH and –OH protons, respectively. Also the ^{1}H NMR spectra for the products **4d** and **4c** indicated two triplet signals near δ 4.30 and 4.46 ppm and δ 4.21 and 4.40 ppm, respectively, assignable to CH_2 group. The ^{13}C NMR spectra of compounds **4d** and **4c** are also in accordance with the proposed structures. Therefore the ^{1}H NMR and ^{13}C NMR of the products **4d** and **4c** revealed that the products most probably exist as an equilibrium of two tautomeric forms (I, II) (50%:50%) as shown in Scheme 5.

On the other hand, the ^{1}H NMR spectra of the product **4f** indicated three kinds of proton signals related to three tautomeric forms. The integration of the spectra indicated that the ratio of the tautomeric form is (I, II, III) (50%:30%:20%) as shown in Scheme 5. The ^{13}C NMR spectra of compounds **4f** are also in accordance with the proposed structures.

Next we investigated the behaviour of the α,α-dioxoketene dithioacetals **2b** and **2c** towards aniline and 4-chloroaniline as nucleophile. Thus the reaction of α,α-dioxoketene dithioacetals **2b** and **2c** with aniline under refluxing ethanol afforded the quinolines **5b** and **5c** in 67–91% yield while the reaction of **2b** with 4-chloroaniline afforded the product **5b** as shown in Scheme 6.

The proposed mechanism for the formation of the products **5a**–**c** is shown in Scheme 7.

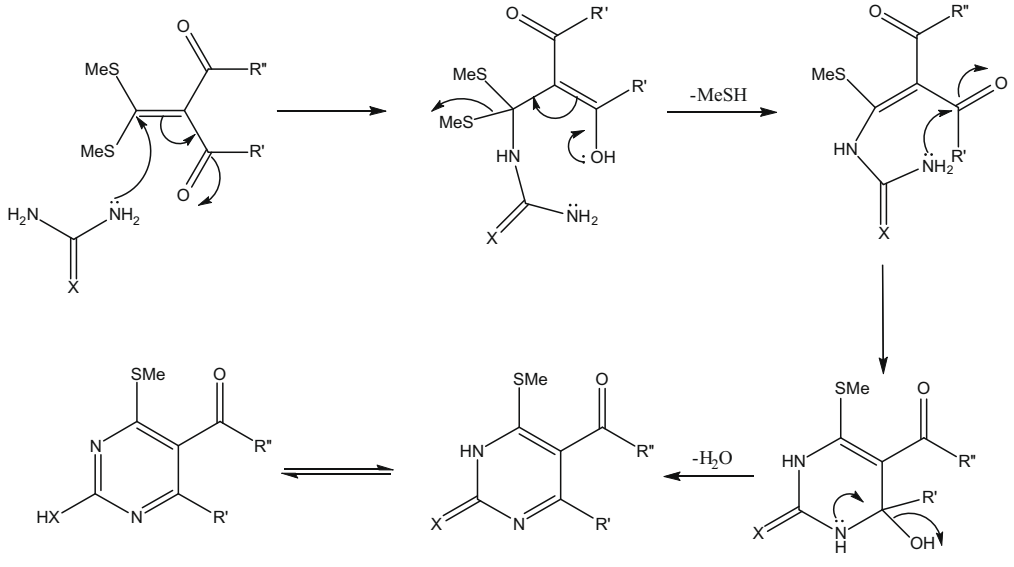
However, the ^{1}H NMR and ^{13}C NMR spectra of compounds **5b** in DMSO-d_6 indicated that such compounds exist as equilibrium of two tautomeric forms. This is because their ^{1}H NMR spectra revealed two characteristic singlet signals near δ 10.58 and 12.98 ppm assignable to –NH and –OH protons, respectively. The integration of the spectra indicated that the ratio of the tautomeric form is (50%:50%).

