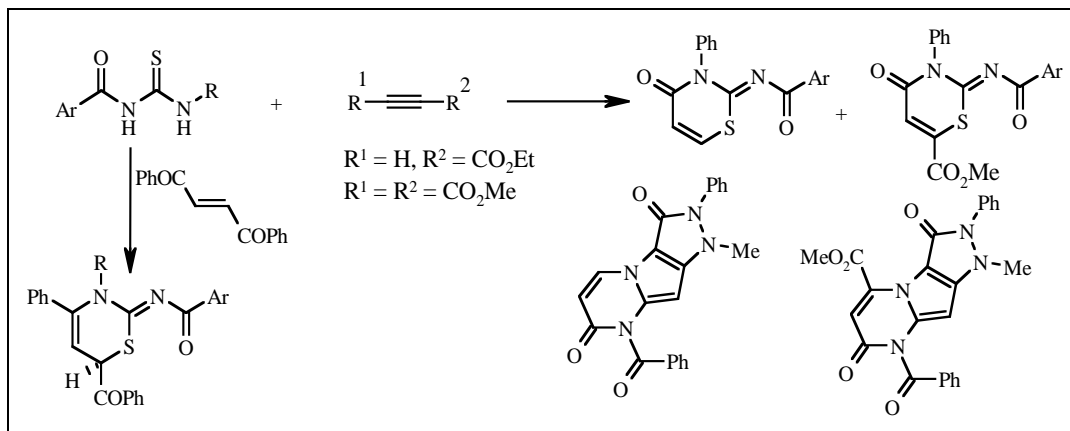


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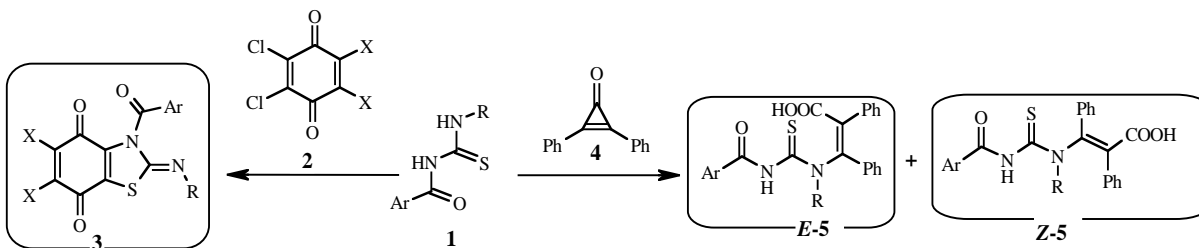
A series of 1,3-thiazines has been synthesized by the reactions of *N*-aroylsubstituted thioureas with ethyl propiolate, dimethyl but-2-ynedioate and (*E*)-1,4-diphenyl-but-2-ene-1,4-dione. The reaction of antipyrinylphenyl thiourea with π -deficient acetylenic reagents did not afford the corresponding 1,3-thiazines, whereas pyrrolo-pyrazolopyrimidines were obtained.

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INTRODUCTION

Five membered ring systems such as imidazolidin-2-thiones were obtained from the oxidative cyclization of 1-dibenzoyl-3-aryl-thioureas with bromine-acetophenone in the presence of excess triethylamine [1,2]. Manaka [3] reported on the one-pot condensation of aroylthiourea with α -halocarbonyl derivatives to afford 2-acylimino-3-alkyl-3*H*-thiazolines. 1,2,4-Triazoles were synthesized by the direct reaction of *N*-aryl-*N'*-benzoylthioureas with hydrazine hydrate [4]. To the best of our knowledge, six membered ring systems were only synthesized as salts from the reaction of aroylthioureas with SOCl_2 in $\text{ClCH}_2\text{-CH}_2\text{Cl}$ followed by 70% HClO_4 to give 31-94% diaminoaryl-oxadiazinium perchlorates, whereas 1,3,5-thiadiazinium salts were prepared by cyclization of aroylthioureas with POCl_3 [5]. Recently, Aly and his group have demonstrated a very convenient procedure to synthesize fused thiazoles **3** from the reaction of aroylphenyl thioureas with π -acceptor quinones (2, 2,3,5,6-tetrachloro-1,4-benzoquinone, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone and 2,3-dichloro-1,4-naphthoquinone, Scheme 1) [6]. However, the reactions of compounds **1** with 2,3-diphenylcyclopropenone (**4**) in acetic acid afforded the *E* and *Z* mixtures of 3-(3'-aroyl-1-substituted-thioureido)-2,3-diphenylcinnamic acids (**5**, Scheme 1) [7]. It was reported that 1-benzoyl-3-(4-hydroxy-phenyl)-urea

reacted, in presence of sodium hydroxide, with benzoyl chloride to provide 1-(3-hydroxyphenyl)-6-oxo-1,6-dihydro-2-thiomethyl-pyrimidine-4-carboxylic acid methyl ester [8]. Additionally, it was known that the reaction of amidinothioureas, imidoylthioureas, thioacylamidines, *O*-methyl-1-aryl-2-thioisbiurets, and 1-aryl-isodithioisbiurets with diethyl azodicarboxylate gave the corresponding thiadiazoles by the oxidative cyclic S-N bond formation [9]. A series of 3-alkyl-5-methylene-2-arylimino-1,3-thiazolidin-4-ones was obtained from the reaction of *N*-alkyl-*N'*-aroylthioureas with dimethyl but-2-ynedioate [10a]. Hyrazinothioureas represented by 1-acylthiosemicarbzides reacted with phenyl propiolate in acetic acid under reflux to afford triazolothiazines [10b]. In light of the aforementioned, it appears that the tendency of substituted-thioureas, as simple molecules, is variable from one reagent to another. The efficiency of our synthetic program has been concerned with the use of facile and elegant methods for the preparation of novel heterocycles rather than those suffering from low yields due to the multiple steps described in their preparation [11]. Herein we report on our findings for the synthesis of various novel thiazinones, during the reaction of various *N*-aroyl thioureas with ethyl propiolate, dimethyl but-2-ynedioate and (*E*)-1,4-diphenyl-but-2-ene-1,4-dione. It is note worthy to mention that 1,3-thiazines have their broad spectrum as anti-microbial agents [12,13].



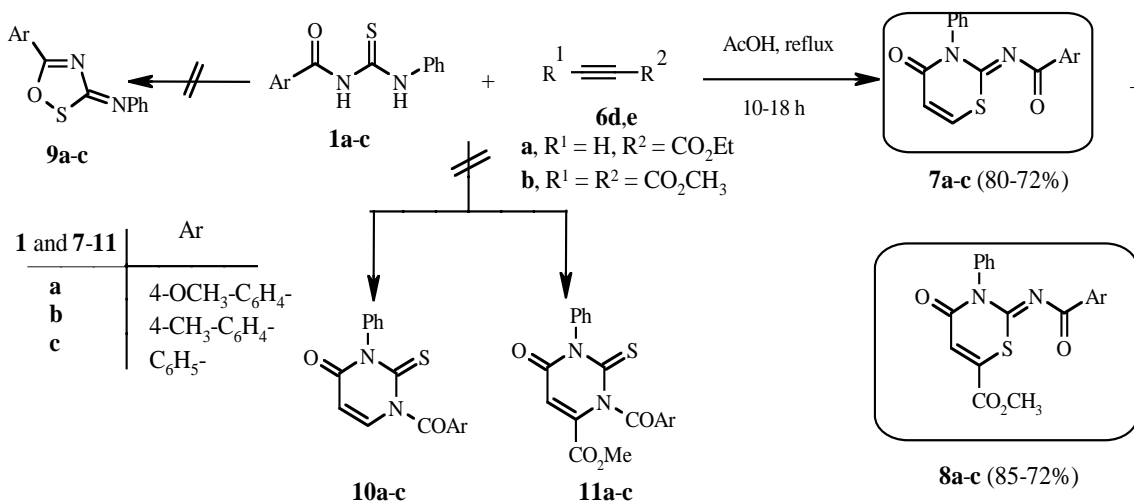
Scheme 1. Reactions of aroylsubstituted thioureas **1** with π -quinones **2** and 2,3-diphenylcyclopropanone (**4**)

