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Unusual Product from the Acid Catalyzed One Pot, Multi-Component Reaction of Thiocarbohydrazide, Aldehydes and Phenacyl bromides

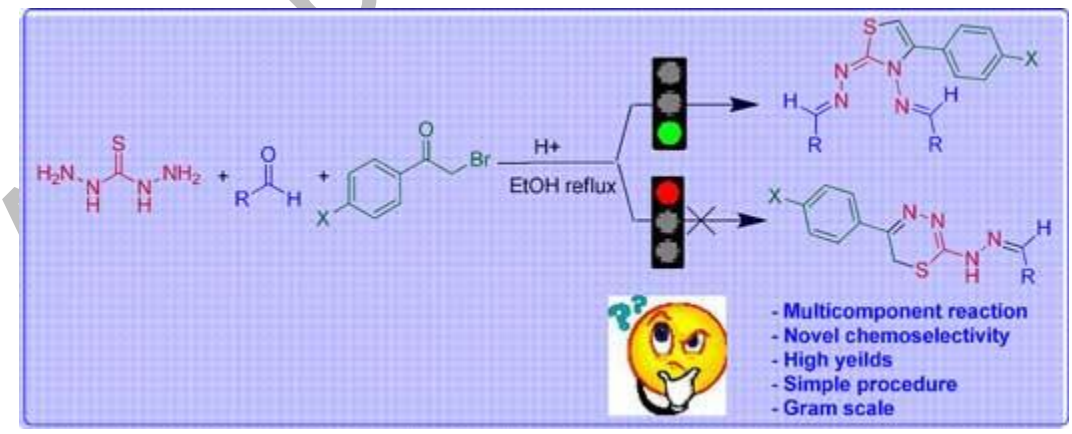
Mohanad shkoor[1], Ayahtallah al-abade[2], Ibtesam Aleteiwib[2], Mahmoud Al-Talib[2], Hasan Tashtoush[2]

[1]Department of Chemistry and Earth Sciences, Qatar University, Doha, Qatar, [2]Chemistry Department, Yarmouk University, Irbid, Jordan

Abstract

A one-pot, three-component protocol for the synthesis of novel five membered thiazole ring bonded to two hydrazone motifs is described. The acid catalyzed reaction of one equivalent of thiocarbohydrazide, two equivalents of aromatic aldehydes and one equivalent of phenacyl bromides afforded the five membered thiazole ring. The reactions proceed with novel chemoselectivity. Similar reported protocols have always afforded 1,3,4-thiadiazines.

Graphical Abstract



KEYWORDS: hydrazones, thiocarbohydrazide, thiocarbohydrazone, thiazole, multicomponent reaction, chemoselectivity

Multicomponent reactions (MCRs) have become increasingly preferred and reliable synthetic tools for synthetic organic and green chemists. Their efficiency stems from the ability of construction of wide range of complex molecules from readily available and easily accessible building blocks in mostly simple single step, atomic economic, time efficient and cost effective procedures. As a result, there will be continuous demand for the discovery and development of new MCRs reactions.[1]

Hydrazones exhibit a wide range of pharmaceutical activities.[2] Among these hydrazones, thiazol-2-yl hydrazones have attracted the attention for their diverse medicinal properties including: anti-tuberculosis,[3] antibacterial,[4] anti-malarial,[5] antifungal activity,[6] histone acetyltransferase anhibitors,[7] human monoamine oxidase (hMAO) A and B enzymes inhibitors,[8] anti-tumor,[9] and many others.

Thiocarbohydrazide has been extensively employed for the construction of heterocyclic compounds with biological and pharmacological interest.[12]

In the course of our research in exploiting thiocarbohydrazide in the construction of substituted thiazoles,[13] we targeted molecules that contain thiazole ring bearing two hydrazine moieties on hope that the additional hydrazone motif will enhance the biological activities of the thiazolyl hydrazone according to the general principles of drug design and discovery.