3. Synthesis of polysubstituted (3,4,5 and 1,3,4,5-substituted pyrazoles) (3a–d)

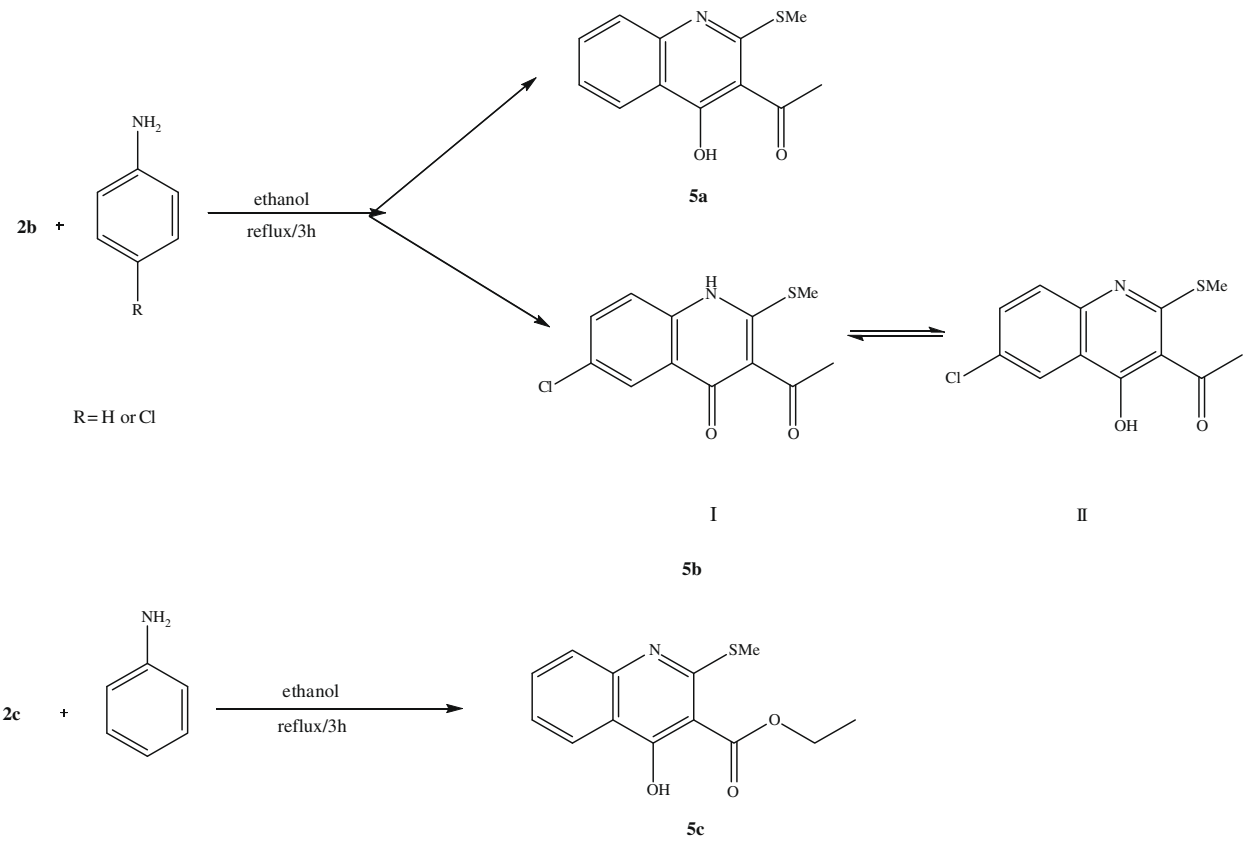
Typical procedure for the synthesis of 3-(4-acetyl-3-methyl-5-(methylthio)-1*H*-pyrazole-1-yl)-3-oxopropanehydrzide (**3a**): A mixture of α,α-dioxoketene dithioacetal (**2a**) (1.023 g, 5 mmol), malonohydrazide (0.7 g, 5 mmol) in absolute ethanol (20 ml) was refluxed for 3 h. After the reaction, the solvent was removed under reduced pressure and the residue was poured into ice-cold water (20 ml); the mixture was then extracted with ethylacetate (2 × 20 ml) followed by washing with water. The organic layer was dried over anhydrous Na_2SO_4, solvent was evaporated and the product obtained was purified by column chromatography using dichloromethane/petroleum ether (4:1) as eluent. (**3a**) obtained as white crystalline solid (0.93 g, 69%) with mp 44–48 °C; IR (KBr) (ν_{max}, cm^{-1}): 3650, 3504, 2968, 1713, 1559, 1519; ^{1}H NMR (400 MHz DMSO-d_6): δ 2.33 (3H, s, –CH_3), 2.49 (3H, s, –$COCH_3$), 2.60 (3H, s, –SCH_3), 3.29 (2H, s, –CH_2–); ^{13}C NMR (100 MHz DMSO-d_6): δ 13.14, 17.56, 29.62, 30.64, 115.61, 143.80, 152.07, 165.01, 170.00, 197.32; Anal. Calcd for $C_{10}H_{14}N_4O_3S$ (270.31): C, 44.43; H, 5.22; N, 20.73. Found: C, 44.34; H, 5.23; N, 20.77.

