

Transformation of 2-(acetamido)-3-(4-chlorophenyl)acrylohydrazide into 1-arylideneamino-4-(4-chlorobenzylidene)-2-methyl-1*H*-imidazolin-5(4*H*)-ones and 4-aryl-1-[2-(acetamido)-3-(4-chlorophenyl)acryloyl]thiosemicarbazides

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Abstract

Six 1-arylideneamino-4-(4-chlorobenzylidene)-2-methyl-1*H*-imidazolin-5(4*H*)-one compounds and two 4-aryl-1-[2-(acetamido)-3-(4-chlorophenyl)acryloyl]thiosemicarbazide compounds were synthesized by reaction of aromatic aldehydes or reaction of aryl isothiocyanates, respectively with 2-(acetamido)-3-(4-chlorophenyl)acrylohydrazide which was prepared starting from 4-chlorobenzaldehyde and acetylglycine via 4-(4-chlorobenzylidene)-2-methyloxazol-5(4*H*)-one. The structures of the synthesized compounds were determined by IR, NMR and mass spectral data.

Keywords. 2-(acetamido)-3-(4-chlorophenyl)acrylohydrazide, imidazolin-5(4*H*)-one, thiosemicarbazide.

1. INTRODUCTION

2-(Acetamido)-3-(4-chlorophenyl)acrylohydrazide (**1**) was synthesized and then, transformed into some *N*-substituted hydrazide [1,2]. Some new compounds were synthesized and an unusual transformation was found out in the further research of transformations of the hydrazide (**1**).

2. EXPERIMENTAL

General procedures: All chemicals and solvents were obtained from commercial sources and used without any further purification. Melting points were determined in open capillaries and the values are uncorrected. IR spectra were recorded in KBr discs on a Shimadzu FTIR 8400S spectrophotometer. NMR spectra were recorded on a Bruker Avance spectrometer (500 MHz for ¹H-NMR and 125 MHz for ¹³C-NMR) using DMSO-*d*₆ as solvent and tetramethylsilane (0.00 ppm) as an internal standard. MS spectra were recorded on a Bruker micrOTOF-Q 10187 spectrometer except two spectra of the (**3a**) and (**3c**) were recorded on an Agilent 6490 spectrometer.

2-(Acetamido)-3-(4-chlorophenyl)acrylohydrazide (2) was synthesized from 4-chlorobenzaldehyde and acetylglycine via 4-(4-chlorobenzylidene)-2-methyloxazol-5(4*H*)-one (**1**) according to the method described in our earlier

work [1, 2]. The hydrazide (**2**) was transformed further into compounds (**3a-f**) and (**4a,b**) as shown in the scheme 1.