The step-wise synthesis of thiazole ring attached to two hydrazone motifs has been reported[14], Scheme 1. The bis-thiocarbohydrazone was cyclized with phenacyl choride to provide the thiazole compound. This type of cyclization is straightforward and no chemoselectivity is involved. Although this two-step synthesis provided the target compound in very good yield, a one-pot multicomponent route would be advantageous since it eliminates the synthesis and purification of the thiocarbohydrazones.

A literature survey revealed that one pot multi-component reaction of one equivalent of thiosemicarbazide, two equivalents of aldehydes or ketones and one equivalent of phenacyl halides afforded thiazol-2-yl hydrazones.[15] Surprisingly the one pot multi-component reactions of thiocarbohydrazide (structurally similar to thiosemicarbazide) with aldehydes or ketones and phenacyl bromides in (1: 2<: 1) equivalent ratios provided always substituted 1, 3, 4-thiadiazine,[16] Scheme 2. The same multicomponent reactions in (1:1:1) equivalent ratios also provided 1, 3, 4-thiadiazine as main product.[17] These reactions proceed by formation of the 2-hydrazino-1,3,4-thiadiazine which then undergoes condensation with aldehydes or ketones.

The reported literature suggested that the only route to thiazole compounds with two hydrazine motifs is only a step-wise synthesis. However, we decided to investigate a one pot multicomponent route to these compounds. At the onset of our experiments, A mixture of thiocarbohydrazide, phenacyl bromide and benzaldehyde (1:1:2) in ethanol was heated at 60°C for two hours in the presence of catalytic amount of acetic acid (20

mol%), after which TLC indicated full consumption of thiocarbohydrazide, scheme 3. The product precipitated on cooling and was recrystallized from ethanol.

The ^{1}HNMR spectrum for the solid (compound **4a**) showed a singlet at 6.80 ppm (*See supporting info.*) which accounts for the five membered ring product. ^{1}HNMR spectrum for the crude solid did not show any signal corresponds to the six membered thiadiazine rings. In all other experiments, Scheme 3, that provided compounds (**4a-j**), table 1, singlet in the range of δ 6.16-7.14 ppm was observed. ^{1}HNMR of crude reactions mixtures showed no thiadiazine ring formation. When the reaction was repeated with catalytic amount of sodium acetate AcONa (20 mol%), same product was obtained with almost the same yield (70%) after two hours heating at 60°C . The increase in the catalyst loading of acetic acid (30 mol%) did not improve the yield. Surprisingly, when the reaction was repeated employing similar procedure reported by Vedula group[16a,b], Only and exclusively the thiazole compound **4a** formed. The reaction afforded compound **4a** upon refluxing for three hours without any catalyst.

A plausible mechanism of the formation of compound **4a** is depicted in Scheme 4. We believe that the reaction starts by the acid catalyzed condensation of thiocarbohydrazide with two equivalents of the aromatic aldehydes to form bis-thiocarbohydrazone. The SN_2 type attack of bis-thiocarbohydrazone sulfur on the C-Br gives intermediate **A**. Subsequent attack of NH nitrogen on the C=O of the phenacyl bromide leads to the formation of intermediate **B** which undergoes acid catalyzed dehydration to form compound **4a**.

The mechanism was proposed based on a set of control experiments, scheme 5. The results of the control experiments suggest that in order to form the five membered thiazole ring in all cases, bis-thiocarbohydrazones must form initially followed by cyclization with phenacyl bromide.

The reaction of thiocarbohydrazide **1** with phenacyl bromide **3a** provided 2-hydrazino-1,3,4-thiadiazine **9**, which implies that the first step in the mechanism should not involve this type of cyclization. The cyclization of the mono-thiocarbohydrazones **5** with phenacyl bromide **3a** afforded substituted thiazole **10**. While the mono-thiocarbohydrazones **6** afforded 1,3,4-thiadiazine **11**. Both chemoselectivities were reported in literature [18]. These different chemoselectivities suggest that reaction pathway should not involve this type of cyclization since all products were five membered thiazole ring exclusively.