Ethyl 3-ethyl-5-(methylthio)-1*H*-pyrazole-4-carboxylate (**3b**) obtained as yellow crystalline solid from (**2b**) (1.2 g, 5 mmol) and hydrazine hydrate (0.24 g, 5 mmol) with yield (0.87 g, 87%), mp 98–100 °C; IR (KBr) (ν_{max}, cm^{-1}): 3252, 3102, 2984, 2920, 1662, 1492; ^{1}H NMR (400 MHz, DMSO-d_3): δ 1.22 (3H, t, –OCH_2CH_3), 2.37 (3H, s, –CH_3), 2.49 (3H, s, –SCH_3), 4.18 (2H, q, –OCH_2–), 13.00 (1H, br, NH); ^{13}C NMR (100 MHz DMSO-d_6): δ 11.93, 13.32, 13.43, 14,70, 59.70, 107.70, 145.99, 163.43; Anal. Calcd for $C_8H_{12}NO_2S$ (200.26): C, 47.98; H, 6.04; N; 13.40. Found: C, 47.84; H, 6.06; N, 13.57.

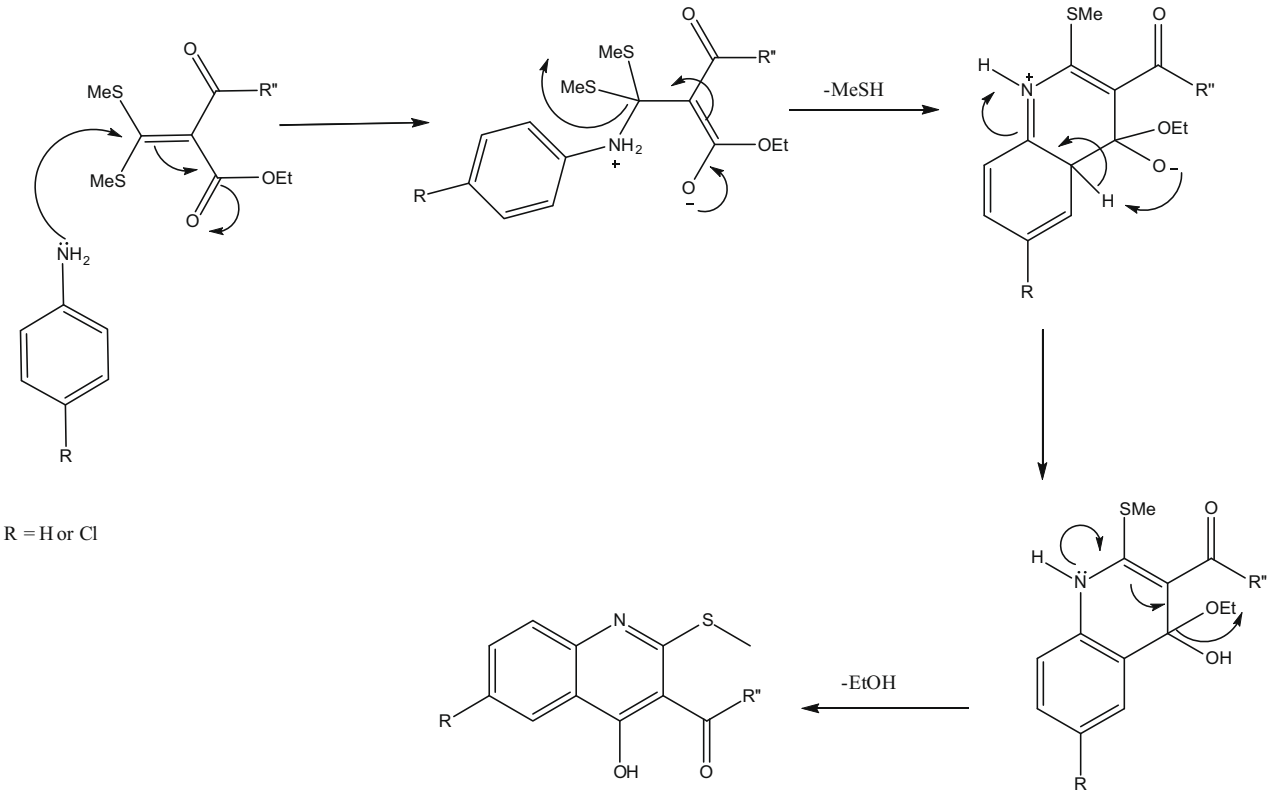
Ethyl-1-(3-hydrazinyl-3-0xopropanoyl)-3-methyl-5-(methylthio)-1*H*-pyrazole-4-carboxylate (**3c**) obtained as yellow oil from (**2b**) (1.2 g, 5 mmol) and malonohydrazide (0.7 g, 5mm0 l) with



Scheme 5.



Scheme 6.



Scheme 7.

