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RESEARCH ARTICLE

Oxidation of aroylthioureas during their reactions with 2,3-diphenylcyclopropenone resulting in (*E/Z*)-3-(aroylthioureido)-2-phenylcinnamic acids

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Isolated (*E/Z*)-3-(aroylthioureido)-2-phenylcinnamic acids have been obtained from the reactions of *N*-substituted-aroylthioureas with 2,3-diphenylcyclopropenone in acetic acid. The abnormal behavior of the reaction was described as due to nucleophilic addition of N^3 followed by hydrolysis, ring opening and oxidation processes.

Keywords: 2,3-Diphenylcyclopropenone; *N*-Substituted-aroylthioureas; (*E*/*Z*)-3-(Aroylthioureido)-2-phenylcinnamic acids

1. Introduction

Derivatives of aryl-disubstituted ureas and thioureas provide a rich source of candidates for development as agrochemical and pharmaceutical products [1–8]. *N*,*N*-Disubstituted thiourea derivatives are also known of potential biological interest, they exhibit a broad spectrum of biological activities including antifungal, insectidical, fungicide, antibacterial and herbicidal properties [9]. In light of the importance of substituted thioureas and their tendencies, which are variable from one reagent to another, we have recently reported on the chemistry of this class of compounds along with their wide and interesting applications [10]. Recently, we have also demonstrated on a very convenient procedure to synthesize of the fused 1,3-thiazoles **3a**–**i** (figure 1) from the reaction of aroylphenylthioureas **1a**–**c** with π-acceptor quinones (CHL-*p*, DDQ and DCHNQ, **2a**–**c**) [11].

Cyclopropenones are known for their reactivity toward dipolar reagents and compounds having a reactive π-system [12]. We have long-term experience in the field of heterocyclic synthesis including 1*H*-1,2,4-triazoles [13], pyridoxazines, benzoxa-(thia)azines and benzoxa-(thia)-azepines [14], 5-benzyl-1*H*-tetrazols [15], 1,4(*H*)-benzoxazepine-2-ones and their *N*-phenyl derivatives [16]. The advantages of our mode of synthesis are the reasonable yields, and the ease with which the reaction can be carried out as a one-pot procedure

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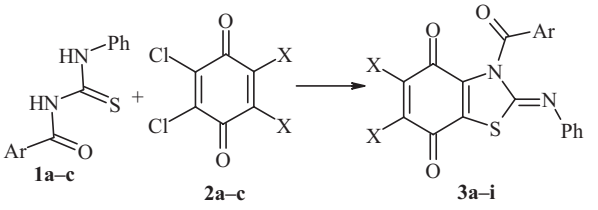


3	X	Yield(%)
a	Cl	70
b	Cl	65
c	Cl	60
d	CN	68
e	CN	65
f	CN	63
g	-CH=CH-CH=CH-	78
h	-CH=CH-CH=CH-	74
i	-CH=CH-CH=CH-	70

Figure 1. Synthesis of fused 1,3-thiazoles.

with readily available starting materials. Recently, we have developed a method for the synthesis of substituted amino-1,2,4-triazolo[4,3-*b*]pyridazine-6-thiones from the reactions of thiosemicarbazides with 2,3-diphenylcyclopropenone [17]. The reaction mechanism was described as *via* [3 + 3]cycloaddition followed by intramolecular rearrangement processess [17]. Herein we present our results of the reaction of 2,3-diphenylcyclopropenone with *N*-substituted-aroylthioureas with emphasis on synthetic and mechanistic implications.

2. Results and discussion

It is known that pyrazolones have proven widespread biological and pharmaceutical applications [18], whereas 1,3-thiazole moiety is considered as a crucial part of vitamin B1 (thiamine) and epothilone [19]. Therefore, it can be anticipated that including pyrazolone and 1,3-thiazole molecules in the structure of aroylthioureas might increase their prospective biological activities. From the aforementioned, we synthesized the aroylthioureas **1d**,**e** utilized by the reaction of benzoyl isothiocyanate with the corresponding amines (4-aminopyrazolone and 2-amino-1,3-thiazole) and fellow up the same methodology mentioned in literature [20].

The structure of thioureas **1d**,**e** was confirmed by ^{1}H NMR, ^{13}C NMR, mass and IR spectra as well as elemental analyses. It is pointed that the ^{1}H NMR spectrum of **1e** showed H-5 as a doublet at $\delta_H = 5.60$ ($J = 7.5$ Hz) and deshielding resulting from the resonance sequence between N^1 lone pair and the thiazole ring (figure 2). Moreover, it is expected that the NH proton (N^1) attached directly to the pyrazolone and/or thiazole molecule appeared more shielded ($\delta_H = 11.71$ and 11.80 in **1d** and **1e**, respectively) compared with the other NH

