ONE POT SYNTHESIS OF THIAZOLYL HYDRAZONE DERIVATIVES AND THEIR CHARACTERIZATION

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ABSTRACT:
As the thiazolyl group has great importance as it appears frequently in the structure of various natural products, biologically active compounds and in some antibiotic drugs, a series seven thiazolyl hydrazone derivatives have been synthesized from substituted aromatic ketones, thiosemicarbazide & α-halo ketones via one-pot approach with good yields. All the synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and Mass Spectroscopy. In the future, the synthesized thiazolyl hydrazones would lead the promising pharmacological properties. Hence, there is enough scope to explore new compounds incorporating substituted thiazolyl moiety, which would lead to the development of novel derivatives with potential activity.

Keywords: Thiazolyl hydrazones, substituted acetophenones, thiosemicarbazide, α-halo ketones, one-pot synthesis.

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1. INTRODUCTION:

Thiazolyl derivatives are one of the most useful scaffolds in drug design and discovery. Molecules with thiazole moiety have displayed wide range of physico-chemical and biological activities including anti-microbial [1], anti-inflammatory and anti-oxidant [2], anti-cancer [3], anti-tubercular [4], anti-diabetic [5] and anti-HIV activities [6]. The thiazolyl group has great importance as it appears constantly in the structure of various natural products and biologically active compounds, some antibiotic drugs like penicillin, micrococcin [6] and naturally occurring compounds such as vitamin B_1 and carboxylase. These compounds attract particular attention in methodology design for its utility as a synthetic building block and widespread occurrence in target structures such as functional materials and biologically relevant compounds. [7-12]

Thus, the heterocycle, 1, 3- thiazole heterocyclic scaffold has been incorporated in the designed molecule along with azomethine (>C=N-NH) moiety due to its interesting pharmacological properties. The pharmacodynamic potential of bioactive hydrazones is primarily due to the presence of pharmacophoric azomethine (>C=N-NH) moiety having broad biological applications such as antimicrobial [13], antimycobacterial [14], antimalarial [15], analgesic, anti-inflammatory [16], anticancer [17], anti-HIV [18], anticonvulsant [19], anti-depressant [20], vasodilator [21], alzheimer diseases [22], hypertension [23] and antiplatelet [24]. The combination of the active scaffolds, thiazole and azomethine may provide synergistic effect to improve the pharmacological properties.

Based on these predictions, we have designed and synthesized a series of thiazolyl hydrazones by considering the importance of biologically active pharmacophores and prepared successfully by the condensation reaction between substituted acetophenones with thiosemicarbazide and appropriate α-haloketones in the presence of catalytic amount of glacial acetic acid.

The growing interest in these compounds and their potential use in medicinal applications are proved by the growing number of publications concerning the synthesis and biological evaluation of hydrazone analogues. The significant biological activity and great utility of the heterocvclic scaffold and azomethine have encouraged us to synthesize hydrazone derivatives.

2. EXPERIMENTAL SECTION:

All the compounds and reagents were commercially available without pre-treatment. All solvents and reagents are analytically pure and no further purification was needed. Melting points were recorded in open capillary tubes and were found uncorrected. Reaction courses and product mixtures were routinely monitored by TLC on Silica gel precoated plates GF-254. IR spectra of compounds were scanned on Thermo scientific spectrometer.^{1}H NMR spectra were recorded in DMSO-d_6 on Bruker AV- 400MHz spectrometer by using TMS as an internal standard (Chemical Shift are given in δ ppm). Advion mass spectrometer of Micromax Company used for mass spectroscopy.

General procedure for the synthesis of thiazolyl hydrazone derivatives (4a-g):

An equimolar mixture of substituted acetophenone (3 mmol), thiosemicarbazide (3 mmol) and glacial acetic acid 2-3 drops in ethanol was heated at 70-80^{o}C for 1.0 to 1.5 h. The progress of reaction was monitored by TLC. Then, the substituted α-haloketone (3mmol) was added and heated at 70-80^{o}C for 5-6 h. The progress of reaction was monitored by TLC. After completion of reaction, the reaction mixture was cooled and poured into ice cold water and the product precipitated out which was filtered, washed. The crude product was recrystallized from ethanol to obtain pure product **(4a-g)**.

