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FACILE SYNTHESIS OF SOME NEW PYRAZOLE-BASED 2-THIOXO-4-THIAZOLIDINONE

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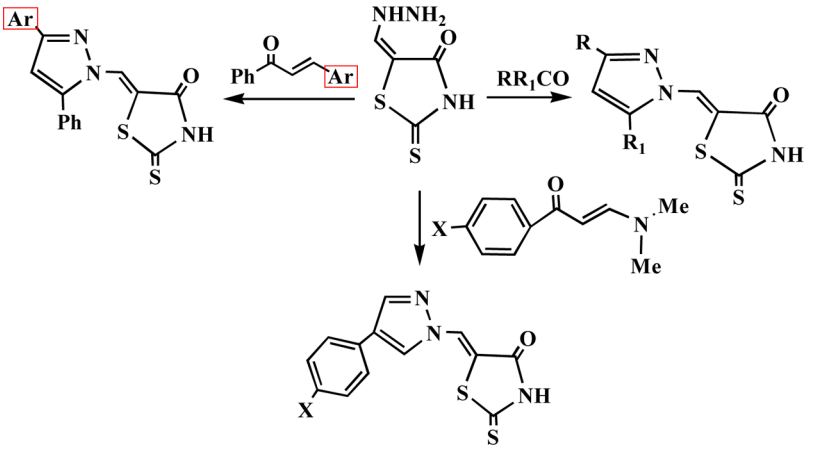
GRAPHICAL ABSTRACT



Abstract *5-Ethoxymethylene-2-thioxo-4-thiazolidinone (**1**) reacts with hydrazine hydrate at room temperature to afford 5-(hydrazinylmethylene)-2-thioxo-4-thiazolidinone (**3**). Compound **3** condensed with different aromatic aldehydes **6a–d** in ethanol in the presence of a few drops of piperidine to give the corresponding Schiff's bases **7a–d**. On the other hand, compound **3** reacts with o-hydroxybenzaldehyde derivatives **8a** and **8b** in refluxing ethanol catalyzed by a few drops of piperidine to yield 1H-inadzolyl-2-thioxo-4-thiazolidinones **9a** and **9b**. Reaction of compound **3** with α-ketoesters **10a** and **10b** or α-diketones **10c–e** in refluxing glacial acetic acid furnished the pyrazolyl-2-thioxo-4-thiazolidinone derivatives **11a–e**. Also, compound **3** reacts with some different enaminones **12a–f** in refluxing glacial acetic acid to afford the new pyrazolyl-2-thioxo-4-thiazolidinone derivatives **13a–f**. Pyrazoles **15a–d** was obtained via reaction of compound **3** with chalcones **14a–d** in dimethylformamide (DMF). The structures of all the newly synthesized products were confirmed on the basis of their elemental and spectral data, and a plausible mechanism has been postulated to account for their formation.*

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Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lsyc.

Keywords 5-Ethoxymethylene-2-thioxo-4-thiazolidinone; 5-hydrazinylmethylene-2-thioxo-4-thiazolidinone; 5-pyrazolyl-2-thioxo-4-thiazolidinones