RESULTS AND DISCUSSION

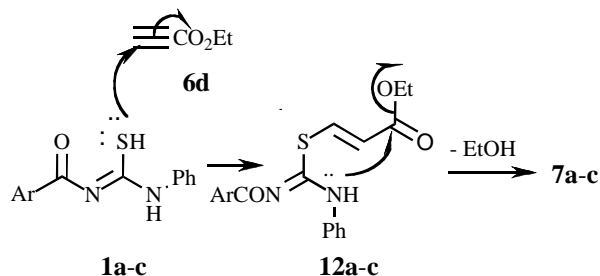
In the present protocol as exhibited in Scheme 2, the reaction of *N*-aroyl-phenyl thioureas **1a-c** with ethyl propiolate (**6d**) and dimethyl but-2-ynedioate ethyl ester (**6e**) under reflux in acetic acid yielded the corresponding 1,3-thiazinones **7a-c** and **8a-c**. Generally, it must be pointed out that the ^1H nmr spectra of **7a-c** did not reveal any proton resonances related to the NH- or -SH groups. Besides, the ^{13}C nmr spectra did not show any significant carbon signal related to the presence of the C=S. The carbon signals related to carbonyl of both the NCOAr and C-4 absorbed at δ_{C} 166.0-167.0 and 170.8-172.0 ppm, respectively were observed. The ir spectra indicated the presence of another carbonyl group at ν_{max} 1700-1680 cm^{-1} . The ^1H nmr spectra of **7a-c** showed the presence of 6- and 5-H protons at δ_{C} 6.50-6.60 and 7.00-7.15 ppm, respectively (see the Experimental Section). The ^{13}C nmr spectra showed the presence of C-5 and C-6 at δ_{C} 118.0-118.8 and 125.8-126.2 ppm, respectively. Besides, the azomethine carbon (C-2), in the ^{13}C nmr spectra, absorbed at δ_{C} 156.8-158.0 ppm. The ir spectra of compounds **8a-c** revealed broad absorption bands at ν_{max} 1680-1720 cm^{-1} corresponding to the carboamide, C-4 and ester groups. The ^1H nmr spectrum for **8a**, as an example, revealed only one singlet at δ_{H} 7.10 ppm related to 5-H. The ^{13}C nmr spectrum showed CH-5 at δ_{C} 135.0 ppm, whereas the methyl-carboxylate and methoxy protons absorbed at δ_{C} 52.6 and 50.8 ppm (see the Experimental Section). The spectral data from nmr, mass and ir as well as the elemental analyses supported that compounds **7a-c** and **8a-c** have the structure of 4-substituted-*N*-(4-oxo-3-phenyl-3,4-dihydro-[1,3]thiazin-(2*Z*)-ylidene)-benzamides and 2-[(*Z*)-4-substituted-benzoyl-imino]-4-oxo-3-phenyl-3,4-dihydro-2*H*-[1,3]thiazine-6-methyl esters. From the aforementioned we excluded any other suggestions such as formation of products **9a-c** (resulting from the oxidative process), **10a-c** or **11a-c** (Scheme 2). The reaction mechanism depends on the presence of a tautomerism between the NH and the C=S into the N=C-SH groups in **1a-c** (Scheme 3). It is believed that attachment by the SH group proceeds faster compared to the aromatic amine (Scheme 3) [6a,14]. Therefore,

reaction of **1a-c** with **6d** can be described as due to nucleophilic attack of the thiol group to the acetylenic carbon to form the intermediate **12a-c**. Thereafter another nucleophilic attack from the NH electron lone pair to the carbonyl in **12a-c** accompanied with ethanol elimination affords the heterocyclic compounds **7a-c** (Scheme 3).

Surprisingly, on reacting 1-benzoyl-1'*H*-pyrazol-4'-yl-thiourea (**1d**) with **6d** or **6e**, the reaction proceeded to give mainly the corresponding fused pyrolopyrimidines **13** and **14** (Scheme 4). Furthermore, the ir and nmr spectra of **13** and **14** supported the disappearance of any thione, thiol, and NH groups or protons. Moreover, the ^1H nmr spectra did not show the presence of the methyl group in position-5 of **1d**, whereas the pyrrole-CH appeared as a singlet at δ_{H} 7.96 ppm in case of **13**. Mass spectrum and elemental analysis confirmed the molecular formula of **13** as $\text{C}_{22}\text{H}_{16}\text{N}_4\text{O}_3$. The ^1H nmr spectrum of **13** revealed two doublets of the pyrimidine ring at δ_{H} 6.00 (5-H, $J = 8.0$ Hz) and 6.60 ppm (6-H, $J = 8.2$ Hz). The ^{13}C nmr spectrum of **13** showed the appearance of several distinctive carbon signals as shown in Figure 1. On the other hand, mass spectrum and elemental analysis supported the molecular formula of **14** as $\text{C}_{24}\text{H}_{18}\text{N}_4\text{O}_5$. The ^1H nmr spectrum of compound **14** revealed two singlets at δ_{H} 7.40 and 7.90 ppm, which were in accord to 6-H and -9, respectively. The ^{13}C nmr spectrum confirmed the ^1H nmr spectral data by the appearance of CH-6 and -9 at δ_{C} 127.4 and 128.4 ppm, respectively. Additionally, the absorptions of numerous carbon signals in the ^{13}C nmr spectrum of **14** could be distinguished as shown in Figure 1. Two methyl groups resonated as two singlets, in the ^1H nmr of **14**, at δ_{H} 3.36 and 3.98 ppm corresponding to the NCH_3 and CH_3 -ester protons. The complete spectral data is in good agreement with the structures of either **13** or **14** (see Figure 1 and the Experimental Section). The NOE experiments of compounds **13** and **14** supported their proposed structures. Hence, irradiation of the 9-H resonance in either **13** or **14**, caused strong enhancement of the *ortho*-proton resonances of the benzoyl group (δ_{H} 7.70-7.74), whereas that irradiation slightly affected the *N*- CH_3 protons signal (Figure 1).



Scheme 2. Reaction of ethyl propiolate (**6d**) and dimethyl but-2-ynedioate ester (**6e**) with aroyl-substituted thioureas **1a-c**; synthesis of 1,3-thiazin-4-ones **7a-c** and **8a-c**.