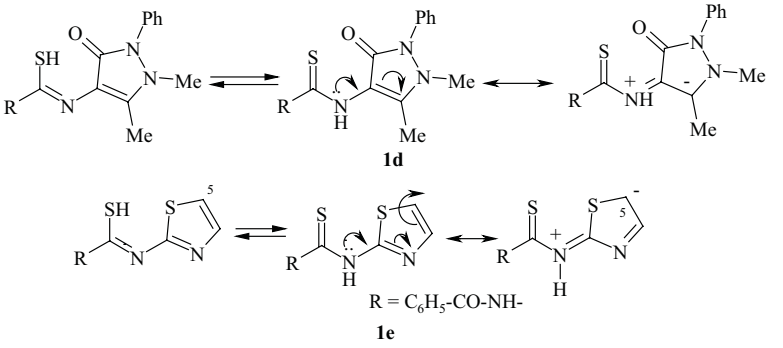
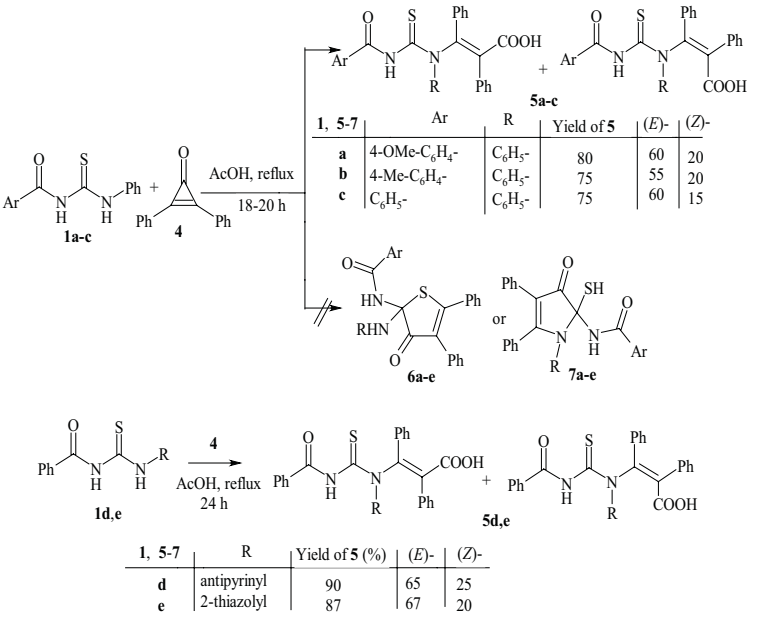


Figure 2. New benzoyl thioureas **1d**, **e** and their resonance structures.



1, 5-7	Ar	R	Yield of 5	(*E*)-	(*Z*)-
a	4-OMe-C_6H_4-	C_6H_5-	80	60	20
b	4-Me-C_6H_4-	C_6H_5-	75	55	20
c	C_6H_5-	C_6H_5-	75	60	15

1, 5-7	R	Yield of 5 (%)	(*E*)-	(*Z*)-
d	antipyrinyl	90	65	25
e	2-thiazolyl	87	67	20

SCHEME 1 Reaction of substituted-aroylthioureas **1a**-**e** with 2,3-diphenylcyclopropenone (**4**)

proton attached to the benzoyl group (N^3) which might be due to the mutual donating resonance between the N^1 and the attached ring system (figure 2).

Scheme 1 outlines the formation of (*E*/*Z*)-3-(aroylthioureido)-2-phenylcinnamic acids **5a**–**e** during the reaction of 2,3-diphenylcyclopropenone (**4**) with *N*-substituted aroylthioureas **1a**–**e** in acetic acid at reflux. The (*E*)- and (*Z*)-forms of **5a**–**e** were chromatographically separated. In particular, the spectral data including the IR, NMR and mass spectra as well as the elemental analyses of **5a**–**e** proved the presence of the skeleton structure of Ar-CO-NH-CS-N(R) (scheme 1). For example, the IR spectrum of **5a** (*E*- or *Z*- forms) showed absorption, as a strong band, related to the respective appearance of the carbonyl of amide and carboxylic groups around ν_{max}/cm^{-1}: 1700–1680. Additionally, a broad medium peak around 3500–3320 cm^{-1} corresponds to the absorptions of the OH and NH groups. The stretching vibration of the thione group appeared in the IR spectrum of **5a** as a stronger absorption broad band at ν_{max} 1265–1260 cm^{-1}.

In the ^{1}H NMR spectrum of **5a**, **t**he NH proton was strongly shielded compared with its δ value of the starting material **1a** and appeared at $\delta_H = 9.40$–9.30 (see the Experimental section), however the other NH proton (N^1) in **5a** has disappeared. The ^{13}C NMR spectrum of each isomer in **5a** indicated the presence of the thione carbon signal at $\delta_H = 180.9$ (for *E*-form) and 181.4 (for *Z*-form). The ^{1}H NMR spectrum of **5a** (*E* and *Z*) confirmed the presence of the carboxylic proton as a singlet at $\delta_H = 10.20$–10.00. Moreover the ^{13}C NMR spectrum of **5a** showed two characteristic carbon signals at $\delta_C = 101.4$ and 152.4 assigned to the vinylic C-2 and C-3, respectively. On the basis that stereoisomerism is a key issue in the study of biological molecules and is potentially useful in the development of drugs. More than any other spectroscopic technique, NMR methods have aided the study of conformation of organic and biological molecules. In both cases, analysis of NMR coupling constants, NOE, and integration can be incisive [21]. Therefore the study of the NMR spectroscopic data of each isomer (*E*- or *Z*-) in compounds **5a**–**e** is of considerable interest (see the Experimental section), whereby conclusive evidence for the proposed structure of compounds **5a**–**e** was obtained from

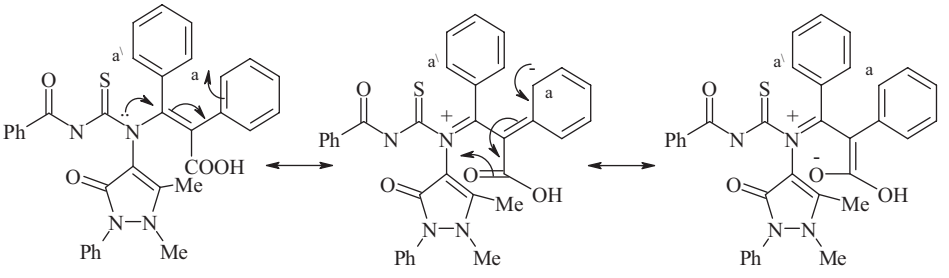


Figure 3. Resonance structures of compound (*Z*)-**5d**.

their NOE experiments. The resonance stabilization between the nitrogen lone-pair and the adjacent π-bond in the two benzene rings enhances their *ortho*-protons to be the most shielded aromatic protons. Consequently, the ^{1}H NMR spectra of **5a–e** revealed two shielded *ortho*-protons of the phenyl groups on the vinylic C-2 and C-3 carbons (see the Experimental section). Accordingly, the NOE experiment of (*Z*)-**5a–e** saturated with H-a causes enhancement to H-a′ (see figure 3), however, the former enhancement disappeared in the case of (*E*)-**5a–e**.