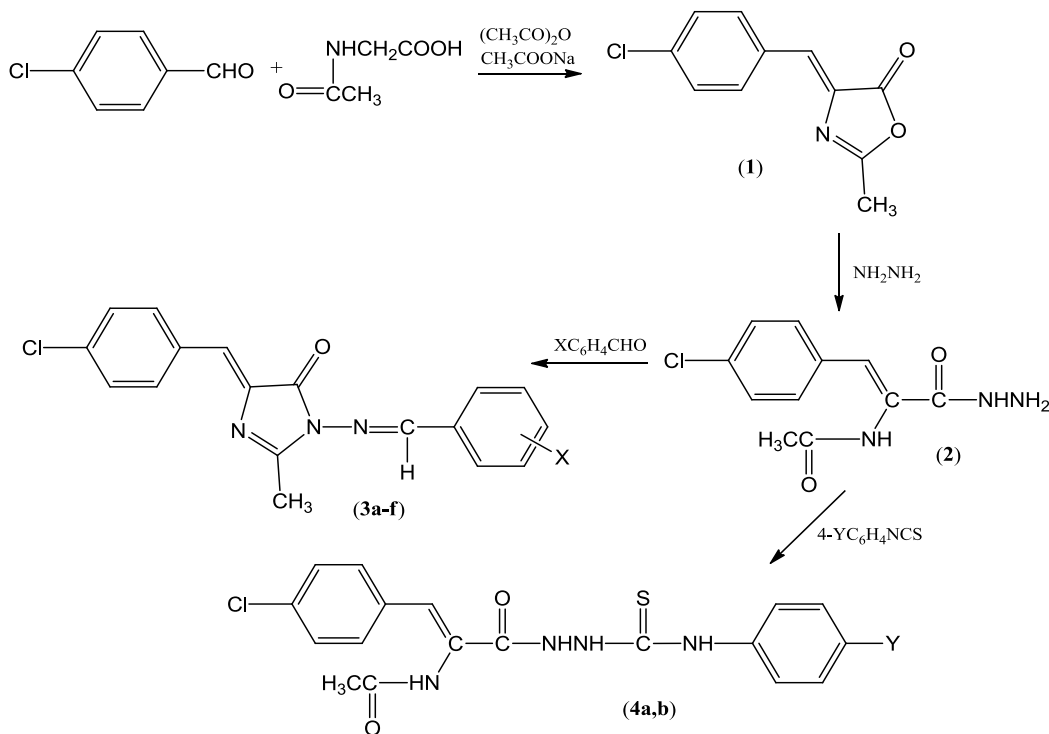
(Z)-4-(4-Chlorobenzylidene)-2-methyloxazol-5(4*H*)-one (1): An equimolar mixture of 4-chlorobenzaldehyde (7.03 g, 0.05 mol) and acetylglycine (5.85 g, 0.05 mol) in freshly distilled acetic anhydride (25 mL) containing fused anhydrous sodium acetate (4.1 g) was refluxed for 3 hours and then cooled. The solid was triturated with cold saturated solution of sodium carbonate and filtered, washed with water, air dried and recrystallized from ethanol. Mp. 158-160 °C (literature [3]: 158-160 °C); yield 60%. IR (ν, cm⁻¹): 1800 and 1772 (C=O); 1661, 1605 and 1584 (C=N, C=C). ¹H-NMR (δ, ppm): 8.19 (2H, *d*, *J* = 8.0 Hz, Ar-H), 7.57 (2H, *d*, *J* = 8.0 Hz, Ar-H), 7.23 (1H, *s*, -CH=C<), 2.39 (3H, *s*, CH₃).

2-(Acetamido)-3-(4-chlorophenyl)acrylohydrazide (2): 4-(4-Chlorobenzylidene)-2-methyloxazol-5-one (**1**) (2.22 g, 0.01 mol) was stirred with a solution of hydrazine hydrate 50 % (10.0 mL, 0.04 mol) in ethanol (50 mL) for 30 min. The deep yellow colour of the oxazolone immediately changed to a light yellow coloured solid, which was filtered, washed and purified by recrystallization from ethanol. Mp. 156-158° C; yield 58 %. IR (ν, cm⁻¹): 3374 and 3217 cm⁻¹ (N-H), 2990 cm⁻¹ (C-H), 1672 cm⁻¹ and 1653 cm⁻¹ (C=O), 1624 cm⁻¹ (C=C). ¹H-NMR (δ, ppm): 9.40 (1H, *s*,

N-H), 9.33 (1H, *s*, N-H), 7.53 (2H, *d*, $J = 9.0$ Hz, Ar-H), 7.43 (2H, *d*, $J = 9.0$ Hz, Ar-H), 6.99 (1H, *s*, -CH=C<), 4.36 (2H, *s*, NH₂), 1.97 (3H, *s*, COCH₃).

General procedure for synthesis of 1-arylideneamino-4-(chlorobenzylidene)-2-methyl-1H-imidazolin-5(4H)-one compounds (3a-f):

Equimolar quantity of hydrazide (2) and a definite aldehyde was refluxed in ethanol for 4 hours. The reaction mixture was cooled down to room temperature and the obtained precipitate was filtered off and crystallized from dioxane. As the result, yellow crystals are obtained for all cases.



Scheme 1: Pathway for synthesis

4-(4-chlorobenzylidene)-1-[(4-methoxybenzylidene)amino]-2-methyl-1H-imidazolin-5(4H)-one (3a). Yield 83%, mp. 176–178 °C; IR (ν , cm⁻¹): 3060, 2930, 1717, 1678, 1605; ¹H-NMR (δ , ppm and J , Hz): 9.44 (1H, *s*, -CH=N), 8.24 (2H, *d*, $^3J = 8.5$, ArH), 7.79 (2H, *d*, $^3J = 8.0$, ArH), 7.52 (2H, *d*, $^3J = 8.5$, ArH), 7.08 (1H, *s*, -CH=C<), 7.05 (2H, *d*, $^3J = 8.0$, ArH), 3.84 (3H, *s*, CH₃O), 2.47 (3H, *s*, CH₃-Hr); ¹³C-NMR (δ , ppm): 165.6, 163.3, 161.8, 154.7, 137.2, 134.7, 133.3, 132.4, 129.2, 128.5, 125.8, 124.5, 114.3, 55.2, 14.8; MS: m/z 354 (M+H)⁺, calculated for C₁₉H₁₆ClN₃O₂: 353.