Scheme 3. Rationale formation of compounds **7a-c**

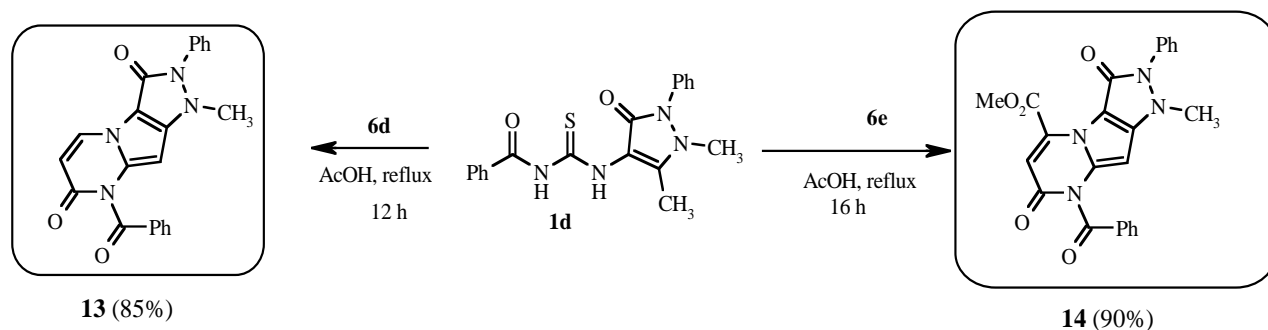
Furthermore, irradiation of the resonances 5-H (or 6-H) of **13** caused mutual strong saturation with 6-H (or 5-H) (Figure 1). Besides, NOE experiment where the 5-H (δ_{H} 6.60 ppm) signal is saturated in **13** affected moderately the 9-H (δ_{H} 7.96 ppm) signal, whereas irradiation of 6-H (δ_{H} 6.00 ppm) in **14** slightly affected of methyl-ester protons.

Interestingly, irradiation of the *N*-CH₃ protons in either **13** or **14** slightly caused enhancement to both the *ortho-N*-Ph protons and 9-H. Figure 1 shows some distinctive δ'

values of the NMR spectra for compounds **13** and **14** along with their distinguished NOE experiments.

Since, the calculated bond distance [15] between the carbonyl group and the thiol group is found to be 1.6 Å, we can suggest a type of hydrogen bond is formed between them. Consequently, this hydrogen bond can offer the formation of another seven member ring (Figure 2), which indicates high reactivity of the NH group in **1d** compared with the thiol group.

The reaction mechanism, in case of the formation of **13**, can be simply described by nucleophilic attacking of *N*³ on terminal acetylenic-CH to form intermediate **15**. Thereafter, the other nitrogen (*N*¹) undergoes nucleophilic attack on the carbonyl ester to form the salt **16** (Scheme 5). Tautomerization of the CH₃-C=C-C=O group in **16** to typical CH₂=C-C=C-OH group occurred *via* proton transfer process (Scheme 5). Spontaneously, cyclization process is occurred *via* nucleophilic addition of the exocyclic-CH₂ on the thiol carbon accompanied by elimination of ethanol and hydrogen sulfide (Scheme 5) to give **17**. Ultimately, elimination of the catalyzed proton affords directly compound **13** (Scheme 5).



Scheme 4. Reaction of *N*-benzoyl-antipyrinyl thioureas **1d** with π -deficient acetylenes **6d,e**

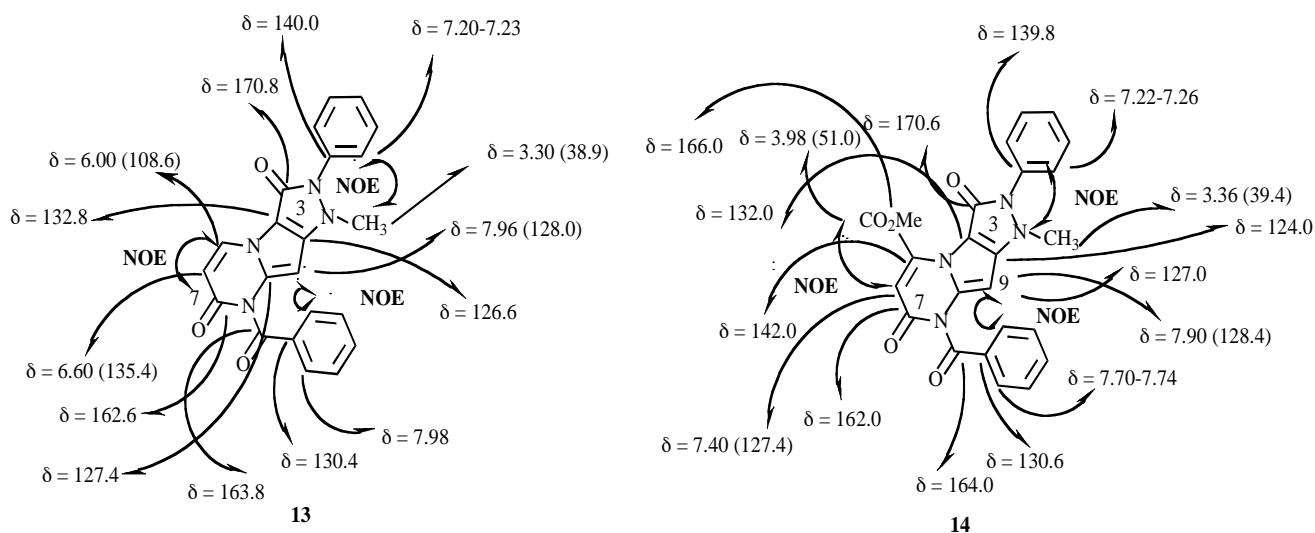


Figure 1. Distinctive δ 's values and NOE experiments of compounds **13** and **14**