As an example, the resonance structures of (*Z*(-**5d** (figure 3) indicated the respective appearance of H-a and H-a′ as two double-doublets at $\delta_H = 7.00$ and 7.30 ($J = 8.0$, 2.0 Hz). The NOE experiment of (*Z*)-**5d** saturated with H-a causes a medium enhancement to H-a′. Moreover, irradiation of the methyl protons of the pyrazole moiety caused enhancement to the carboxylic protons. However and in the case of (*E*)-**5d**, irradiation of the methyl-pyrazole did not affect the carboxylic proton. The chemical shifts (δ_H and δ_C) of some distinctive protons and carbons of compounds **5d** and **5e** are shown in tables 1 and 2. The spectroscopic data confirmed that we have, in hand, compounds **5a–e** and excluded any other suggestions such as the formation of compounds **6a–e** and **7a–e** (scheme 1). The yields of the (*E*)-forms of **5a–e** predominated over those of their (*Z*)-forms (scheme 1, see also the Experimental section).

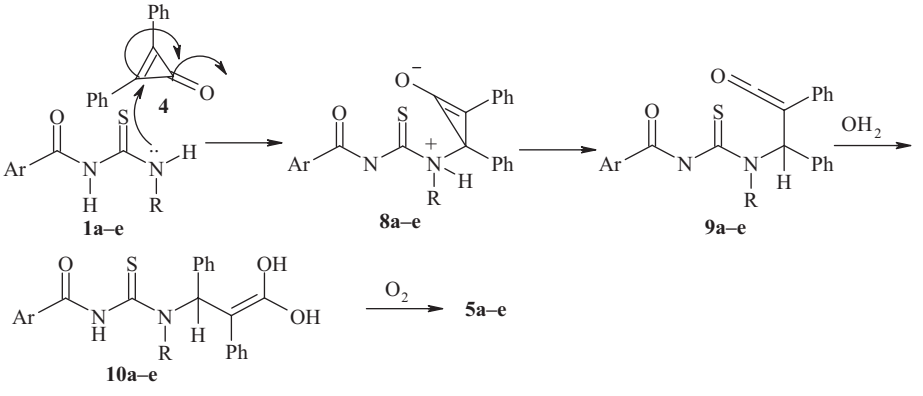
From a mechanistic viewpoint, the formation of **5a–e** may be visualized as occurring through attack of the nitrogen nucleophile N^1 lone pair in **1a–e** at either C-2 or C-3 of **4** to give salts **8a–e** (scheme 2). The intermediate in the case of **8a–e** is capable of creating the corresponding ketenes **9a–e** [22], which on nucleophilic addition of a water molecule gave **10a–e** (scheme 2). Subsequently, we suggested aerial oxidation process would occur to **10a–e** to give the

Table 1. Some distinctive δ values of ^{1}H- and ^{13}C-NMR spectra of compounds (*E*)- and (*Z*)-**5d**.

Compd.	Distinctive protons and carbons	δ_H	δ_C	Compd.	δ_H	δ_C
(***E***)-**5d**	- pyrazol-CH_3	2.10	11.3	(***Z***)-**5d**	2.00	10.9
	- pyrazol-*N*-CH_3	3.30	34.4		3.20	34.0
	- H-a′	7.00			7.14	
	- H-a	7.30			7.28	
	- CONH	10.50	166.8		10.60	166.4
	- COOH	10.80	169.2		11.00	169.6
	- pyrazol-C-3		107.8			108.4
	- vinylic-C-2		102.0			102.4
	- vinylic-C-3		152.2			151.8
	- pyrazol-Ph-CH, (CH-4′)		124.2			124.8
	- pyrazol-C-4		138.6			138.2
	- pyrazol-Ph-C-N		152.8			152.6
	- pyrazol-C=O		178.2			178.8
	- C=S		180.0			180.8

Table 2. Some distinctive δ values of ^{1}H- and ^{13}C-NMR spectra of compounds (*E*)- and (*Z*)-**5e**.

Compd.	Distinctive protons and carbons	δ_H	δ_C	Compd.	δ_H	δ_C
(***E***)-**5e**	- H-a′	7.20		(**Z**)-**5e**	7.22	
	- H-a	7.40			7.34	
	- CONH	9.80	169.8		9.90	169.8
	- COOH	10.50	170.6		11.20	170.2
	- thaizole-CH-5	5.80	120.9		5.94	121.0
	- thiazol-CH-4	6.85	128.4		6.90	128.6
	- vinylic-C-2		102.8			102.2
	- vinylic-C-3		153.0			151.0
	- thiazol-C-2		156.8			156.9
	- C=S		180.6			180.0



SCHEME 2 Mechanistic pathways of the reactions between **1a–e** and **4**

stable products **5a–e** (scheme 2). Eicher *et al.* have isolated oxidative products as a result of aerial oxidation process during the reaction of benzylidene azines with **4** [23]. More conclusive evidence of an aerial oxidation process during the reaction of compounds having amino functional group with **4** was also supported by literature [24]. Ambiphilic molecules such as **9a–e** are readily prepared *in situ* during the reaction of diphenylcyclopropenone with Lewis acids [25]. It was reported that compounds having thioamide functional group normally selectively add on the C-2 (or C-3) of **4** [22, 26]. In conclusion, *N*-substituted-aroylthioureas were selectively added to 2,3-diphenylcyclopropenone *via* nucleophilic addition followed by an oxidation process.