yield (1.2 g, 80%); IR (neat) (ν_{max}, cm^{-1}); 3635, 2928, 1733, 1530, 1461; ^1H NMR (400 MHz DMSO-d_6): δ 1.28 (3H, t, $-CH_3$), 2.47 (3H, s, $-CH_3$), 2.49 (3H, s, $-SCH_3$), 3.34 (2H, s, $-CH_2-$), 4.25 (2H, q, $-OCH_2CH_3$); ^{13}C NMR (100 MHz DMSO-d_6): δ 13.74, 17.89, 33.00, 60.93, 104.18, 126.16, 140.18, 143.53, 158.38, 163.06, 169.90; Anal. Calcd for $C_{11}H_{16}N_4O_4S$ (302.31): C, 43.99; H, 5.37; N, 18.65. Found: C, 43.91; H, 5.41; N, 18.57.

Ethyl 3-ethoxy -5-(methylthio)-1*H*-pyrazole-4-carboxylate (**3d**) obtained as crystalline white solid from (**2c**) (1.32 g, 5 mmol) and hydrazine hydrate (0.24 g, 5 mmol) with yield (0.98 g, 86%), mp 125–128 °C; IR (KBr) (ν_{max}, cm^{-1}); 3212, 2930, 1665, 1575, 1481; ^1H NMR (400 MHz DMSO-d_6): δ 1.14 (3H, t, $-CH_3$), 1.19 (3H, t, $-CH_3$), 2.21 (3H, s, $-SCH_3$), 3.99 (2H, q, OCH_2), 4.01 (2H, q, OCH_2), 7.09 (1H, br, –NH); ^{13}C NMR (100 MHz DMSO-d_6): δ 11.90, 14.79, 57.26, 89.70, 145.50, 164.30, 166.40; Anal. Calcd for $C_9H_{14}N_2O_3S$ (230.28): C, 46.94; H, 6.13; N, 12.16. Found: C, 46.86; H, 6.19; N, 12.13.