4-(4-chlorobenzylidene)-1-[(4-methylbenzylidene)amino]-2-methyl-1H-imidazolin-5(4H)-one (3b). Yield 68 %, mp. 182–184 °C; IR (ν , cm⁻¹): 3040, 2924, 1705, 1651, 1589; ¹H-NMR (δ , ppm and J , Hz): 9.52 (1H, *s*, -CH=N), 8.28 (2H, *d*, $^3J = 8.5$, ArH), 7.75 (2H, *d*, $^3J = 8.0$, ArH), 7.55 (2H, *d*, $^3J = 8.5$, ArH), 7.32 (2H, *d*, $^3J = 8.0$, ArH), 7.10 (1H, *s*, -CH=C<), 2.48 (3H, *s*, CH₃Ar), 2.37 (3H, *s*, CH₃-Hr); ¹³C-NMR (δ , ppm): 165.9, 163.6, 154.6, 141.6, 137.3, 135.0, 133.7, 132.7, 130.9, 129.6, 128.9, 127.7, 124.9, 21.1, 15.2;

HR-MS: m/z 360.0867 (M+Na)⁺, calculated for C₁₉H₁₆ClN₃O: 337.0982.

1-(benzylideneamino)-4-(4-chlorobenzylidene)-2-methyl-1H-imidazolin-5(4H)-one (3c). Yield 80 %, mp 173–174 °C; IR (ν , cm⁻¹): 1713, 1651, 1589; ¹H-NMR (δ , ppm and J , Hz): 9.58 (1H, *s*, -CH=N), 8.28 (2H, *d*, $^3J = 8.5$, ArH), 7.87 (2H, *dd*, $^3J = 8.0$, $^4J = 2.0$, ArH), 7.55 (5H, *m*, ArH), 7.12 (1H, *s*, -CH=C<), 2.49 (3H, *s*, CH₃-Hr); ¹³C-NMR (δ , ppm): 165.9, 163.6, 154.3, 137.2, 135.1, 133.7, 133.6, 132.6, 131.5, 129.0, 128.9, 127.7, 125.0, 15.2; MS: m/z 324 (M+H)⁺, calculated for C₁₈H₁₄ClN₃O: 323.

4-(4-chlorobenzylidene)-1-[(4-fluorobenzylidene)amino]-2-methyl-1H-imidazolin-5(4H)-one (3d). Yield 73%, mp. 205–207 °C; IR (ν , cm⁻¹): 2946, 1713, 1651, 1589; ¹H-NMR (δ , ppm and J , Hz): 9.59 (1H, *s*, -CH=N), 8.29 (2H, *d*, $^3J = 8.5$, ArH), 7.95 (2H, *d-d*, $^3J = 8.0$, $^4J_{H-F} = 6.0$, ArH), 7.56 (2H, *d*, $^3J = 8.5$, ArH), 7.37 (2H, *d-d*, $^3J = 8.0$, $^3J_{H-F} = 8.0$, ArH), 7.13 (1H, *s*, -CH=C<), 2.50 (3H, *s*, CH₃-Hr); ¹³C-NMR (δ , ppm): 165.9, 163.5, 163.0 (*d*, $J_{C-F} = 250$ Hz), 153.1, 137.2, 135.1, 133.7, 132.6, 130.3, 130.1 (*d*, $^3J_{C-F} = 8.8$ Hz),

128.9, 125.0, 116.1 (d , $^2J_{C-F} = 21.3$ Hz), 15.2; HR-MS: m/z 342.0818 ($M+H$)⁺, calculated for C₁₈H₁₃ClFN₃O: 341.0731.