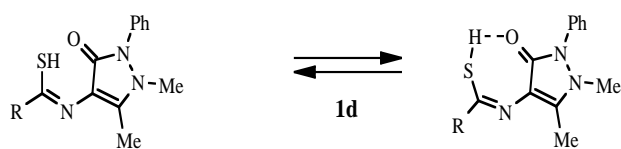


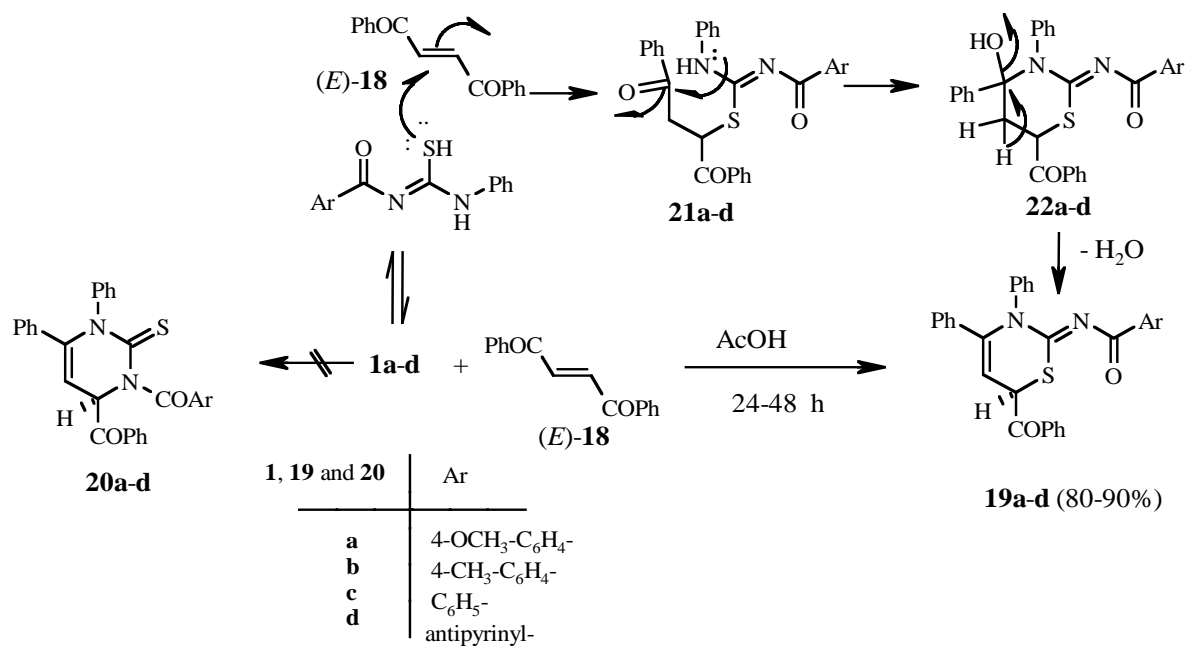
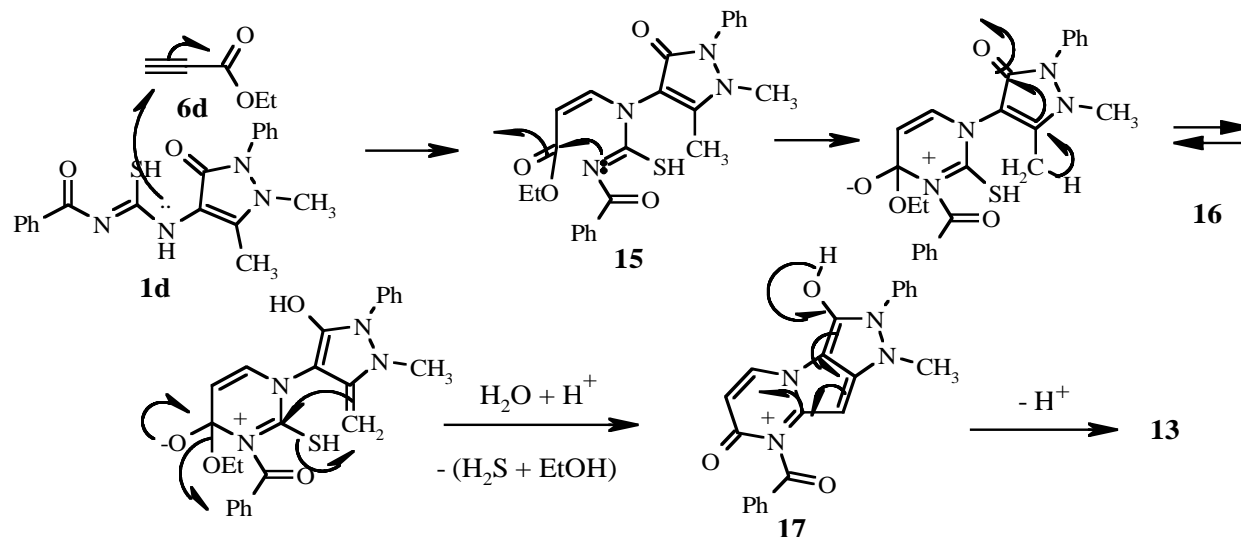
Figure 2. Hydrogen bond formed between the thiol and carbonyl groups in **1d**

In order to explore the above mode of synthesis for another class of heterocycles, under similar reaction conditions, the reaction of (*E*)-1,4-diphenyl-but-2-ene-1,4-dione (*E*-**18**) with thioureas **1a-d** successfully proceeded to afford the corresponding 1,3-thiazines **19a-d** (Scheme 6). The ^1H nmr spectrum of **19a**, as an example, revealed the presence of OCH_3 , C-6 (thiazine), C-5 (thiazine) and *N*-Ph 2 CH_2 at δ_{H} 3.94, 4.80 ppm (1 H, d, $J = 11.5$ Hz), 6.30 (1 H, d, $J = 11.4$ Hz) and 6.70 (dd, $J = 8.0, 1.2$ Hz) ppm. The ^{13}C nmr spectrum supported the ^1H nmr spectroscopic data by the distinctive appearance of the carbon signals represented the thiazine skeleton and its environments at δ_{C} 44.4 (CH_6), 54.0 (OCH_3), 100.0 (CH_5), 115.0 (*N*-Ph 2 CH_2), 116.2 (Ph 2 CH_2), 142.6 (C-4), 144.2 (*N*-PhC), 160.8 (CH_3OArC), 162.8 (C=N, C-2), 168.0 (*N*-C=O) and 180.0 ppm (COPh). The ^1H nmr spectrum of **19a** apparently supported the (*R*)-configuration due to the presence of H-6 in *trans*-form ($J = 11.5$ Hz) in relation to H-5 ($J = 11.4$ Hz). In the case of **19d**, the ^{13}C nmr spectrum revealed several distinctive carbon signals such as at δ_{C} 15.7, 35.8, 45.2, 93.0, 106.0, 130.0, 130.4, 142.0, 143.4, 160.0, 162.0, 166.6, and 179.2 ppm corresponding to CH_3 -pyrazole, pyrazole *N* CH_3 , CH 6, CH 5, pyrazole C-4, pyrazole C-3, thiazine C-3, thiazine C-4, *N*-Ph C, pyrazole-CO, thiazine C-2, *N*-C=O and C=O, respectively (see the Experimental Section). Compound **1d** did not show any abnormal reactivity

during its reaction with (*E*)-**18** and *N*-[(*R*)-6-benzoyl-3-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl]-4-phenyl-3,6-dihydro-[1,3]-thiazin-(2*Z*)-ylidene]-4-methyl-benzamide (**19d**) was obtained (Scheme 6). The difference in reactivity during the reaction of **1d** with either **6d** and/or **18** might be attributed to the steric effect. In other meaning, the combination between **1d** and **18** might constitute a type of steric that enables the thiol group to react more easily compared with NH group. The spectral data along with the elemental analysis excluded the suggested formation of other products such as **20a-d** (Scheme 6). The reaction mechanism can be simply outlined as shown in Scheme 6. In conclusion, we have thus demonstrated a very convenient procedure to synthesize of 1,3-thiazines by the reaction of but-2-ynedioic acid, propynoic acid ethyl ester, and (*E*)-1,4-diphenyl-but-2-ene-1,4-dione with aroyl-substituted thioureas under reflux in acetic acid.

EXPERIMENTAL

General Consideration. All mps were recorded on a Gallenkamp apparatus. ^1H NMR and ^{13}C NMR spectra (Bruker AM 400, ^1H : 400.13 MHz, ^{13}C : 100.6 MHz); s = singlet, d = doublet, dd = double-doublet and m = multiplet. The NMR samples were dissolved in dimethyl sulfoxide- d_6 solutions. Coupling constants were expressed in Hz. Elemental analyses were carried at the Assuit Microanalysis Center of Assiut University. Mass spectroscopy was performed with a Finnigan MAT 8430 spectrometer at 70 eV, Institute of Organic Chemistry, Technical University-Braunschweig, Germany. IR spectra were run on a Shimadzu 470 spectrometer using potassium bromide pellets.