CHARACTERISATION:

Compound 4a

Yield: 87%, **MF:** $C_{17}H_{15}N_3S$/ 293.1, **Yellow solid; MP.** 242^{o}C

IR: 3205.35, 3057.04, 1615.55, 1600.52, 1515.79, 1496.47 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$): δ= 2.62 (3H, s, -CH_3), 6.79 (1H, s, thiazole –CH), 7.47-7.55 (6H, m, Ar-H), 7.76-7.84 (4H, m, Ar-H), 12.73 (1H, s, -NH)

^{13}C NMR: (400 MHz, $CDCl_3$): δ= 15.00, 101.89, 125.67, 126.59, 128.64, 129.45, 130.09, 130.45, 169.93.

MS: m/z 294.1

Compound 4b

Yield: 88%, **MF:** $C_{17}H_{13}Cl_2N_3OS$/ 377.02, **Pale yellow solid; MP.** 280^{o}C

^{1}H NMR: (400 MHz, $CDCl_3$): δ= 2.33 (3H, s, -CH_3), 6.76-6.80 (2H, m, Ar-H), 7.13-7.14 (1H, m, Ar-H), 7.32-7.35 (1H, m, thiazole –CH), 7.46-7.48 (1H, m, Ar-H), 7.59-7.61 (2H, m, Ar-H), 7.66-7.68 (1H, m, Ar-H), 7.72-7.73 (1H, m, Ar-H).

Compound 4c

Yield: 93%, **MF:** $C_{17}H_{12}Cl_2N_4O_2S$/ 406.01, **Yellow solid; MP.**192^{o}C

IR: 3211.99, 3065.10, 1600, 1563.52, 1526.02, 1463.72, 1344.96 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$): δ= 2.26 (3H, s, -CH_3), 7.28-7.30 (3H, m, Ar-H), 7.48 (1H, s, thiazole –CH), 7.59-7.63 (1H, t, J= 8 Hz, Ar-H), 7.78-7.80 (1H, d, J= 8 Hz, Ar-H), 8.14-8.16 (1H, d, J= 8 Hz, Ar-H), 8.23-8.25 (1H, d, J= 8 Hz, Ar-H), 8.58 (1H, s, Ar- H).
^{13}C NMR: (400 MHz, $CDCl_3$): δ= 12.94, 110.00, 120.75, 123.53, 127.28, 129.46, 130.29, 131.51, 131.60, 131.75, 132.55, 133.96, 139.22, 143.86, 146.28, 148.63, 167.96.

Compound 4d
Yield: 90%, **MF:** $C_{17}H_{13}ClN_4O_2S$/ 372.6, **Yellow solid; MP.** 270°C
IR: 3220.58, 3070.07, 2972.95, 1617.00, 1597.19, 1506.51, 1237.91 cm^{-1}.
^{1}H NMR: ($CDCl_3$, 400MHz): δ = 2.45 (3H, s, -CH_3), 7.02 (1H, s, thiazole -H), 7.39-7.41 (2H, d, Ar-H), 7.61-7.67 (2H, m, Ar-H), 7.82-7.85 (2H, m, Ar-H), 8.19-8.23 (1H, m, Ar-H), 8.63-8.64 (1H, t, Ar-H), 10.95 (1H, broad s, -NH)
^{13}C NMR: ($CDCl_3$, 400MHz); δ= 15.14, 101.74, 118.85, 120.71, 123.78, 125.78, 127.49, 129.00, 129.07, 130.91, 145.82, 154.88, 156.56, 168.52.

Compound 4e
Yield: 89%, **MF:** $C_{17}H_{14}N_4O_2S$/ 338.08, **Yellow solid; MP.** 278°C
IR: 3120.24, 2973.60, 2922.19, 1608.08, 1526.29, 1480.65, 1348.65 cm^{-1}.
^{1}H NMR: (400 MHz, $CDCl_3$): δ= 2.23 (3H, s, -CH_3), 6.97 (1H, s, thiazole –CH), 2.23 7.30-7.33 (1H, m, Ar-H), 7.39-7.42 (2H, m, Ar-H), 7.57-7.61(1H, t, Ar-H), 7.80-7.82 (2H, d, J= 8 Hz, Ar-H), 8.14-8.16 (1H, d, Ar-H), 8.21-8.24 (1H, d, Ar-H), 8.57 (1H, s, Ar-H), 9.49 (1H, s, NH)
^{13}C NMR: (400 MHz, $CDCl_3$): δ= 12.88, 104.35, 120.68, 123.33, 125.97, 127.93, 128.71, 129.37, 131.47, 134.69, 139.46, 143.30, 148.59, 151.54, 169.15.
MS: m/z 339.2