4-(4-chlorobenzylidene)-1-[(2-fluorobenzylidene)amino]-2-methyl-1H-imidazolin-5(4H)-one (3e). Yield 82%, mp. 196-197 °C; IR (ν , cm⁻¹): 3048, 1717, 1651, 1591; ¹H-NMR (δ , ppm and J , Hz): 9.79 (1H, s , -CH=N), 8.22 (2H, d , $^3J = 8.5$, ArH), 7.99 (1H, dd , $^3J_1 = ^3J_2 = 7.5$, ArH), 7.58 (1H, m , ArH), 7.50 (2H, d , $^3J = 8.5$, ArH), 7.33 (2H, m , ArH), 7.06 (1H, s , -CH=C<), 2.49 (3H, s , CH₃-Hr); ¹³C-NMR (δ , ppm): 165.6, 162.8, 161.0 (d , $J_{C-F} = 251$ Hz), 146.6, 136.8, 134.8, 133.3, 133.0 (d , $^3J_{C-F} = 8.8$ Hz), 132.2, 128.4, 126.3, 124.9, 124.6 (d , $^4J_{C-F} = 3.5$ Hz), 120.9 (d , $^3J_{C-F} = 9.8$ Hz), 115.3 (d , $^2J_{C-F} = 20.6$ Hz), 14.5; HR-MS: m/z 342.0824 ($M+H$)⁺, calculated for C₁₈H₁₃ClFN₃O: 341.0731.

4-(4-chlorobenzylidene)-1-[(4-hydroxy-3-methoxybenzylidene)amino]-2-methyl-1H-imidazolin-5(4H)-one (3f). Yield 64.5 %, mp. 221-222 °C; IR (ν , cm⁻¹): 3410, 2924, 1712, 1667, 1589; ¹H-NMR (δ , ppm and J , Hz): 9.78 (1H, br , OH), 9.35 (1H, s , -CH=N), 8.28 (2H, d , $^3J = 8.5$, ArH), 7.55 (2H, d , $^3J = 8.5$, ArH), 7.42 (1H, d , $^4J = 2.0$, ArH), 7.28 (1H, $d-d$, $^3J = 8.0$, $^4J = 2.0$, ArH), 7.09 (1H, s , -CH=C<), 6.89 (1H, d , $^3J = 8.0$, ArH), 3.84 (3H, s , CH₃O), 2.49 (3H, s , CH₃-Hr); ¹³C-NMR (δ , ppm): 166.1, 164.1, 156.3, 150.5, 148.3, 137.6, 135.3, 133.9, 132.8, 129.1, 125.0, 124.9, 123.1, 115.8, 110.3, 55.9, 15.4; HR-MS: m/z 370.0975 ($M+H$)⁺, calculated for C₁₉H₁₆ClN₃O₃: 369.0880.

Synthesis of 4-aryl-1-[2-(acetamido)-3-(4-chlorophenyl)acrylyl]thiosemicarbazide (4a,b): Equimolar quantity of hydrazide (3) and arylisothiocyanate were refluxed in ethanol for 1 hours. After cooling, the precipitate was filtered off, dried, and recrystallized from ethanol to give white crystals.

4-(4-methylphenyl)-1-[2-(acetamido)-3-(4-chlorophenyl)acryloyl] thiosemicarbazide (4a): yield 82%. M.p. 208-209 °C; IR (ν , cm⁻¹): 3379 and 3217 (N-H), 1667 (C=O), 1196 (C=S); ¹H-NMR (δ , ppm and J , Hz): 10.41 (1H, s , N-H), 10.05 (1H, s , N-H), 9.73 (1H, s , N-H), 9.14 (1H, s , N-H), 7.61 (2H, d , $J = 8.5$ Hz, Ar-H), 7.54 (2H, d , $J = 8.5$, Ar-H), 7.48 (2H, d , $J = 8.5$, Ar-H), 7.13 (2H, d , $J = 8.5$, Ar-H), 6.90 (1H, s , =CH), 2.28 (3H, s , CH₃), 2.08 (3H, s , CH₃); ¹³C-NMR: 181.3, 170.8, 164.1, 136.1, 133.9, 133.3, 132.4, 131.4, 128.9, 128.6, 128.5, 125.2, 123.8, 23.0, 20.5; HR-MS: m/z 403.0980 ($M+H$)⁺, calculated for C₁₉H₁₉ClN₄O₂S: 402.0917.