Starting materials. Aroylthioureas **1a-c** and **1d** were prepared according to literatures [14] and [7], respectively.

Reaction of 1a-d with 6d,e and (E)-18, General procedure. Into a 250 cm³ two-necked round bottom flask containing a solution of **1a-d** (2 mmol) in glacial acetic acid (50-80 mL), a solution of 2 mmol of either **6d,e** (or *E*-**18**) in glacial acetic (20 mL) was dropwisely added with stirring. The mixture was stirred at room temperature for 1 h and then gently refluxed with stirring (the reaction was monitored by TLC analyses). In the case of products **7a-d** and **8a-d**, the solvent was evaporated under vacuum and the formed solid products were purified by

dissolving in dry acetone (30-50 mL) and subjected to preparative plates chromatography (silica gel), toluene: ethyl acetate (10:1). In the case of reaction of **1a-d** with (*E*-**18**), the formed solid products **19a-d** were collected by filtration and the precipitates were washed with water and ethanol until the odor of acetic acid disappeared. The obtained products were recrystallized from the stated solvents.

4'-Methoxy-N-[4-oxo-3-phenyl-3,4-dihydro-[1,3]-thiazin-(2Z)-ylidene]-benzamide (7a) was obtained as yellow crystals (0.54 g, 80%), mp 260 °C (ethanol); ¹H nmr (dimethyl sulfoxide-d₆): δ 3.90 (3 H, s, OCH₃), 6.60 (1 H, d, J = 7.0 Hz, 6-

H), 6.92 (2 H, dd, $J = 8.0, 1.4$ Hz, Ar H), 7.10 (1 H, d, $J = 7.2$ Hz, 5-H), 7.34-7.42 (4 H, m, Ar H), 7.75-7.90 (3 H, m, Ar H) ppm; ^{13}C nmr (dimethyl sulfoxide- d_6): δ 53.0 (OCH₃), 118.8 (CH-6), 126.2 (CH-5), 126.8 (Ph CH, CH^{4'}), 127.0, 127.6, 128.0, 130.0 (Ar 2 CH), 133.8 (Ar C-CO), 138.9 (*N*-Ar C), 150.0 (H₃COAr C), 158.0 (C-2), 167.0 (=NCOAr), 172.0 (C-4) ppm; ir (potassium bromide): 3060-2980 (Ar CH, w), 2930-2860 (aliph. CH, m), 1700-1680 (C=O, s), 1600 (C=N, s), 1496 (C=C, m), 1450 (s), 920 (m) cm⁻¹; uv (CH₃CN): λ_{max} nm (log ϵ) 420 (3.90); ms (electron impact, 70 eV): m/z (%) 339 ([M⁺], 24%), 338 ([M⁺], 100), 323 (14), 307 (28), 230 (40), 202 (54), 152 (26), 136 (82), 86 (24), 77 (40). *Anal.* Calcd. for C₁₈H₁₄N₂O₃S (338.39): C, 63.89; H, 4.17; N, 8.28; S, 9.48. Found: C, 63.75; H, 4.10; N, 8.20; S, 9.40.

4'-Methyl-N-[4-oxo-3-phenyl-3,4-dihydro-[1,3]-thiazin-(2Z)-ylidene]-benzamide (7b) was obtained as yellow crystals (0.48 g, 75%), mp 298 °C (ethanol); ^1H nmr (dimethyl sulfoxide- d_6): δ 2.34 (3 H, s, CH₃), 6.58 (1 H, d, $J = 7.2$ Hz, 6-H), 7.15 (1 H, d, $J = 7.0$ Hz, 5-H), 7.28-7.36 (4 H, m, Ar H), 7.60-7.80 (5 H, m, Ar H) ppm; ^{13}C nmr (dimethyl sulfoxide- d_6): δ 32.8 (CH₃), 118.4 (CH-6), 126.2 (CH-5), 126.6 (Ph-CH, CH-4'), 127.0, 127.4, 127.8, 129.6 (Ar 2CH), 133.6 (Ar C-CO), 134.6 (CH₃Ar C), 138.2 (*N*-ArC), 157.2 (C-2), 166.6 (=NCOAr), 171.2 (C-4) ppm; ir (potassium bromide): 3050-2986 (Ar CH, w), 2930-2860 (aliph. CH, m), 1700-1685 (C=O, s), 1596 (C=N, s), 1494 (C=C, m), 1450 (s), 918 (m) cm⁻¹; uv (CH₃CN) λ_{max} nm (log ϵ) 418 (3.80); ms (electron impact, 70 eV): m/z (%) 322 ([M⁺], 100), 306 (30), 230 (34), 202 (50), 188 (12), 152 (26), 144 (20), 136 (82), 120 (24), 86 (24), 77 (30). *Anal.* Calcd. for C₁₈H₁₄N₂O₃S (322.39): C, 67.06; H, 4.38; N, 8.69; S, 9.95. Found: C, 67.12; H, 4.34; N, 8.62; S, 9.90.

N-[4-Oxo-3-phenyl-3,4-dihydro-[1,3]-thiazin-(2Z)-ylidene]-benzamide (7c) was obtained as pale yellow crystals (0.44 g, 72%), mp 238 °C (ethyl acetate/benzene); ^1H nmr (dimethyl sulfoxide- d_6): δ 6.50 (1 H, d, $J = 7.0$ Hz, 6-H), 7.00 (1 H, d, $J = 7.0$ Hz, 5-H), 7.10-7.26 (5 H, m, Ph H), 7.54-7.76 (5 H, m, Ph H) ppm; ^{13}C nmr (dimethyl sulfoxide- d_6): δ 118.0 (CH-6), 125.8 (CH-5), 126.0, 126.8 (Ph-CH, CH-4'), 128.2, 128.6, 128.8, 129.2 (Ph 2CH), 133.8 (Ar C-CO), 138.0 (*N*-Ph C), 156.8 (C-2), 166.0 (=NCOAr), 170.8 (C-4) ppm; ir (potassium bromide): 3040-2980 (Ph CH, w), 1700-1682 (C=O, s), 1600 (C=N, s), 1496 (C=C, m), 1450 (s), 918 (s) cm⁻¹; uv (CH₃CN) λ_{max} nm (log ϵ) 410 (3.60); ms (electron impact, 70 eV): m/z (%) 308 ([M⁺], 100), 230 (26), 202 (48), 188 (16), 150 (24), 142 (20), 136 (32), 105 (60), 86 (20), 77 (26). *Anal.* Calcd. for C₁₇H₁₂N₂O₃S (308.36): C, 66.22; H, 3.92; N, 9.08; S, 10.40. Found: C, 66.12; H, 3.89; N, 9.00; S, 10.30.