The cyclization of bis-thiocarbohydrazones **7** and **8** with phenacyl bromide **3a** provided substituted thiazole ring **4a** and **4h** respectively in slightly higher yields than the multicomponent protocol. This was an additional proof of the suggested structure resulted from the one-pot multicomponent protocol. These results imply that the mechanism of the reaction involves the cyclization of bis-thiocarbohydrazones with phencyl bromides.

The results also prove that the one pot multicomponent synthesis is more efficient than the cyclization of bis-thiocarbohydrazones with phenacyl bromides since it reduces number of steps and minimizes purification efforts without significantly affecting the yield

To the best of our knowledge, this is the first report where a one pot-multicomponent reaction of an aldehyde, phenacyl bromide and thiocarbohydrazide provides a five membered thiazole ring.

In conclusion, in contrast of the reported examples, the acid catalyzed one-pot multi-component reaction of one equivalent of thiocarbohydrazide, two equivalents of aromatic aldehydes and one equivalent of phenacyl bromides afforded the five membered thiazole ring bonded to two hydrazone moieties.

Procedure For The Synthesis Of Compound 4c: (Detailed Procedures And Spectroscopic Data Are Provided In The Supporting Information)

a mixture of 4-anisaldehyde (1.36 gm, 1.22 mL, 10 mmol), thiocarbohydrazide (0.53 gm, 5 mmol), phenacyl bromide (1.00 gm, 5 mmol) and catalytic amount (20 mol%) of acetic acid in ethanol (15 mL) was heated at 60^{o} C for 2 hours. The progress of the reaction was monitored by TLC. After reaction completion, the mixture was cooled down and the solid obtained was filtered off and recrystallized from ethanol to give **4c** as ligh yellow needles, mp 147-148 ^{o}C, 1.79 gm, 81% yield. **^{1}H NMR** (CDCl3, 400 MHz) δ 3.81 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.88-6.92 (m, 5H CH), 7.39 (m, 5H, CH), 7.69 (d, J= 8.8 Hz , 2H, CH), 7.88 (d, J= 8.8 Hz , 2H, CH), 8.02 (s, 1H, NCH), 9.50 (s, 1H, NCH). ^{13}C

NMR ($CDCl_3$, 100 MHz): 55.4, 55.5, 106.6, 114.2, 114.4, 122.8, 125.5, 127.2, 129.2, 129.8, 130.2, 132.9, 140.1, 153.3, 162.1, 162.5, 164.2, 169.9. IR (KBr) cm^{-1}: 1603(C=N), 1568, 1512 (C=C) aromatic. Anal. calcd for $C_{25}H_{22}N_4O_2S$: C, 67.85; H, 5.01; N, 12.66; S, 7.25. Found: C, 67.60; H, 5.33; N, 12.69; S, 7.05.

ACKNOWLEDGMENT

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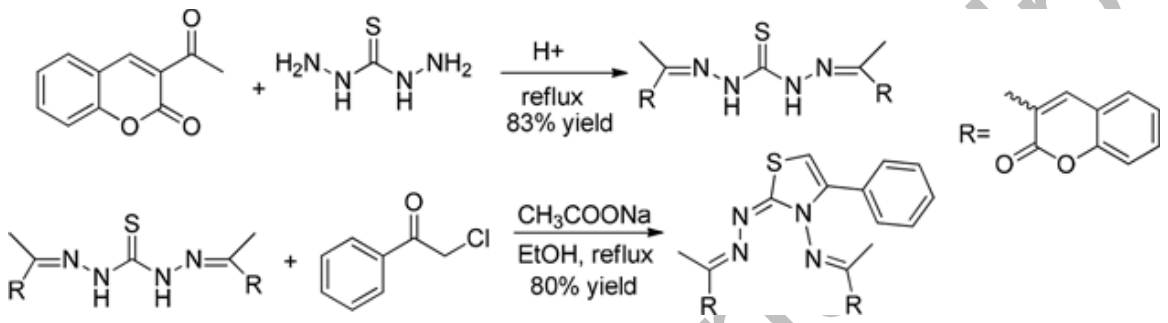
Table 1 Acid catalyzed three-component reaction of thiocarbohydrazide with aldehydes and phenacyl bromides