4. Synthesis of 1-(4-ethoxy-6-methylpyrimidin-5-yl)ethanone (4a)

α,α-Dioxoketene dithioacetal (**2a**) (1.02 g, 5 mmol) was added to a stirred solution of sodium ethoxide (0.01 mol, prepared in situ from 0.23 g of sodium metal and 5 ml ethanol) in ethanol (20 ml) at room temperature. After 15 min, Urea (0.30 g, 5 mmol) was added at the same temperature and the reaction mixture was refluxed for 3 h. After the reaction, the solvent was evaporated under reduced pressure and diluted with water (20 ml). It was then extracted into dichloromethane (2 × 20 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure yielded the crude product and later it was purified by column chromatography over silica gel using dichloromethane/petroleum ether (3:1) as eluent.

1-(4-Ethoxy-6-methylpyrimidin-5-yl)ethanone (**4a**) obtained as white crystalline solid with yield (0.75 g, 76%), mp 57–60 °C, IR (KBr) (ν_{max}, cm^{-1}): 3284, 3140, 2989, 1623, 1468; ^1H NMR (400 MHz DMSO-d_6): δ 1.20 (3H, t, $-CH_3$), 2.43 (3H, s, $-CH_3$), 2.49 (3H, s, $-CH_3$), 4.07 (2H, q, $-OCH_2$), 5.57 (1H, s, –OH); ^{13}C NMR (100 MHz DMSO-d_6): δ 11.25, 14.19, 30.58, 50.19, 107.24, 145.27, 149.66, 162.93, 206.33; Anal. Calcd for $C_9H_{12}N_2O_3$ (196.08): C, 55.09; H, 6.16; N, 14.28. Found: C, 55.12; H, 6.14; N, 14.24.

5. General procedure for the synthesis of polysubstituted (2,4,5,6-pyrimidines) (4b)

A typical procedure for the synthesis of 1-(2-hydroxy-4-methyl-6-(methylthio)pyrimidin-5-yl)ethanone (**4b**): To the solution of α,α-dioxoketene dithioacetal (**2a**) (1.02 g, 5 mmol) in ethanol (20 ml), urea (0.30 g, 5 mmol) was added. The reaction mixture was refluxed for 3 h until all starting materials had disappeared as indicated by TLC. After the reaction, the solvent was removed under pressure and the resultant pasty mass was extracted into dichloromethane (2 × 20 ml) followed by washing with water. The organic layer was dried over anhydrous Na_2SO_4; solvent was evaporated and the product (**4b**) was obtained as white crystalline solid with yield (0.70 g, 70%), mp 52–55 °C, IR (KBr) (ν_{max}, cm^{-1}); 3262, 2991, 1644, 1525. ^1H NMR (400 MHz DMSO-d_6): δ 2.08 (3H, s, $-CH_3$), 2.38 (3H, s, $-CH_3$), 2.49 (3H, s, $-SCH_3$), 6.17 (1H, s, –OH); ^{13}C NMR (100 MHz DMSO-d_6): δ 13.95, 16.47, 30.05, 113.26, 156.30 161.39, 191.74; Anal. Calcd for $C_8H_{18}N_2O_2S$ (198.05): C, 48.47; H, 5.08; N, 14.13. Found: C, 48.38; H, 5.12; N, 14.10.

1-(2-Mercapto-4-methyl-6-(methylthio)pyrimidin-5-yl)ethanone (**4c**) obtained as white crystalline solid from (**2b**) (1.2 g, 5 mmol) and thiourea (0.38 g, 5 mmol) with yield (0.66 g, 66%), mp 118–120 °C, IR (KBr) (ν_{max}, cm^{-1}); 3664, 3156, 2995, 2941, 1590, 1486; ^1H NMR (400 MHz DMSO-d_6): δ 2.09 (3H, s, $-CH_3$), 2.39 (3H, s, $-CH_3$), 2.50 (3H, s, $-SCH_3$), 6.18 (1H, s, –SH). ^{13}C NMR (100 MHz DMSO-d_6): δ 13.09, 17.05, 31.76, 111.03, 164.03 167.55, 181.40, 197.11; Anal. Calcd for $C_8H_{10}N_2OS_2$ (214.31): C, 44.84; H, 4.70; N, 13.07. Found: C, 44.75; H, 4.73; N, 12.93.