2-[(Z)-4-Methoxy-benzoylimino]-4-oxo-3-phenyl-3,4-dihydro-2H-[1,3]thiazine-6-carboxylic acid methyl ester (8a) was obtained as yellow crystals (0.67 g, 85%), mp 212 °C (ethanol); ^1H nmr (dimethyl sulfoxide- d_6): δ 3.90 (3 H, s, ester OCH₃), 3.96 (3 H, s, OCH₃), 6.85 (1 H, s, $J = 7.0$ Hz, 5-H), 7.35-7.42 (2 H, m, Ar H), 7.48-7.60 (5 H, m, Ar-H), 7.96-7.98 (2 H, dd, $J = 8.0, 1.2$ Hz, Ar H) ppm; ^{13}C nmr (dimethyl sulfoxide- d_6): δ 50.8 (OCH₃), 52.6 (ester OCH₃), 125.8 (Ph CH, CH-4'), 128.9, 130.5, 131.8, 132.8 (Ar 2CH), 132.8 (Ar C-CO), 133.8 (CH-5), 136.4 (*N*-Ar C), 152.0 (CH₃OAr C), 155.0 (C-6), 158.4 (C-2), 165.4 (C=O-ester), 167.8 (=NCOAr), 171.4 (C-4) ppm; ir (potassium bromide): 3080-2990 (Ar CH, m), 2960-2870 (aliph. CH, m), 1720-1680 (C=O, br, s), 1610 (C=N, s), 1500 (C=C, s), 1460 (m), 920 (s) cm⁻¹; uv (CH₃CN) λ_{max} nm (log ϵ) 3.9 (3.60); ms (electron impact, 70 eV): m/z (%) 396 ([M⁺], 100), 135 (64),

107 (16), 92 (10), 77 (26), 64 (14). *Anal.* Calcd. for C₂₀H₁₆N₂O₅S (396.42): C, 60.60; H, 4.07; N, 7.07; S, 8.09. Found: C, 60.75; H, 4.00; N, 7.00; S, 8.02.

2-[(Z)-4-Methyl-benzoylimino]-4-oxo-3-phenyl-3,4-dihydro-2H-[1,3]thiazine-6-carboxylic acid methyl ester (8b) was obtained as yellow crystals (0.61 g, 80%), mp 198 °C (methanol); ^1H nmr (dimethyl sulfoxide- d_6): δ 2.34 (3 H, s, CH₃), 3.94 (3 H, s, ester OCH₃), 7.06 (1 H, s, $J = 7.2$ Hz, 5-H), 6.95-7.30 (7 H, m, Ar H), 7.60 (2 H, dd, $J = 8.2, 1.2$ Hz, Ar H) ppm; ^{13}C nmr (dimethyl sulfoxide- d_6): δ 32.8 (CH₃), 50.4 (ester OCH₃), 125.5 (Ph CH, CH-4'), 126.8, 127.2, 127.6, 128.2 (Ar 2CH), 130.4 (Ar C-CO), 135.4 (CH-5), 137.8 (H₃C-Ar C), 138.0 (*N*-Ar C), 155.2 (C-6), 158.2 (C-2), 165.5 (C=O-ester), 167.6 (=NCOAr), 173.4 (C-4) ppm; ir (potassium bromide): 3084-3005 (Ar CH, m), 2980-2890 (aliph. CH, m), 1716-1684 (C=O, br, s), 1608 (C=N, s), 1520 (C=C, s), 1460 (s), 918 (s) cm⁻¹; uv (CH₃CN) λ_{max} nm (log ϵ) 3.7 (3.50); ms (electron impact, 70 eV): m/z (%) 380 ([M⁺], 100), 365 (20), 288 (60), 260 (54), 135 (64), 120 (24), 112 (34), 77 (40). *Anal.* Calcd. for C₂₀H₁₆N₂O₄S (380.43): C, 63.15; H, 4.24; N, 7.36; S, 8.43. Found: C, 63.05; H, 4.20; N, 7.34; S, 8.42.

2-[(Z)-Benzoylimino]-4-oxo-3-phenyl-3,4-dihydro-2H-[1,3]-thiazine-6-carboxylic acid methyl ester (8c) was obtained as yellow crystals (0.52 g, 72%), mp 210 °C (methanol); ^1H nmr (dimethyl sulfoxide- d_6): δ 3.94 (3 H, s, ester OCH₃), 6.95 (1 H, s, $J = 7.0$ Hz, 5-H), 6.94-7.20 (6 H, m, Ph H), 7.40-7.50 (2 H, m, Ph H), 7.66 (2 H, dd, $J = 8.0, 1.2$ Hz, Ph H) ppm; ^{13}C NMR (dimethyl sulfoxide- d_6): δ 50.2 (ester-OCH₃), 125.0, 125.8 (Ph CH, CH^{4'}), 126.8, 127.6, 128.0, 128.2 (Ph 2 CH), 130.0 (Ph C-CO), 134.2 (CH-5), 138.6 (*N*-Ph C), 155.0 (C-6), 158.0 (C-2), 165.8 (C=O-ester), 167.0 (=NCOAr), 172.6 (C-4) ppm; ir (potassium bromide): 3070-3008 (Ph CH, m), 1718-1680 (C=O, br, s), 1610 (C=N, m), 1560 (C=C, m), 1450 (m), 916 (s) cm⁻¹; uv (CH₃CN) λ_{max} nm (log ϵ) 3.6 (3.40); ms (electron impact, 70 eV): m/z (%) 366 ([M⁺], 100), 288 (54), 260 (64), 126 (22), 112 (32), 77 (50). *Anal.* Calcd. for C₁₉H₁₄N₂O₄S (366.40): C, 62.29; H, 3.85; N, 7.65; S, 8.75. Found: C, 65.15; H, 3.80; N, 7.64; S, 8.70.

8-Benzoyl-1-methyl-2-phenyl-1H-pyrazolo-[3',4':4,5]pyrrolo-[1,2-a]-pyrimidine-3,7-(2H,8H)-dione (13) was obtained as pale brown crystals (0.70 g, 85%), mp 242 °C (ethanol); ^1H nmr (dimethyl sulfoxide- d_6): δ 3.30 (3 H, s, NCH₃), 6.00 (1 H, d, $J = 8.0$ Hz, 5-H), 6.60 (1 H, d, $J = 8.2$ Hz, 6-H), 7.00-7.30 (6 H, m, Ph H), 7.60-7.70 (2 H, m), 7.96 (1 H, s, pyrrole-H-9), 7.98 (2 H, dd, $J = 8.0, 1.4$ Hz, CO-Ph CH^{2'}). 7.96 (1 H, s, pyrrole-H-9) ppm; ^{13}C nmr (dimethyl sulfoxide- d_6): δ 38.9 (NCH₃), 108.6 (CH-5), 126.6 (C-9a), 126.8, 127.2 (Ph CH, CH-4'), 127.4 (C-8a), 128.0 (CH-9), 128.4, 128.6, 128.8, 129.0 (Ph 2CH), 130.6 (Ph-C CO), 132.8 (C-3a), 135.4 (CH-6), 140.0 (*N*-Ph C), 162.6 (C-7), 163.8 (benzoyl-CO), 170.8 (C-3) ppm; ir (potassium bromide): 3060-2990 (Ar CH, m), 2960-2840 (aliph. CH, m), 1710 (CO, s), 1680 (C=O, s), 1600 (C=N, m), 1498 (C=C, m), 1450 (m), 922 (m) cm⁻¹; uv (CH₃CN) λ_{max} nm (log ϵ) 390 (3.82). MS (electron impact, 70 eV): m/z (%) 384 ([M⁺], 100), 368 (20), 306 (34), 292 (36), 278 (40), 196 (18), 170 (26), 105 (64), 91 (38), 56 (60). *Anal.* Calcd. for C₂₂H₁₆N₄O₃ (384.40): C, 68.74; H, 4.20; N, 14.58. Found: C, 68.69; H, 4.30; N, 14.50.