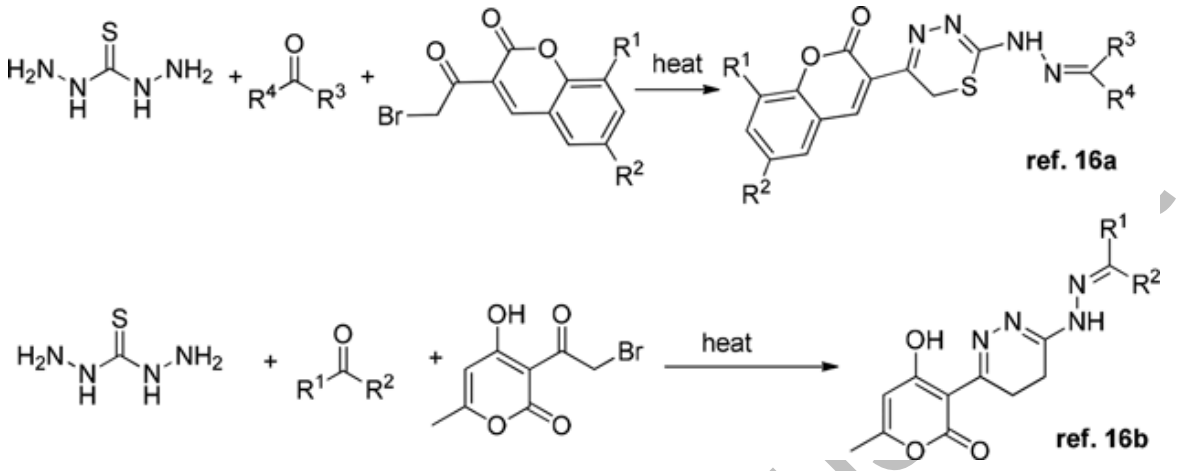
Comp.	**Ar**	**X**	**Yield%**[a]
2a, 4a	C_6H_5-	H	72
2a, 4b	C_6H_5-	Br	68
2b, 4c	p-$CH_3OC_6H_4$-	H	81
2b, 4d	p-$CH_3OC_6H_4$-	Br	76
2c, 4e	p-$CH_3C_6H_4$-	H	74
2c, 4f	p-$CH_3C_6H_4$-	Br	72
2d, 4g	p-$(CH_3)_2NC_6H_4$-	Br	64
2e, 4h	2-furyl-	Br	86
2f, 4i	2-thienyl-	H	88
2f, 4j	2-thienyl-	Br	85

[a]Isolated yield

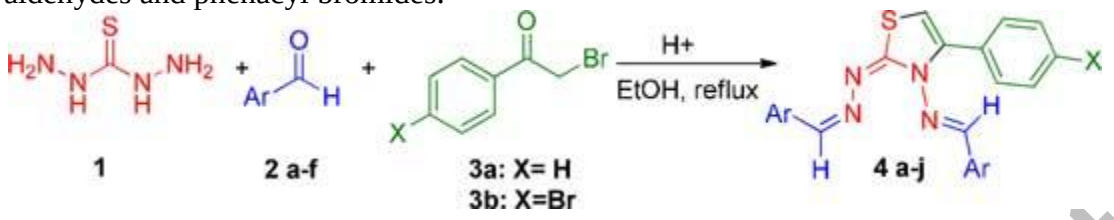
Scheme 1 The step-wise synthesis of thiazole ring



Scheme 2 Reported one pot-multi component reactions of thiocarbohydrazide with excess of aldehydes or ketones and phenacyl bromides