Ethyl 2-hydroxy-4-methyl-6-(methylthio)pyrimidin-5-carboxylate (**4d**) obtained as white crystalline solid from (**2b**) (1.2 g, 5 mmol) and urea (0.30 g, 5 mmol) with yield (0.82 g, 72%), mp 48–50 °C; IR (KBr) (ν_{max}, cm^{-1}); 3448, 3337, 2985, 2925, 1676, 1533, 1426. ^1H NMR (400 MHz DMSO-d_6): δ 1.27 (3H, t, $-CH_3$), 2.18 (3H, s, $-CH_3$), 2.49 (3H, s, $-SCH_3$), 4.30 (2H, q, $-OCH_2-$), 6.16 (1H, s, –OH); ^{13}C NMR (100 MHz DMSO-d_6): δ 13.95, 14.25, 16.29, 58.96, 104.19 150.10, 153.30, 161.35, 164.03; Anal. Calcd for $C_9H_{12}N_2O_3S$ (228.27): C, 47.35; H, 5.30; N, 12.27. Found: C, 47.32; H, 5.32; N, 12.22.

Ethyl 2-mercapto-4-methyl-6-(methylthio) pyrimidin-5-carboxylate (**4e**) obtained as yellow crystalline solid from (**2b**) (1.2 g, 5 mmol) and thiourea (0.38 g, 5 mmol) with yield (0.91 g, 71%), mp 146–148 °C; IR (KBr) (ν_{max}, cm^{-1}); 3145, 2974, 1725, 1563, 1443. ^1H NMR (400 MHz DMSO-d_6): δ 1.23 (3H, t, $-CH_3$) 2.05 (3H, s, $-CH_3$), 2.49 (3H, s, $-SCH_3$), 4.21 (2H, q, $-OCH_2-$), 4.26 (2H, q, $-OCH_2-$), 12.26 (1H, br, –SH), 13.28 (1H, br, –NH). ^{13}C NMR (100 MHz DMSO-d_6): δ 13.88, 15.91, 18.00, 61.09, 104.04, 110.18 148.04, 158.19, 163.17, 163.70, 173.66, 175.83, 181.69; Anal. Calcd for $C_9H_{12}N_2O_2S_2$ (244.03): C, 44.24; H, 4.93; N, 11.47. Found: C, 43.11; H, 4.49; N, 11.36.

Ethyl 4-ethoxy-2-hydroxy-6-(methylthio) pyrimidin-5-carboxylate (**4f**) obtained as red oil from (**2c**) (1.32 g, 5 mmol) and urea (0.30 g, 5 mmol) with yield (1.1 g, 85%); IR (neat), (ν_{max}, cm^{-1}); 3645, 2983, 1736, 1531, 1445. ^1H NMR (400 MHz DMSO-d_6): δ 1.23 (3H, t, $-CH_3$), 2.45 (2H, s, $-SCH_3$), 4.23 (2H, q, $-OCH_2$), 5.45 (1H, s, –OH), 5.71 (1H, br, –NH), 5.82 (1H, br, –NH). ^{13}C NMR (100 MHz DMSO-d_6): δ 13.94, 14.94, 16.67, 61.62, 148.04, 153.26, 158.19, 163.98, 166.42; Anal. Calcd for $C_{10}H_{14}N_2O_4S$ (258.29): C, 46.50; H, 5.46; N, 10.85. Found: C, 46.44; H, 5.51; N, 10.79.