4-phenyl-1-[2-(acetamido)-3-(4-chlorophenyl)acryloyl]thiosemicarbazide (4b):

Yield 79%. M.p. 202-204 °C (literature [10]: 202-204 °C); IR (ν , cm⁻¹): 3341 and 3287 (N-H), 1690 (C=O), 1651 (C=C), 1196 (C=S); ¹H-NMR (δ , ppm and J , Hz): 10.45(1H, s , N-H), 10.10 (1H, s , N-H), 9.83 (1H, s , N-H), 9.22 (1H, s , N-H), 7.72 (2H, d , $J = 7.5$ Hz, Ar-H), 7.63 (2H, d , $J = 8.5$, Ar-H), 7.49 (2H, d , $J = 8.5$, Ar-H), 7.35 (2H, dd , $J_1 = J_2 = 7.5$, Ar-H), 7.16 (1H, dd , $J_1 = J_2 = 7.5$, Ar-H), 6.92 (1H, s , =CH), 2.11 (3H, s , CH₃); ¹³C-NMR: 180.0, 171.7, 164.0, 139.0, 133.3, 132.4, 131.4, 128.9, 128.6, 128.1, 125.2, 124.7, 123.7, 23.0; HR-MS: m/z 389.0855 ($M+H$)⁺, calculated for C₁₈H₁₇ClN₄O₂S: 388.0761.

3. RESULTS AND DISCUSSION

Oxazolone (1) is an unsaturated lactone, so its IR spectrum shows two peaks related to the C=O stretching vibration. This phenomenon was explained by the Fermi resonance between the carbonyl stretching vibration and the overtones or combinations of other low-frequency vibrations [4].

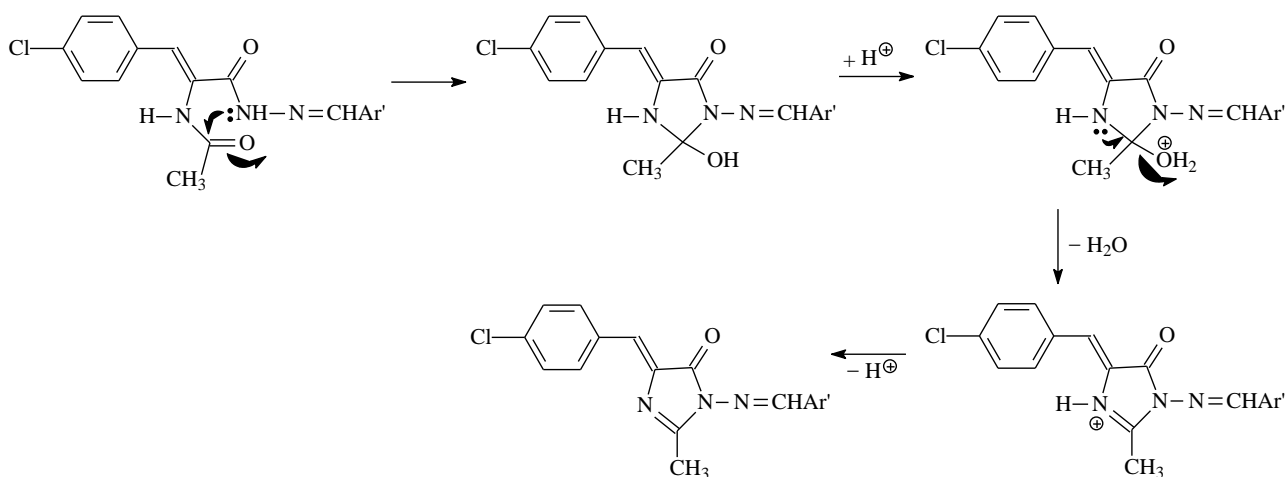
Reaction of hydrazide and aldehydes normally gives *N*-substituted hydrazides and the formation of *N*-arylidene 2-(acetamido)-3-(4-chlorophenyl)acrylohydrazides was confirmed in our earlier reports [1, 2]. According to these reports, the hydrazide reacted with aldehydes for 1 hour to afford the corresponding *N*-substituted hydrazides. However, after 3 hours of the reaction, some products were not *N*-substituted hydrazides. In the IR spectra of the products, there was not only a lack of stretching bands for N-H bonds but also an appearance of the absorption signal of carbonyl group at a higher frequency in comparison with the IR spectra of the *N*-substituted hydrazides [1, 2]. The ¹H-NMR spectra of the products did not show any signals of active proton in N-H groups too. These phenomena may indicate that all of the NH groups in the molecule of hydrazide were transformed. Besides that, in the ¹H-NMR spectra of the products, the signals of methyl group (CH₃) at 2.47-2.50 ppm are in downfield zone compared with signals of the methyl group in *N*-substituted hydrazide molecules at 2.01-2.03 ppm [1, 2]. At downfield zone, around 9.44-9.75 ppm in the ¹H-NMR spectra of each product, there was a *singlet* which in the HMBC spectra made cross peak with signal of carbon atom in the benzene ring of benzylidene moiety bonded to nitrogen. These *singlets* were assigned to protons of the azomethine groups and their chemical shifts were also similar to chemical shifts of the azomethine protons in the ¹H-NMR of 1-arylideneamino-4-arylidene-2-phenyl-1H-imidazolin-5(4H)-one compounds [3].