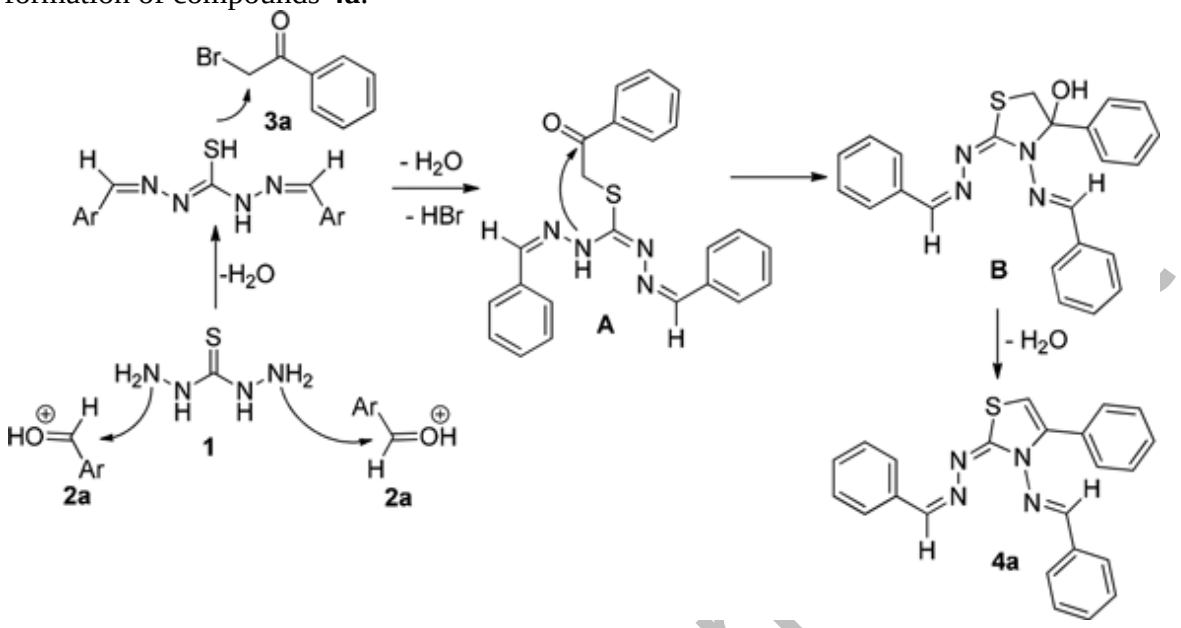


Scheme 3 One pot multi-component reaction of thiocarbohydrazide with aromatic aldehydes and phenacyl bromides.



1 2 a-f 3a: X= H 3b: X=Br 4 a-j

Scheme 4 A plausible mechanism for the acid catalyzed one pot three-component formation of compounds **4a**.



Scheme 5 Control experiments to probe the mechanism of formation of compounds **4**.