3. Experimental section

3.1 *General consideration*

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra (Bruker AM 400, ^{1}H: 400.13 MHz, ^{13}C: 100.6 MHz) were obtained from DMSO-d_6 solutions. Coupling constants are expressed in Hz. Elemental analyses were carried at the Assuit Microanalysis Center of Assuit 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 KBr pellets.

3.2 *Starting materials*

Aroylthioureas **1a–c** were prepared from 3 mmols of the starting materials according to the reported literature [20]. On the other side, thioureas **1d**,**e** were prepared from the reaction of benzoyl isothiocyanate with 4-aminopyrazolone (4-aminoantipyrine) and/or 2-amino-1,3-thiazole, respectively and followed up the same methodology as mentioned in literature [20]. The former heterocyclic amines were bought from Fluka. The corresponding acid chlorides were distilled. The physical and spectroscopic data of compounds **1d**,**e** are as following.

3.2.1 1-Benzoyl-3-(1′,5′-dimethyl-3′-oxo-2′-phenyl-2′,3′-dihydro-1′H-pyrazol-4′-yl)-thiourea (1d). Was obtained as yellow crystals (1.0 g, 90%), mp 320 °C (ethanol). δ_H (400 MHz, $CDCl_3$): 2.22 (3 H, s, CH_3), 3.12 (3 H, s, NCH_3), 7.34–7.44 (3 H, m, Ph-H), 7.50–7.56 (4 H, m, Ph-H), 7.64–7.66 (1 H, m, Ph-H), 7.97–8.10 (2 H, m, Ph-H), 11.58 (1 H, br, s, 1 NH, N^1), 11.71 (1 H, br s, 1 NH, N^3). δ_C (100.6 MHz, $CDCl_3$): $\delta = 11.5$ (CH_3), 35.6 (NCH_3), 108.3 (pyrazol-C-3), 123.8 (Ph-CH, CH-4′), 126.5, 128.4, 128.6, 129.1 (2 Ph-CH), 133.1 (pyrazol-Ph-CH), 134.9 (Ph-C), 138.4 (pyrazol-C-4), 153.0 (pyrazol-Ph-C-N), 166.3 (NH-C=O), 171.6 (C=O), 182.1 (C=S). ν_{max} (cm^{-1}): 3380 (m, NH), 3040–2990 (w, Ar-CH), 2950–2870 (m, aliph.-CH), 1660 (s, C=O), 1600 (s, C=N), 1490 (m, C=C), 1450 (s), 1240 (s, C=S), 920 (m). λ_{max} (CH_3CN, nm, lg ε): 400 (3.6). EI + mass spectrum (m/z, %): 366 ([M^+], 100), 352 (30), 336 (20), 288 (34), 260 (42), 256 (16), 194 (20), 136 (18), 105 (38), 77 (20). C, H, N (%): found C, 62.34; H, 4.92; N, 15.34; S, 8.72. $C_{19}H_{18}N_4O_2S$ (366.44): requires C, 62.28, H 4.95, N 15.29, S, 8.75.

3.2.2 1-Benzoyl-3-(1′,3′-thiazol-2-yl)-thiourea (1e). Was obtained as yellow crystals (0.68 g, 86%), mp 340 °C (ethanol).

δ_H (400 MHz, $CDCl_3$): 5.60 (1 H, d, thiazol-H-5, $J = 7.5$ Hz), 6.60 (d, 1 H, thiazol-H-4, $J = 7.6$ Hz), 7.10–7.30 (5 H, m, Ph-H), 11.30 (1 H, br, s, 1 NH, N^1), 11.80 (1 H, br s, 1 NH, N^3). δ_C (100.6 MHz, $CDCl_3$): $\delta = 120.8$ (thiazole-CH-5), 126.8 (Ph-CH, CH-4′), 127.2 (thiazole-CH-4), 128.0, 128.4 (2 Ph-H), 134.8 (Ph-C), 159.0 (thiazole-C-2), 164.0 (NH-C=O), 180.8 (C=S). ν_{max} (cm^{-1}): 3400–3380 (m, NH), 3080–3030 (m, Ar-CH), 1665 (s, C=O), 1608 (s, C=N), 1592 (s, C=C), 1448 (s), 1260 (s, C=S), 920 (s). λ_{max} (CH_3CN, nm, lg ε): 415 (3.8). EI + mass spectrum (m/z, %): m/z (%) 264 ([M + 1], 30), 263 ([M^+], 100), 186 (30), 180 (24), 158 (24), 142 (34), 105 (20), 77 (30). C, H, N (%): found C, 50.00; H, 3.40; N, 15.90; S, 24.30. $C_{11}H_9N_3OS_2$ (263.34): requires C, 50.17, H, 3.44; N, 15.96; S, 24.35.

3.3 *Reaction of 1a–e with 4*

3.3.1 General procedure. In a 250 cm^3 two-necked round flask, glacial acetic acid (50 mL) and a mixture of **1a–e** (2 mmol) and **4** (412 mg, 2 mmol) was placed. The mixture was gently refluxed under stirring for 20–24 h (the reaction was monitored by TLC analyses). The solvent was evaporated under vacuum and the formed solid product was dissolved in acetone (10–30 mL) and subjected to preparative plates chromatography (silica gel) using toluene to provide the crude products of the (*E*)-forms of **5a–e** which was separated as the fastest migrating zones, whereas the (*Z*)-form as the slowest zones. The obtainable products **5a–e** were recrystallized from the stated solvents.