Methyl 8-benzoyl-1-methyl-3,7-dioxo-1-phenyl-2,3,7,8-tetrahydro-1H-pyrazolo-[3',4':4,5]pyrrolo-[1,2-a]-pyrimidine-5-carboxylate (14) was obtained as pale brown crystals (0.83 g, 90%), mp 202 °C (methanol); ^1H nmr (dimethyl sulfoxide- d_6): δ 3.36 (3 H, s, NCH₃), 3.98 (3 H, s, CH₃-ester), 7.10-7.30 (6 H, m, Ph H), 7.40 (1 H, s, 6-H), 7.60-7.64 (2 H, m), 7.70-7.74 (2 H, m,

CO-Ph CH₂'), 7.90 (1 H, s, 9-H) ppm; ¹³C nmr (dimethyl sulfoxide-d₆): δ 39.4 (NCH₃), 51.0 (CH₃-ester), 124.0 (C-9a), 127.0 (C-8a), 127.4 (CH-6), 127.6, 127.8 (Ph-CH, CH-4'), 128.4 (CH-9), 128.0, 128.4, 128.6, 128.8 (2 Ph CH), 130.6 (Ph C-CO), 132.0 (C-3a), 139.8 (N-Ph C), 142.0 (C-5), 162.0 (C-7), 164.0 (benzoyl-CO), 166.0 (CO ester), 170.6 (C-3) ppm; ir (potassium bromide): 3060-2990 (Ar CH, m), 2960-2840 (aliph. CH, m), 1716 (CO, s), 168.0 (C=O, s), 1600 (C=N, m), 1498 (C=C, m), 1450 (m), 922 (m) cm⁻¹; uv (CH₃CN) λ_{max} nm (log ε) 430 (4.24); ms (electron impact, 70 eV): m/z (%) 442 ([M⁺], 100), 410 (18), 365 (40), 366 (60), 245 (38), 228 (66), 186 (44), 119 (44), 105 (82), 91 (38), 77 (62), 56 (46). *Anal.* Calcd. for C₂₂H₁₈N₄O₅ (442.43): C, 65.15; H, 4.10; N, 12.66. Found: C, 65.30, H, 4.10; N, 12.60.

N-[(R)-6-Benzoyl-3,4-diphenyl-3,6-dihydro-[1,3]thiazin-(2Z)-ylidene]-4'-methoxy-benzamide (19a) was obtained as pale brown crystals (0.91 g, 90%), mp 312 °C (ethanol); ¹H nmr (dimethyl sulfoxide-d₆): δ 3.94 (3 H, s, OCH₃), 4.80 (1 H, d, J = 11.5 Hz, H-6), 6.30 (1 H, d, J = 11.4 Hz, H-5), 6.70 (2 H, dd, J = 8.0, 1.2 Hz), 6.90 (2 H, dd, J = 8.2, 1.4 Hz), 7.00-7.20 (5 H, m), 7.30-7.35 (1 H, m), 7.45-7.64 (7 H, m), 7.80 (2 H, dd, J = 8.2, 1.4 Hz) ppm; ¹³C nmr (dimethyl sulfoxide-d₆): δ 44.4 (CH-6), 54.0 (OCH₃), 100.0 (CH-5), 115.0 (N-Ph 2 CH₂'), 116.2 (CH₃OPh 2CH₂'), 118.8 (N-Ph CH₄'), 126.0, 126.6 (Ph CH CH₄'), 127.4, 128.0, 128.2, 128.6, 129.4 (Ph 2CH), 132.0, 134.6 (Ph C), 135.6 (CH₃OPh-2 CH₃'), 136.8 (Ph C-CO), 142.6 (C-4), 144.2 (N-Ph C), 160.8 (CH₃O-Ph C), 162.8 (C=N, C-2), 168.0 (N-C=O), 180.0 (COPh) ppm; ir (potassium bromide): 3072-2980 (Ar CH, m), 2970-2880 (aliph. CH, m), 1700-1690 (C=O, s), 1598 (C=N, m), 1496 (C=C, m), 1452 (m), 920 (m) cm⁻¹; uv (CH₃CN) nm λ_{max} nm (log ε) 420 (3.83); ms (electron impact, 70 eV): m/z (%) 504 ([M⁺], 30), 398 (12), 324 (10), 310 (12), 105 (100), 99 (24), 57 (16). *Anal.* Calcd. for C₃₁H₂₄N₂O₃S (504.61): C 73.79, H 4.79, N 5.55, S 6.35. Found C, 73.86; H, 4.80; N, 5.50; S, 6.35.

N-(R)-6-Benzoyl-3,4-diphenyl-3,6-dihydro-[1,3]thiazin-(2Z)-ylidene]-4'-methyl-benzamide (19b) was obtained as pale brown crystals (0.83 g, 85%), mp 330 °C (ethyl acetate); ¹H NMR (dimethyl sulfoxide-d₆): δ 3.38 (3 H, s, CH₃), 4.72 (1 H, d, J 13.7 Hz), 5.45 (1 H, d, J = 13.8 Hz), 6.60 (2 H, dd, J = 8.2, 1.2 Hz), 6.95-7.25 (8 H, m), 7.30-7.70 (9 H, m) ppm; ¹³C NMR (dimethyl sulfoxide-d₆): δ 32.8 (CH₃), 44.0 (CH-6), 92.6 (CH-5), 114.8 (N-Ph 2 CH₂'), 118.4 (N-Ph CH₄'), 126.0, 126.6 (Ph CH CH₄'), 127.2, 127.6, 128.0, 128.2, 128.4, 128.6, 128.8 (Ph 2CH), 132.2, 132.6 (Ph C), 134.8 (CH₃Ph C), 136.6 (Ph C-CO), 142.4 (C-4), 143.8 (N-Ph C), 162.2 (C=N, C-2), 166.8 (N-C=O), 179.5 (COPh) ppm; ir (potassium bromide): 3060-2990 (Ar CH, m), 2980-2886 (aliph. CH, m), 1700-1692 (C=O, s), 1595 (C=N, s), 1496 (C=C, m), 920 (m) cm⁻¹; uv (CH₃CN) λ_{max} nm (log ε) 416 (3.6); ms (electron impact, 70 eV): m/z (%) 488 ([M⁺], 28), 472 (20), 396 (40), 368 (24), 324 (20), 312 (24), 172 (24), 108 (38), 91 (30), 77 (100). *Anal.* Calcd. for C₃₁H₂₄N₂O₃S (488.61): C, 76.20; H, 4.95; N, 5.73; S, 6.56. Found C, 76.00; H, 4.90; N, 5.70; S, 6.50.