Obviously, signals of these azomethine protons are in upfield zone in comparison with signals of corresponding protons in *N*-substituted hydrazide molecules at 8.34-8.51 ppm [1, 2]. Also, mass spectra of the products showed molecular ion peaks with mass reduced 18mu in comparison with molecular mass of the corresponding *N*-substituted hydrazides but these molecular ion peaks were absolutely conformed with molecular mass of the 1-arylideneamino-4-(4-chlorobenzylidene)-2-methyl-1*H*-imidazolin-5(4*H*)-one compound.

Formation of 1-arylideneamino-4-arylidene-2-methyl-1*H*-imidazolin-5(4*H*)-ones from *N*-arylidene-2-acetamido-4-arylacrylohydrazides on treatment with acetic acid has been described in literature [5]. However, in this reference, the structures of the imidazolin-5-(4*H*)-one compounds

were only verified by elemental analysis and IR spectra without any other spectral data. Besides that, some 1-arylideneamino-4-arylidene-2-phenyl-1*H*-imidazolin-5(4*H*)-ones were also formed from corresponding aryldene-2-benzamido-4-arylacrylohydrazides by treatment with acetic acid [6, 7] or by hexamethyldisilazane [3]. It is possible that *N*-substituted hydrazide molecule formed in process of the reaction is transformed continuously to give 1,2,4-trisubstituted imidazole-5-one.

It should be remarked that the first nitrogen atom in the hydrazino group possesses a pair of free electrons, so it may attack to carbon carbonyl in the acetamido group. A transformation may be continued as showing on the Scheme 2 to give 1-arylideneamino-4-arylidene-2-methyl-1*H*-imidazolin-5(4*H*)-one compounds.



Scheme 2: Formation of the 1-arylideneamino-4-(4-chlorobenzylidene)-2-methyl-1*H*-imidazolin-5(4*H*)-ones

The hydrazide (**2**) was refluxed with arylisothiocyanates in absolute ethanol to give corresponding 4-aryl-1-[2-(acetamido)-3-(4-chlorophenyl)acryloyl]thiosemicarbazides (**4a,b**). This is the conventional method to synthesize thiosemicarbazides reported previously [9-11] and the formation of the 4-phenyl-1-[2-(acetamido)-3-(4-chlorophenyl)acryloyl]thiosemicarbazide (**4b**) was also described in literature [11]. The IR spectra of (**4a,b**) exhibited a strong C=S absorption at 1196 cm^{-1} . The ^{13}C -NMR signal of this group was observed at $\delta = 180.0 - 181.3$ ppm. The ^1H -NMR of each compound displayed four *singlets* due to four different N-H groups above 9.0 ppm. Molecular ion peak of thiosemicarbazides (**4a,b**) was agreement with assumed structures.

4. CONCLUSION

1-Arylideneamino-4-(chlorobenzylidene)-2-methyl-1*H*-imidazolin-5(4*H*)-ones were formed as superseded products of the corresponding *N*-substituted hydrazides while treating 2-(acetamido)-3-(4-chlorophenyl)acrylohydrazide with some aldehydes under condition of extended time. Besides that, two 4-aryl-1-[2-(acetamido)-3-(4-chlorophenyl)acryloyl]thiosemicarbazides were synthesized. The structures of the new compounds were confirmed by IR, ^1H -NMR, ^{13}C -NMR and mass spectral data.

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