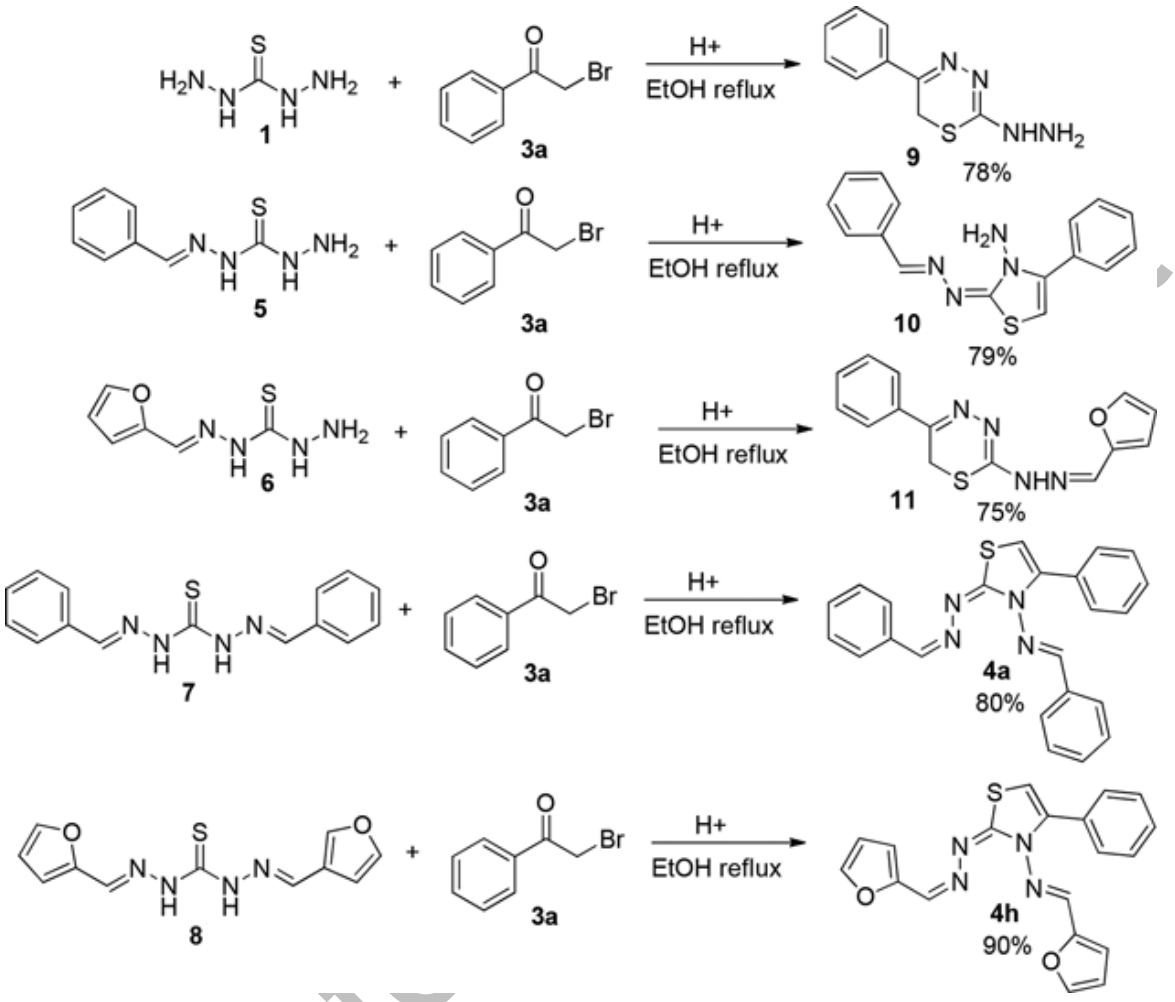
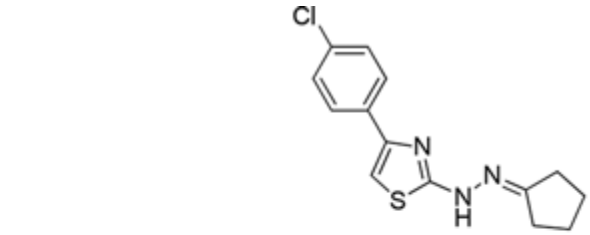
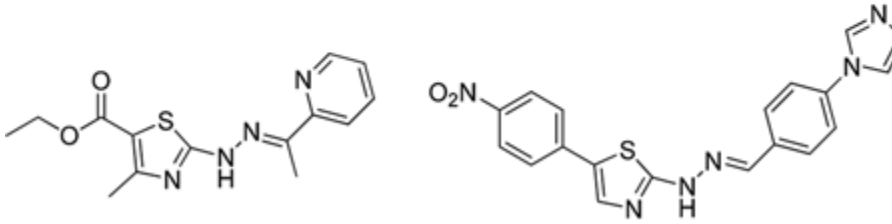


Figure 1. Thiazol-2-yl hydrazones of reported biological activities



CPTH2
Histone Acetyltransferase Inhibitor



thiazolylhydrazone-based active antitubercular agents (ref. 10, 11)