N-[(R)-6-Benzoyl-3,4-diphenyl-3,6-dihydro-[1,3]thiazin-(2Z)-ylidene]-benzamide (19c) was obtained as pale brown crystals (0.74 g, 80%), mp 320 °C (acetone). ¹H nmr (dimethyl sulfoxide-d₆): δ 4.70 (1 H, d, J = 13.8 Hz), 5.50 (1 H, d, J = 13.8 Hz), 6.62 (2 H, dd, J = 8.2, 1.2 Hz), 6.95-7.25 (8 H, m), 7.30-7.70 (9 H, m) ppm; ¹³C nmr (dimethyl sulfoxide-d₆): δ 44.2 (CH-6), 92.2 (CH-5), 115.2 (N-Ph 2 CH₂'), 118.0 (N-Ph CH₄'), 125.8, 126.2, 126.8 (Ph CH 4'), 127.4, 128.2, 128.6, 129.0, 129.6, 130.2, 131.0 (Ph 2CH), 132.4, 132.8 (Ph C), 136.3 (Ph C-

CO), 142.0 (C-4), 143.4 (N-Ph C), 162.0 (C=N, C-2), 166.6 (N-C=O), 179.2 (COPh) ppm; ir (potassium bromide): 3080-2996 (Ar CH, m), 1696-1690 (C=O, s), 1600 (C=N, s), 1500 (C=C, w), 918 (s) cm⁻¹; uv (CH₃CN) λ_{max} (log ε) 410 (3.4); ms (electron impact, 70 eV): m/z (%) 474 ([M⁺], 32), 396 (38), 368 (34), 264 (34), 186 (20), 105 (100), 91 (24), 77 (60). *Anal.* Calcd. for C₃₀H₂₂N₂O₂S (474.59): C, 75.93; H, 4.67; N, 5.90; S, 6.76. Found C, 76.10; H, 4.70; N, 5.82; S, 6.72.

N-[(R)-6-Benzoyl-3-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-4-phenyl-3,6-dihydro-[1,3]thiazin-(2Z)-ylidene]-4-methyl-benzamide (19d) was obtained as pale brown crystals (1.0 g, 87%), mp 342 °C (acetone); ¹H nmr (dimethyl sulfoxide-d₆): δ 1.68 (3 H, s, pyrazole CH₃), 2.50 (3 H, s, N-pyrazole CH₃), 4.68 (1 H, d, J = 13.8 Hz), 5.40 (1 H, d, J = 13.9 Hz), 6.70 (2 H, dd, J = 8.0, 1.2 Hz, N-pyrazole-Ph 2CH 2'), 6.95-7.60 (10 H, m), 7.80-7.98 (8 H, m) ppm; ¹³C nmr (dimethyl sulfoxide-d₆): δ 15.7 (CH₃ pyrazole), 35.8 (CH₃-N pyrazole), 45.2 (CH-6), 93.0 (CH-5), 106.0 (pyrazole C-4), 114.2 (N pyrazole Ph 2CH₂'), 118.0 (N pyrazole-PhCH 4'), 126.8, 127.0, 127.2 (PhCH 4'), 127.6, 128.0, 128.4, 128.6, 129.0, 129.6, 130.2 (Ph 2 CH), 130.8 (pyrazole C-3), 132.4, 132.8 (Ph C), 136.3 (Ph C-CO), 142.0 (C-4), 143.4 (N-Ph C), 160.0 (pyrazole CO), 162.0 (C=N, C-2), 166.6 (N-C=O), 179.2 (COPh) ppm; ir (potassium bromide): 3080-2994 (Ar CH, m), 2990-2894 (aliph. CH, m), 1706-1692 (C=O, s), 1600 (C=N, s), 1500 (C=C, s), 918 (s) cm⁻¹; uv (CH₃CN) λ_{max} nm (log ε) 435 (3.81); ms (electron impact, 70 eV): m/z (%) 584 ([M⁺], 40), 568 (14), 554 (16), 506 (18), 478 (42), 402 (24), 396 (30), 296 (30), 186 (20), 105 (100), 91 (24), 77 (54). *Anal.* Calcd. for C₃₅H₂₈N₄O₃S (584.70): C, 71.90; H, 4.83; N, 9.58; S, 5.48. Found C, 72.10; H, 4.80; N, 9.50; S, 5.40.

REFERENCES

- [1] Hartung, J.; Rosenbaum, K.; Beyer, L.; Losade, J.; Fernandez, V. *J. Prakt. Chem.* **1991**, 333, 557.
- [2] Zeng, R.-S.; Zou, J.-P.; Zhi, S.-J.; Chen, J.; Qi Shen, *Org. Lett.* **2003**, 5, 1657.
- [3] Manaka, A.; Ishii, T.; Takahashi, K. *Tetrahedron Lett.* **2005**, 46, 419.
- [4] Kodomari, M.; Suzuki, M.; Tanigawa, K.; Aoyama, T. *Tetrahedron Lett.* **2005**, 46, 5841.
- [5] Hartmann, H.; Liebscher, J.; Czerney, P. *Tetrahedron* **1985**, 41, 5371.
- [6] a) Aly, A. A.; Ahmed, E. K.; El-Mokadam, K. M. *J. Sulf. Chem.* **2006**, 27, 419; b) For a review on update survey on aroyl substituted thioureas and their applications. Aly, A. A.; Ahmed, E. K.; El-Mokadam, K. M.; Hegazy, M. El.-A. **2007**, *ibid.* 28, 737.
- [7] Aly, A. A.; Ahmed, E. K.; El-Mokadam, K. M. *J. Sulf. Chem.* **2007**, 28, 285.
- [8] Agarwal, S. K.; Saxena, A. K.; Jain, P. C.; Sur, R. N.; Srimal, R. C.; Dhawan, B. N.; Anand, N. *Indian J. Chem.* **1987**, 26B, 642.
- [9] Kihara, Y.; Kabashima, S.; Uno, K.; Okawara, T.; Yamasaki, T.; Furukawa, M. *Synthesis* **1970**, 1020.
- [10] a) Kuznetsov, Y. V.; Dzardanov, D. V.; Polunin, E. V. and b) Danilkina, N. A.; Mikhailov, L. E.; Ivin, B. A. In the 3rd Euro-Asian Heterocyclic Meeting "Heterocycles in Organic and Combinatorial Chemistry" (EAHM-2004) September 12-17, **2004**, Novosibirsk, Russia.
- [11] a) Aly, A. A. *Org. Biomol. Chem.* **2003**, 1, 756; b) Aly, A. A. *Tetrahedron* **2003**, 59, 1739; c) Aly, A. A.; Ehrhardt, S.; Hopf, H.; Dix, I.; Jones, P. G. *Eur. J. Org. Chem.* **2006**, 335; d) Hopf, H.; Aly, A. A.; Swaminathan, V. N.; Ernst, L.; Dix, I.; Jones, P. G. *Eur. J. Org. Chem.* **2005**, 68; e) Aly, A. A.; Hopf, H.; Ernst, L.; Dix, I.; Jones, P. G. *Eur. J. Org. Chem.* **2006**, 3001; f) Aly, A. A.; Hopf, H.; Dix, I.; Jones, P. G.

Tetrahedron **2006**, *62*, 4498.

[12] Bakulev, V. A.; Berseneva, V. S.; Belskaia, N. P.; Morzherin, Yu.; Zaitsev, A.; Dehaen, W.; Luyten, I.; Toppet, S. *Russia. Org. & Biomol. Chem.* **2003**, *1*, 134.

[13] Notzel, M. W.; Labahn, T.; Es-Sayed, M.; De Meijere, A. *Eur. J. Org. Chem.* **2001**, 3025.

[14] Brindley, J. C.; Caldwell, J. M.; Meakins, G. D.; Plackett, S. J. Price, *J. Chem. Soc. Perkin Trans I*, **1987**, 1153.

[15] Allinger, N. L. PM3 (91) force field Program, obtained from Quantum Chemistry Program, Indiana University; Molecular Mechanics PM3 Program (ACD/3D), Advanced Chemical Development Inc., Toronto, Canada, 1988.