(E)-3-[3-(4′-Methoxybenzoyl)-1-phenyl-thioureido]-2,3-diphenylcinnamic acid (***E***)-**5a** was obtained as yellow crystals (0.61 g, 60%), mp 238 °C (ethanol).

δ_H (400 MHz, $CDCl_3$): 3.85 (3 H, s, OCH_3), 6.56 (2 H, dd, J = 8.2, 1.4 Hz, MeOPhH-3′), 7.00 (2 H, dd, J = 8.0, 2.0 Hz, Ph-H-2), 7.20 (2 H, dd, J = 8.0, 2.0 Hz, Ph-H-2′), 7.38–7.50 (7 H, m, Ph-H), 7.60–7.70 (4 H, m, Ph-H), 7.95 (2 H, 2 H, dd, J = 8.0, 1.2 Hz, Ar-H), 9.30 (1 H, s, NH), 10.00 (1 H, s, COOH). δ_C (100.6 MHz, $CDCl_3$): δ = 51.0 (OCH_3), 101.4 (C-2), 125.6, 126.0, 126.8 (Ph-CH, CH-4′), 127.2, 127.8, 128.0, 128.7, 130.2, 130.4, 130.8 (2 Ar-CH), 132.6, 133.0, 133.2 (Ph-C), 133.6 (2 Ar-CH), 139.0 (Ph-C-N), 150.0 (Ar-C-OCH_3), 152.4 (C-3), 168.0 (NH-C=O), 170.6 (COOH), 180.9 (C=S). ν_{max} (cm^{-1}): 3490–3320 (m, OH, NH), 3040–2980 (w, Ar-CH), 2950–2870 (m, aliph.-CH), 1700–1680 (s, C=O), 1592 (s, C=N), 1590 (m, C=C), 1290 (m, C-O), 1265 (s, C=S), 920 (m). λ_{max} (CH_3CN, nm, lg ε): 420 (3.9). EI + mass spectrum (m/z, %): 509 ([M + 1], 20), 508 ([M^+], 100), 490 (24), 477 (18), 400 (30), 372 (54), 300 (18), 223 (16), 152 (14), 136 (20), 129 (18), 91 (22), 77 (30). C, H, N (%): found C, 70.80, H, 4.70, N, 5.42; S, 6.20. $C_{30}H_{24}N_2O_4S$ (508.60): requires C, 70.85; H, 4.76; N, 5.51; S, 6.30.

(Z)-3-[3-(4′-Methoxybenzoyl)-1-phenyl-thioureido]-2,3-diphenylcinnamic acid (**Z**)-**5a** was obtained as yellow crystals (0.20 g, 20%), mp 258 °C (ethanol).

δ_H (400 MHz, $CDCl_3$): 3.87 (3 H, s, OCH_3), 6.60 (2 H, dd, J = 8.2, 1.4 Hz, MeOPhH-3′), 7.08 (2 H, dd, J = 8.0, 2.0 Hz, Ph-H-2), 7.18 (2 H, dd, J = 8.0, 2.0 Hz, Ph-H-2′), 7.32–7.60 (11 H, m, Ph-H), 8.00 (2 H, 2 H, dd, J = 8.2, 1.2 Hz, Ar-H), 9.40 (1 H, s, NH), 10.20 (1 H, s, COOH). δ_C (100.6 MHz, $CDCl_3$): δ = 51.4 (OCH_3), 101.0 (C-2), 125.0, 126.2, 126.8 (Ph-CH, CH-4′), 127.0, 127.6, 128.0, 128.6, 130.2, 130.6, 131.0 (2 Ar-CH), 132.4, 132.8, 133.1 (Ph-C), 133.4 (2 Ar-CH), 139.2 (Ph-C-N), 150.2 (Ar-C-OCH_3), 152.0 (C-3), 168.4 (NH-C=O), 172.0 (COOH), 181.4 (C=S). ν_{max} (cm^{-1}): 3500–3330 (m, OH, NH), 3060–2990 (w, Ar-CH), 2960–2880 (m, aliph.-CH), 1698–1680 (s, C=O), 1596 (s, C=N), 1595 (m, C=C), 1450 (s), 1300 (m, C-O), 1260 (s, C=S), 780 (m). λ_{max} (CH_3CN, nm, lg ε): 428 (4.1). EI + mass spectrum (m/z, %): 508 ([M^+], 100), 490 (22), 477 (20), 400 (34), 372 (50), 300 (24), 223 (18), 152 (48), 136 (24), 91 (22), 77 (40). C, H, N (%): found C, 70.78, H, 4.72, N, 5.50; S, 6.24. $C_{30}H_{24}N_2O_4S$ (508.60): requires C, 70.85; H, 4.76; N, 5.51; S, 6.30.

(E)-3-[3-(4′-Methylbenzoyl)-1-phenyl-thioureido]-2,3-diphenylcinnamic acid (**E**)-**5b** was obtained as yellow crystals (0.54 g, 55%), mp 220 °C (ethanol).