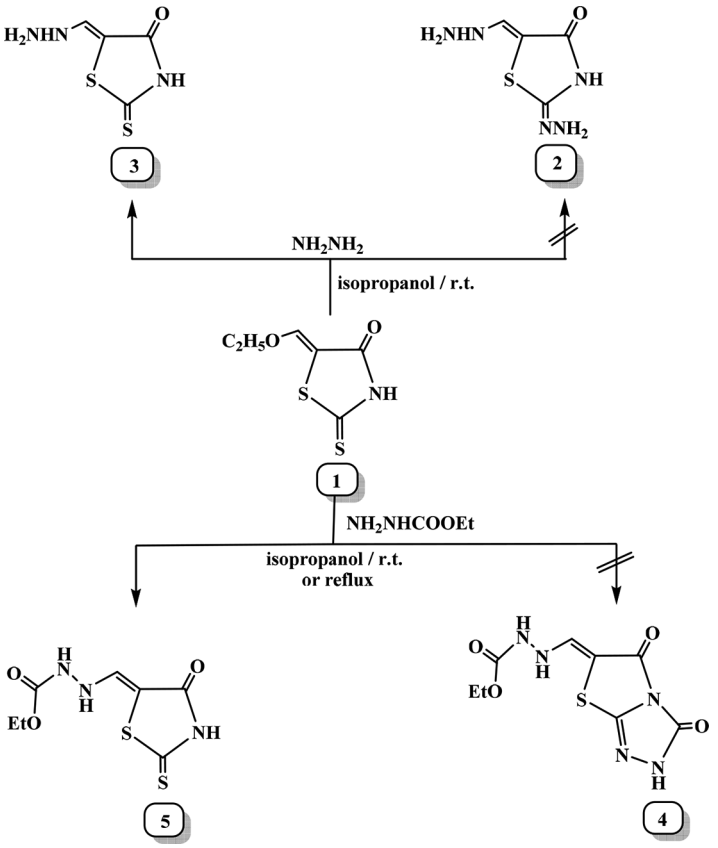
INTRODUCTION

2-Thioxo-4-thiazolidinone has a wide spectrum of biological activity as antibacterial,[1–3] antiviral,[4] antidiabetic,[5] antitubercular,[6,7] anti-HIV,[8,9] antiparasitic,[10] hypnotic,[11] and anathematic agents[12] and as intermediates in the synthesis of dyes. 2-Thioxo-4-thiazolidinone-based molecules have been popular as small molecule inhibitors of numerous targets such as HCV protease, aldo reductase, and others.[13] Also, pyrazoles have diverse and interesting of biological activities such as antiviral,[14] antibacterial,[15,16] antifungal, [17] anti-inflammatory,[18,19] analgesic,[20] and other activities.[21,22] We have worked to synthesize heterocyclic systems containing thiazolidine rings.[23–33] In view of all this, it is interesting to construct new heterocyclic systems containing both thiazolidinone and pyrazole rings, starting from 5-ethoxymethylene-2-thioxo-4-thiazolidinone (**1**) as key synthon for our objective.

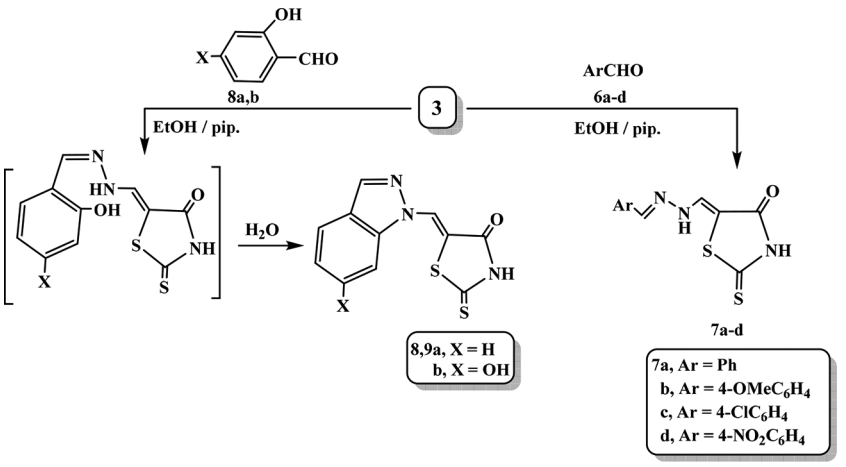
RESULTS AND DISCUSSION

5-Ethoxymethylene-2-thioxo-4-thiazolidinone (**1**) reacts with hydrazine hydrate at room temperature to afford a colored product **3** (Scheme 1). The structure of the isolated product **3** was confirmed by its elemental analysis and spectral data (infrared [IR], ^{1}H NMR, ^{13}C NMR, and mass spectrometry [MS]). The IR spectrum of the reaction product showed absorption bands at ν_{max} 3424, 3215, 3050, and 1680 cm^{-1} corresponding to NH_2, NH, and CO groups, respectively. The ^{1}H NMR spectrum of product revealed the disappearance of the usual quartet and triplet signals of ethoxy protons and instead revealed three D_2O exchangeable singlet signals at $\delta = 5.01$, 9.30, and 12.48 ppm attributable the NH_2 and the two NH protons, respectively, in addition to a singlet signal at $\delta = 7.36$ ppm assigned to vinylic CH proton. Also, ^{13}C NMR showed signals at $\delta = 110$, 149, 165, 191 ppm corresponding to vinylic (CH=C-), carbonyl (CO), and thiocarbonyl (C=S) carbons. Elemental analysis with mass spectrum m/z 175 (M^+) established the formula $C_4H_5N_3OS_2$, which indicated that the reaction between compound **1** and hydrazine hydrate proceeded with elimination of ethanol. Based on these data, structure **3** was assigned for the product and the other structure **2** was ruled out. Similarly, the reaction of compound **1** with ethyl hydrazinecarboxylate in ethanol at room temperature or refluxing in absolute ethanol gave the corresponding ethyl 2-[(4-oxo-2-thioxothiazolidin-5-ylidene) methyl]hydrazine-1-carboxylate (**5**). Spectral and analytical data are in complete agreement with structure **5,** which was assigned for this product (Scheme 1).