6. General procedure for the synthesis of substituted 2,3,4-substituted quinolines (5a–c)

Typical procedure for the synthesis of 1-(4-hydroxy-2-(methylthio) quinolin-3-yl)ethanone (**5a**): To the solution of α,α-dioxoketene dithioacetal (**2b**) (2.34 g, 10 mmol) in ethanol (30 ml), aniline (0.9 ml 10 mmol) was added. The reaction mixture was refluxed for 3 h until all starting materials had disappeared as indicated by TLC. After the reaction, the solvent was removed under pressure and then water (20 ml) was added. The mixture was then extracted with chloroform (2 × 20 ml) followed by washing with water. The organic layer was dried over anhydrous Na_2SO_4; solvent was evaporated and the product was obtained (**5a**) as white crystalline solid with yield (0.92 g, 79%), mp 218–225 °C (sublimate) (from ethanol), IR (KBr) (ν_{max}, cm^{-1}); 3321, 3040, 1613, 1446; ^1H NMR (400 MHz DMSO-d_6): δ 2.48 (3H, s, $-CH_3$), 2.49 (3H, s, $-SCH_3$), 6.97 (1H, t, ArH), 7.28 (1H, t, ArH), 7.44 (1H, d, ArH), 8.61 (1H, s, –OH). ^{13}C NMR (100 MHz DMSO-d_6): δ 17.07, 29.00, 109.70, 112.01, 118.13, 121.75, 128.72, 139.64, 145.20, 152,47; Anal. Calcd for $C_{12}H_{11}NO_2S$ (233.05): C, 61.78; H, 4.75; N, 6.00. Found: C, 61.69; H, 4.70; N, 6.09.

1-(6-Chloro-4-hydroxy-2-(methylthio) quinolin-3-yl)ethanone (**5b**) obtained as yellow crystalline solid from (**2b**) (2.34 g, 10 mmol) and 4-chloroaniline (1.3 g, 10 mmol) with yield (0.89 g, 66%), mp >120 °C (decomposed), (from ethanol), IR (KBr) (ν_{max}, cm^{-1}); 3134, 3051, 2999, 1636, 1489; ^1H NMR (400 MHz DMSO-d_6): δ 2.57 (3H, s, $-COCH_3$), 2.73 (3H, s, $-SCH_3$), 7.30 (2H, m, ArH), 8.09 (1H, d, ArH), 10.58 (1H, br, –OH), 12.97 (1H, br, –NH).

^{13}C NMR (100 MHz DMSO-d_6): δ 13.05, 32.18, 100.89, 124.38, 126.17, 128.97, 131.03, 153.64, 174.98, 199.94; Anal. Calcd for $C_{12}H_{10}ClNO_2S$ (267.73): C, 53.83; H, 3.76; N, 5.23. Found: C, 53.78; H, 3.71; N, 5.19.

Ethyl 4-hydroxy-2-(methylthio) quinolin-carboxylate (**5c**) obtained as Yellow crystalline solid from (**2c**) (2.64 g, 10 mmol) and aniline (0.9 ml 10 mmol) with yield (0.91 g, 69%), mp 188–190 °C (from ethanol), IR (KBr) (ν_{max}, cm^{-1}); 3296, 3056, 2973, 1688, 1539; ^{1}H NMR (400 MHz DMSO-d_6): δ 1.21 (3H, t, –OCH_2CH_3), 2.49 (3H, s, –SCH_3), 4.17 (2H, q, –OCH_2–), 7.06 (1H, t, ArH), 7.32 (1H, t, ArH), 7.60 (1H, d, ArH), 10.13 (1H, s, –OH). ^{13}C NMR (100 MHz DMSO-d_6): δ 13.98, 14.27, 61.02, 104.23, 119.09, 123.36, 128.72, 138.93, 158.49, 163.14, 165.40; Anal. Calcd for $C_{13}H_{13}NO_3S$ (263.31): C, 59.30; H, 4.98; N, 5.32. Found: C, 59.35; H, 4.92; N, 5.29.

7. Conclusion

In conclusion, we have synthesized new polysubstituted pyrazoles, pyrimidines and quinolines through the cyclocondensation of some α,α-dioxoketene dithioacetals with some different nucleophiles and the tautomeric forms of some of the products are characterized.

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