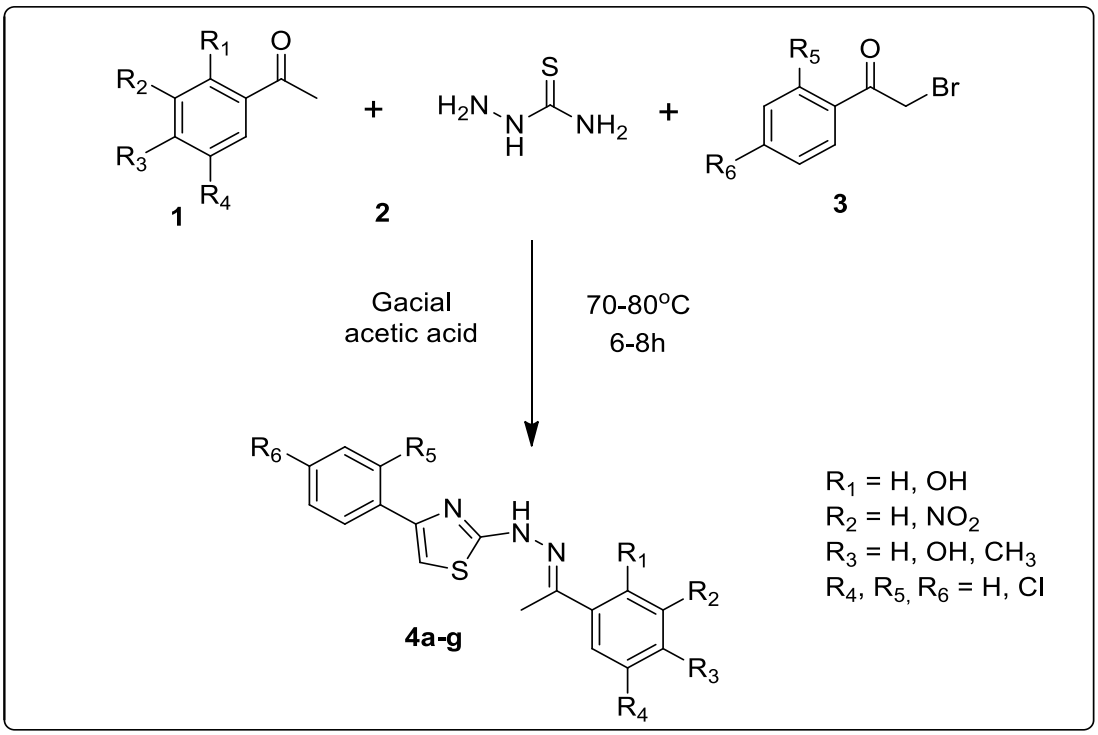
Compound 4f
Yield: 86%, **MF:** $C_{18}H_{17}N_3S$/ 307.11, **Yellow solid; MP.** 270°C
IR: 3240, 3041.83, 1617.78, 1565.82, 1366.89, 1111.73 cm^{-1}.
^{1}H NMR: (400 MHz, $CDCl_3$): δ= 2.42 (3H, s, -CH_3), 2.59 (3H, s, -CH_3), 6.78 (1H, s, thiazole –CH), 7.25-7.27 (2H, d, J= 8 Hz, Ar-H), 7.47-7.54 (3H, m, Ar-H) 7.71-7.77 (4H, m, Ar-H), 12.71 (1H, s, NH).
^{13}C NMR: (400 MHz, $CDCl_3$): δ= 16.11, 21.38, 100.91, 125.65, 126.69, 127.32, 129.40, 129.64, 130.48, 133.27, 140.98, 141.16, 156.66, 169.91.
MS: m/z 308.1