Condensation of compound **3** with different aromatic aldehydes **6a–d** in ethanol in the presence of a few drops of piperidine gave the corresponding Schiff's bases **7a–d** (Scheme 2). The structure of the isolated products was inferred from their analytical and spectral data. Thus, IR spectrum of compound **7a** taken as typical example of the prepared series **7a–d** showed absorption bands at ν_{max} 3220, 3017, and 1680 cm^{-1} corresponding to NH and CO groups, respectively. The ^{1}H NMR spectrum of product **7a** revealed a singlet signal at $\delta = 7.58$ ppm attributable



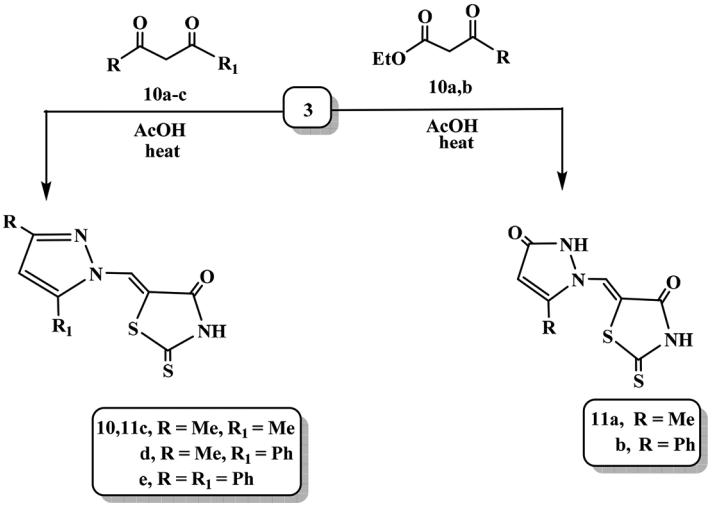
Scheme 1. Synthetic route to 5-hydrazinyl-2-thioxo-4-thiazolidinone (**3**) and ethyl 2-[(4-oxo-2-thioxothiazolidin-5-ylidene)methyl]hydrazine-1-carboxylate (**5**).



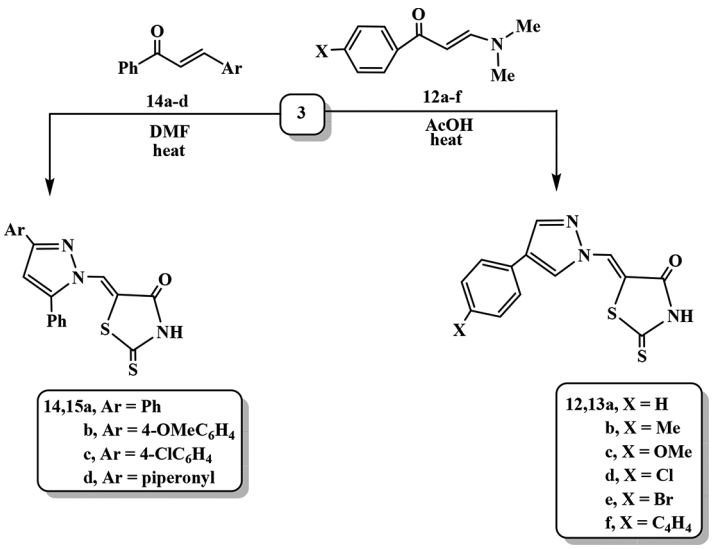
Scheme 2. Synthetic pathway to 4-thiazolidinones **7a–d** and 5-[1*H*-indazol-1-yl)methylene]-4-thiazolidinone derivatives **9a** and **b**.