δ_H (400 MHz, $CDCl_3$): 2.38 (3 H, s, CH_3), 7.12 (2 H, dd, J = 8.0, 1.8 Hz, PhH-2), 7.28 (2 H, dd, J = 8.0, 1.8 Hz, Ph-H-2′), 7.35–7.64 (11 H, m, Ph-H), 7.78 (4 H, m, Ph-H), 9.40 (1 H, s, NH), 10.20 (1 H, s, COOH). δ_C (100.6 MHz, $CDCl_3$): δ = 32.8 (CH_3), 101.6 (C-2), 126.0, 126.4, 126.8 (Ph-CH, CH-4′), 127.0, 127.6, 128.0, 128.4, 130.0, 130.4, 130.8, 131.4 (2 Ar-CH), 132.4, 133.2, 133.8, 134.2 (Ph-C), 139.2 (Ph-C-N), 151.2 (C-3), 166.8 (NH-C=O), 172.6 (COOH), 180.2 (C=S). ν_{max} (cm^{-1}): 3490–3340 (m, OH, NH), 3030–2990 (w, Ar-CH), 2960–2830 (m, aliph.-CH), 1700–1684 (s, C=O), 1596 (s, C=N), 1584 (m, C=C), 1430 (s), 1320 (m, C-O), 1260 (s, C=S), 920 (m). λ_{max} (CH_3CN, nm, lg ε): 410 (3.8). EI+mass spectrum (m/z, %): 492 ([M^+], 100), 476 (24), 400 (24), 322 (16), 246 (26), 120 (38), 91 (22), 77 (34). C, H, N (%): found C, 73.00, H, 4.90, N, 5.62; S, 6.50. $C_{30}H_{24}N_2O_3S$ (492.60): requires C, 73.15; H, 4.91; N, 5.69; S, 6.51.

(Z)-3-[3-(4′-Methylbenzoyl)-1-phenyl-thioureido]-2,3-diphenylcinnamic acid (**Z**)-**5b** was obtained as yellow crystals (0.20 g, 20%), mp 216 °C (methanol).

δ_H (400 MHz, $CDCl_3$): 2.36 (3 H, s, CH_3), 7.20 (2 H, dd, J = 8.0, 2.0 Hz, PhH-2), 7.32 (2 H, dd, J = 8.0, 2.0 Hz, PhH-2′), 7.48–7.62 (9 H, m, Ph-H), 7.70–7.82 (4 H, m, Ph-H), 7.68 (2 H, dd, J = 8.2, 1.2 Hz), 9.30 (1 H, s, NH), 10.30 (1 H, s, COOH). δ_C (100.6 MHz, $CDCl_3$): δ = 32.6 (CH_3), 101.4 (C-2), 126.2, 126.6, 127.0 (Ph-CH, CH-4′), 127.4, 127.6, 128.2, 128.8, 130.2, 130.6, 131.2, 131.4 (2 Ar-CH), 132.6, 133.4, 133.8, 134.0 (Ph-C), 139.6 (Ph-C-N), 150.8 (C-3), 168.0 (NH-C=O), 174.0 (COOH), 181.0 (C=S). ν_{max} (cm^{-1}): 3495–3340 (m, OH, NH), 3028–2994 (w, Ar-CH), 2970–2850 (m, aliph.-CH), 1695–1672 (s, C=O), 1600 (s, C=N), 1590 (s, C=C), 1320 (m, C-O), 1262 (m, C=S), 780 (m). λ_{max} (CH_3CN, nm, lg ε): 420 (4.3).

EI + mass spectrum (m/z, %): 492 ([M^+], 100), 476 (24), 400 (24), 322 (16), 246 (26), 120 (38), 91 (22), 77 (34). C, H, N (%): found C, 73.08, H, 4.95, N, 5.66; S, 6.48. $C_{30}H_{24}N_2O_3S$ (492.60): requires C, 73.15; H, 4.91; N, 5.69; S, 6.51.

(E)-3-(3-Benzoyl-1-phenyl-thioureido)-2,3-diphenylcinnamic acid (***E***)-**5c** was obtained as pale yellow crystals (0.57 g, 60%), mp 202 °C (acetone).

δ_H (400 MHz, $CDCl_3$): 7.14 (2 H, dd, $J = 8.0$, 2.0 Hz, PhH-2), 7.28 (2 H, dd, $J = 8.0$, 2.0 Hz, PhH-2′), 7.40–7.60 (9 H, m, Ph-H), 7.68–7.80 (5 H, m, Ph-H), 7.94 (2 H, dd, $J = 8.2$, 1.2 Hz, Ph-H), 9.30 (1 H, s, NH), 10.30 (1 H, s, COOH). δ_C (100.6 MHz, $CDCl_3$): $\delta = 102.0$ (C-2), 126.2, 126.8, 127.2, 127.8 (Ph-CH, CH-4′), 128.0, 128.4, 128.6, 128.8, 130.2, 130.4, 130.8, 131.2 (2 Ar-CH), 132.4, 132.6, 133.2 (Ph-C), 139.0 (Ph-C-N), 150.6 (C-3), 166.0 (NH-C=O), 172.0 (COOH), 180.0 (C=S). ν_{max} (cm^{-1}): 3498–3330 (m, OH, NH), 3028-2990 (w, Ar-CH), 1695–1672 (s, C=O), 1610 (s, C=N), 1590 (m, C=C), 1428 (s), 1310 (m, C-O), 1256 (s, C=S), 920 (s). λ_{max} (CH_3CN, nm, lg ε): 400 (3.6). EI + mass spectrum (m/z, %): 478 ([M^+], 100), 460 (18), 402 (22), 324 (26), 314 (22), 246 (30), 120 (38), 77 (50). C, H, N (%): found C, 72.88, H, 4.62, N, 5.80; S, 6.70. $C_{29}H_{22}N_2O_3S$ (478.57): requires C, 72.78; H, 4.63; N, 5.85; S, 6.70.

(Z)-3-(3-Benzoyl-1-phenyl-thioureido)-2,3-diphenylcinnamic acid (***Z***)-**5c** was obtained as pale yellow crystals (0.14 g, 15%), mp 178 °C (ethyl acetate).