Compound 4g
Yield: 88%, **MF:** $C_{17}H_{14}ClN_3OS$/ 343.05, **Yellow solid; MP.** 228°C
IR: 3436.69, 3189.69, 3058.30, 2919.57, 1597.21, 1562.78, 1478.65 cm^{-1}.
^{1}H NMR: (400 MHz, $CDCl_3$): δ= 2.58 (3H, s, -CH_3), 4.76 (1H, s, -OH), 6.86 (1H, s, thiazole –CH), 6.99-7.01 (1H, d, J= 8 Hz, Ar-H), 7.30-7.33 (1H, m, Ar-H), 7.45-7.52 (4H, m, Ar-H), 7.76-7.78 (2H, d, J= 8 Hz, Ar-H), 11.04 (1H, s, NH).
MS: m/z 344.2

3. RESULT AND DISCUSSION:

3.1CHEMISTRY:

We have synthesized a series of seven thiazolyl hydrazone derivatives **4a-g (Table 1)** Firstly the condensation reaction between substituted acetophenones **1** with thiosemicarbazide **2** in the presence of catalytic amount of glacial acetic acid using ethanol as reaction medium, gives thiosemicarbazone derivatives as a reactive intermediate, secondly the reaction between thiosemicarbazone and appropriate α-haloketones **3** gave thiazolyl hydrazone derivatives. The mechanism for formation of thiazolyl hydrazone derivatives **4a-g** suggested that first nucleophilic sulphur attack on the electron deficient carbon of α-haloketones in which halogen (i.e. leaving group) is attached followed by attack of imine lone pair on carbonyl carbon which on cyclization and condensation gives target molecules.
All the synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and Mass Spectroscopy.



Reagents and conditions: Glacial acetic acid, ethanol, 70-80 ºC, 6-8 h.

Table 1: Synthesized differently substituted thiazolyl hydrazones (4a-g)

Sr. No	Entry	Substituents						Yield (%)	Mp (ºC)
		R_1	R_2	R_3	R_4	R_5	R_6		
1	**4a**	H	H	H	H	H	H	87	242
2	**4b**	H	H	OH	H	Cl	Cl	88	280
3	**4c**	H	NO_2	H	H	Cl	Cl	93	192
4	**4d**	H	NO_2	H	H	H	Cl	90	270
5	**4e**	H	NO_2	H	H	H	H	89	278
6	**4f**	H	H	CH_3	H	H	H	86	270
7	**4g**	OH	H	H	Cl	H	H	88	228

The IR spectrum of substituted thiazolyl hydrazones showed the disappearance of >C=S, and -NH_2 stretches indicate that formation of thiazole derivatives. Different substituted-2,4-thiazoles derivatives showed the absorption bands at ~3250 cm^{-1} due to presence of –NH stretch and the absorption bands at ~3040 and ~2921 cm^{-1} were due to aromatic –C-H stretch and aliphatic –C-H stretches of –CH_3 groups respectively. While the absorption band observed at ~1600-1615 and ~1550-1570 cm^{-1} due to presence of (>C=N), (>C=C<) respectively. The absorption bands at ~1471 and ~1221 cm^{-1} due to N-N and C-S linkages.

^{1}H NMR spectra of some representative compounds were recorded which shows the characteristic peaks at δ ~2.20 and ~2.70 ppm for –CH_3 group of aromatic and aliphatic system respectively. A singlet at δ ~6.75-7.49 ppm integrated to the proton of 1,3-thiazole ring. Aromatic protons resonated between δ 7.0-7.8 ppm. The proton of –NH moiety adjacent to 1,3-thiazole resonated at δ ~9.40-12.80 ppm as singlet. The ^{13}C NMR spectrum of 2-(2-hydrazinyl) thiazole derivatives shows that all aromatic carbon resonated at ~δ 120-170 ppm while thiazole sp^2 hybridized C-5 carbon resonated at δ ~100-110 ppm. The methyl carbon of aliphatic and aromatic system resonated between δ ~12-20 ppm.

Mass spectra of the representative compound confirm the molecular formula and molecular weight of the derivatives.

4. CONCLUSION:

We have efficiently designed and synthesized seven differently substituted thiazolyl hydrazones from differently substituted acetophenones, thiosemicarbazides and α-halo ketones via one-pot approach with excellent yields without formation of any side products. The synthesized thiazolyl hydrazones would lead the promising pharmacological properties in the future.

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