to olefinic CH proton and two board singlet signals at $\delta = 11.87$ and 12.92 ppm assigned to the two NH protons. The ^{13}C NMR of compound **7a** revealed a signal at $\delta = 145$ ppm due to –CH=N carbon, beside to the other expected signals for aromatic and thiazolidine carbons. The mass spectrum together with the elemental analysis are in consistent with the structure **7**. On the other hand, compound **3** reacts with *o*-hydroxybenzldehyde derivatives **8a** and **b** in refluxing ethanol catalyzed by few drops of piperidine to yield colored solids **9a** and **b**. The structure of **9** was confirmed by elemental analysis and spectral data (IR, ^1H NMR, ^{13}C NMR, and MS). The IR spectrum of the isolated product **9a** showed absorption bands at ν_{max} 3200 and 1676 cm^{-1} corresponding to NH and CO groups. ^1H NMR spectrum of this isolated product revealed two singlet signals at $\delta = 7.55$ and 8.52 ppm due to the olfinic and pyrazole protons, respectively. Besides the expected protons for aromatic and NH protons. Also, ^{13}C NMR showed signal at $\delta = 141$ ppm due to pyrazole carbon (C=N), in addition to the expected signals assigned for aromatic and thiazolidine carbons. The mass spectrum with elemental analysis are assigned the structures **9a** and **b**.

Our study was extended to construct a pyrazole moiety on thiazole ring which has wide applications in different biological and medicinal fields beside their application in organic chemistry. Thus, the reaction of compound **3** with α-ketoester **10a** and **b** or α-diketones **10c–e** in refluxing glacial acetic acid gave the 5-pyrazolyl-2-thioxo-4-thiazolidinone derivatives **11a–e** (Scheme 3). The structures were confirmed on their elemental analysis and spectral data (IR, ^1H NMR, and MS). The IR spectrum of the isolated product **11a** showed absorption bands at ν_{max} 3223–3110, 1687, and 1681 cm^{-1} corresponding to NH and two CO groups. ^1H NMR spectrum of this isolated product revealed two broad singlet signals at $\delta = 12.76$ and 13.13 ppm due to two NH protons, in addition to two singlet signals at $\delta = 7.13$ and 7.71 ppm corresponding to olefinic and pyrazole protons,



Scheme 3. Synthetic route to 5-pyrazoyl-2-thioxo-4-thiazolidinone derivatives **11a–e**.



Scheme 4. Synthetic pathway to 5-pyrazoyl-4-thiazolidinone derivatives **13a–f** and **15a–d**.

respectively. The mass spectrum with elemental analysis are in agreement with the proposed structure **11**.

Also, compound **3** reacts with some different enaminones **12a–f** in refluxing in glacial acetic acid to afford the new pyrazole derivatives **13a–f** (Scheme 4). The structures were confirmed by elemental analysis and spectral data (IR, ^{1}H NMR, and MS). The IR spectrum of the isolated product **13a** showed absorption bands at ν_{max} 3121, 1684 cm^{-1} corresponding to NH and CO groups. ^{1}H NMR spectrum of this isolated product revealed three singlet signals at $\delta = 7.20$, 7.94, and 8.37 ppm due to olefinic and pyrazole protons, respectively. In addition to a broad signal at $\delta =$ 12.86 ppm corresponding to NH proton. The mass spectrum with elemental analysis is in agreement with the proposed structure **13**. The formation of **13** was assumed to proceed via elimination of dimethylamine molecule, followed by dehydrative cyclization to 5-pyrazolyl-4-thiazolidinone derivative **13**. Cyclocondensation of compound **3** with chalcones **14a–d** in refluxing acetic acid afforded isolated products **15a–d** (Scheme 4). The structure of compounds **15a–d** was established by elemental analysis and spectral data (IR, ^{1}H NMR, and MS). The IR spectrum of product **15a** showed absorption bands at ν_{max} 3218, 1683, and cm^{-1} corresponding to NH and CO groups. Also, ^{1}H NMR spectrum of product **15a** revealed a broad signal at $\delta = 12.85$ ppm corresponding to NH. The formation of **15** was assumed to proceed via Michael addition followed by dehydrative cyclization to 5-pyrazolyl-4-thiazolidinone derivative **15** (Scheme 4).

CONCLUSION

In conclusion, we have described an efficient synthesis of some new 5-[(2-benzylidenehydrazinyl)methylene]-2-thioxothiazolidin-4-ones, 5-[1*H*-Indazol-1-yl) methylene]-4-thiazolidinones, and 5-pyrazoyl-2-thioxo-4-thiazolidinones via the

reaction of readily accessible starting material, 5-(hydrazinylmethylene)-2-thioxo-4-thiazolidinone, with some chemical reagents.

SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

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