δ_H (400 MHz, $CDCl_3$): 7.12 (2 H, dd, $J = 8.0$, 2.0 Hz, PhH-2), 7.26 (2 H, dd, $J = 8.0$, 2.0 Hz, PhH-2′), 7.36–7.50 (5 H, m, Ph-H), 7.64–7.78 (9 H, m, Ph-H), 7.90 (2 H, dd, $J = 8.2$, 1.2 Hz, PhH), 9.34 (1 H, s, NH), 10.50 (1 H, s, COOH). δ_C (100.6 MHz, $CDCl_3$): $\delta = 102.4$ (C-2), 126.2, 126.6, 127.0, 127.6 (Ph-CH, CH-4′), 128.0, 128.2, 128.4, 128.8, 130.0, 130.2, 130.8, 131.4 (2 Ar-CH), 132.2, 132.6, 133.0 (Ph-C), 139.4 (Ph-C-N), 150.8 (C-3), 166.2 (NH-C=O), 172.6 (COOH), 180.4 (C=S). ν_{max} (cm^{-1}): 3500–3340 (m, OH, NH), 3030–2996 (m, Ar-CH), 1695–1670 (s, C=O), 1608 (C=N), 1594 (s, C=C), 1426 (s), 1295 (m, C-O), 1254 (m, C=S), 780 (m). λ_{max} (CH_3CN, nm, lg ε): 412 (3.8). EI + mass spectrum (m/z, %): 478 ([M^+], 100), 460 (20), 402 (20), 324 (24), 316 (26), 246 (34), 120 (24), 77 (54). C, H, N (%): found C, 72.82, H, 4.60, N, 5.84; S, 6.74. $C_{29}H_{22}N_2O_3S$ (478.57): requires C, 72.78; H, 4.63; N, 5.85; S, 6.70.

3-(3-Benzoyl-1-phenyl-thioureido)-1-(1′,5′-dimethyl-3′-oxo-2′-phenyl-2′,3′-dihydro-1′H-pyrazol-4′-yl)-3-phenylcinnamic acid (***E***)-**5d** was obtained as orange crystals (0.76 g, 65%), mp 312 °C (acetone).

δ_H (400 MHz, $CDCl_3$): 2.10 (3 H, s, pyrazol-CH_3), 3.30 (3 H, s, pyrazol-*N*-CH_3), 7.00 (2 H, dd, $J = 8.0$, 2.0 Hz, PhH-2), 7.30 (2 H, dd, $J = 8.0$, 2.0 Hz, PhH-2′), 7.64–7.96 (9 H, m, Ph-H), 7.20–7.40 (7 H, m, Ph-H), 7.60–7.70 (2 H, m, Ph-H), 7.95 (2 H, dd, $J = 8.1$, 1.2 Hz), 10.50 (1 H, s, NH), 10.80 (1 H, s, COOH). – δ_C (100.6 MHz, $CDCl_3$): $\delta = 11.3$ (CH_3), 34.4 (NCH_3), 102.8 (C-2), 107.8 (pyrazol –C-3), 124.2 (pyrazol -Ph-CH, CH-4′), 126.2, 126.8, 127.2 (Ph-CH, CH-4′), 127.5, 128.0, 128.4, 128.6, 128.8, 129.0, 130.2 (2 Ar-*C*H), 132.4, 132.6, 133.2 (Ph-C), 133.1 (pyrazol-Ph-CH), 138.6 (pyrazol-C-4), 152.2 (C-3), 152.8 (pyrazol-Ph-C-N), 166.8 (NH-C=O), 169.2 (COOH), 178.2 (pyrazol-C=O), 180.0 (C=S). ν_{max} (cm^{-1}): 3498–3330 (m, OH, NH), 3028–2990 (w, Ar-CH), 2970–2850 (m, aliph.-CH), 1700–1672 (br, s, C=O), 1610 (s, C=N), 1590 (m, C=C), 1318 (s, C-O), 1256 (s, C=S), 920 (s). λ_{max} (CH_3CN, nm, lg ε): 430 (4.2). EI + mass spectrum (m/z, %): 589 ([M + 1], 30), 588 ([M^+], 100), 572 (16), 558 (22), 510 (16), 480 (16), 468 (20), 434 (24), 424 (16), 400 (20), 324 (26), 314 (22), 246 (30), 238 (40), 187 (34), 77 (40). C, H, N (%): found C, 69.28, H, 4.74, N, 9.50; S, 5.40. $C_{34}H_{28}N_4O_4S$ (588.69): requires C, 69.37; H, 4.79; N, 9.52; S, 5.45.

(Z)-3-(3-benzoyl-1-phenyl-thioureido)-1-(1′,5′-dimethyl-3′-oxo-2′-phenyl-2′,3′-dihydro-1′H-pyrazol-4′-yl)-3-phenylcinnamic acid (***Z***)-**5d** was obtained as orange crystals (0.29 g, 25%), mp 280 °C (acetone).

δ_H (400 MHz, $CDCl_3$): 2.00 (3 H, s, pyrazol-CH_3), 3.20 (3 H, s, pyrazol-*N*-CH_3), 7.14 (2 H, dd, J = 8.0, 2.0 Hz, PhH-2), 7.28 (2 H, dd, J = 8.0, 2.0 Hz, PhH-2′), 7.38–7.48 (5 H, m, Ph-H), 7.60–7.76 (11 H, m, Ph-H), 10.60 (1 H, s, NH), 11.00 (1 H, s, COOH). δ_C (100.6 MHz, $CDCl_3$): δ = 10.9 (CH_3), 34.0 (NCH_3), 108.4 (pyrazol -C-3), 102.4 (C-2), 124.8 (pyrazol - Ph-CH, CH-4′), 126.0, 126.2, 127.2 (Ph-CH, CH-4′), 127.5, 127.6, 127.8, 128.0, 128.4, 128.6, 130.0 (2 Ar-*C*H), 132.0, 132.2, 133.0 (Ph-C), 133.0 (pyrazol-Ph-CH), 138.2 (pyrazol-C-4), 151.8 (C-3), 152.6 (pyrazol-Ph-C-N), 161.0 (pyrazol-C-4), 166.4 (NH-C=O), 169.6 (COOH), 178.6 (pyrazol-C=O), 180.8 (C=S). ν_{max} (cm^{-1}): 3490–3340 (m, OH, NH), 3030–2990 (w, Ar-CH), 2980–2860 (m, aliph.-CH), 1704–1670 (br, s, C=O), 1608 (s, C=N), 1596 (m, C=C), 1330 (s, C-O), 1250 (s, C=S), 780 (s). λ_{max} (CH_3CN, nm, lg ε): 422 (4.1). EI+mass spectrum (m/z, %): 589 ([M + 1], 30), 588 ([M^+], 100), 572 (16), 558 (22), 510 (16), 480 (16), 468 (20), 434 (24), 424 (16), 400 (20), 324 (26), 314 (22), 246 (30), 238 (40), 187 (34), 77 (40). C, H, N (%): found C, 69.28, H, 4.74, N, 9.50; S, 5.40. $C_{34}H_{28}N_4O_4S$ (588.69): requires C, 69.37; H, 4.79; N, 9.52; S, 5.45.

(E)-3-(3-benzoyl-1-phenyl-thioureido)-3-(1′, 3′-thiazol-2-yl)-thiourea-3-phenylcinnamic acid (***E***)-**5e** was obtained as orange crystals (0.65 g, 67%), mp 312 °C (acetone).

δ_H (400 MHz, $CDCl_3$): 5.80 (1 H, d, thiazol-H-5, J = 6.40 Hz), 6.85 (1 H, d, thiazol H-4, J = 6.40 Hz), 7.20 (2 H, dd, J = 8.0, 2.0 Hz, PhH-2), 7.40 (2 H, dd, J = 8.0, 2.0 Hz, PhH2′), 7.50–7.64 (7 H, m, Ph-H), 7.72–7.80 (5 H, m, Ph-H), 9.80 (1 H, s, NH), 10.50 (1 H, s, COOH). δ_C (100.6 MHz, $CDCl_3$): δ = 102.8 (C-2), 120.9 (thiazole-CH-5), 126.6, 127.0, 127.2 (Ph-CH, CH-4′), 127.8, 127.9, 128.2 (2 Ph-CH), 128.4 (thiazol-CH-4), 129.0, 129.4, 130.0 (2 Ph-CH), 130.6, 130.8 132.0 (Ph-C), 153.0 (C-3), 156.8 (thiazol-C-2), 169.8 (NH-C=O), 170.6 (COOH), 180.6 (C=S). ν_{max} (cm^{-1}): 3498–3330 (m, OH, NH), 3028–2990 (w, Ar-CH), 1695–1672 (s, C=O), 1610 (s, C=N), 1590 (m, C=C), 1320 (s, C-O), 1256 (s, C=S), 920 (s). λ_{max} (CH_3CN, nm, lg ε): 450 (4.6). EI + mass spectrum (m/z, %): 486 ([M^+], 100), 468 (22), 410 (28), 381 (18), 304 (24), 246 (24), 236 (36), 84 (24), 77 (42). C, H, N (%): found C, 64.26, H, 4.10, N, 8.58; S, 13.15. $C_{26}H_{20}N_3O_3S_2$ (486.60): requires C, 64.18; H, 4.14; N, 8.64; S, 13.18.

(Z)-3-(3-benzoyl-1-phenyl-thioureido)-3-(1′,3′-thiazol-2-yl)-thiourea-3-phenylcinnamic acid (***Z***)-**5e** was obtained as orange crystals (0.19 g, 20%), mp 260 °C (acetonitrile).

δ_H (400 MHz, $CDCl_3$): 5.94 (1 H, d, J = 6.20 Hz, thiazol-H-5), 6.80 (1 H, d, thiazol H-4, J = 6.40 Hz), 7.22 (2 H, dd, J = 8.0, 1.8 Hz, PhH-2), 7.34 (2 H, dd, J = 8.0, 2.0 Hz, PhH-2′), 7.56–7.70 (10 H, m, Ph-H), 7.82–7.88 (2 H, m, Ph-H), 9.90 (1 H, s, NH), 11.20 (1 H, s, COOH). δ_C (100.6 MHz, $CDCl_3$): 102.2 (C-2), 121.0 (thiazole-CH-5), 126.6, 127.0, 127.2 (Ph-CH, CH-4′), 127.8, 127.9 (2 Ph-CH), 128.6 (thiazol-CH-4), 128.8, 129.0, 129.4 (2 Ph-CH), 130.0, 130.2 132.0 (Ph-C), 151.0 (C-3), 156.9 (thiazol-C-2), 169.8 (NH-C=O), 170.2 (COOH), 180.0 (C=S). ν_{max} (cm^{-1}): 3500–3330 (m, OH, NH), 3034–2990 (w, Ar-CH), 1695–1672 (s, C=O), 1612 (s, C=N), 1594 (m, C=C), 1326 (s, C-O), 1250 (s, C=S), 780 (s). λ_{max} (CH_3CN, nm, lg ε): 442 (4.5). EI + mass spectrum (m/z, %): 486 ([M^+], 100), 468 (20), 410 (26), 380 (24), 304 (20), 246 (18), 236 (34), 84 (24), 77 (54). C, H, N (%): found C, 64.30, H, 4.12, N, 8.60; S, 13.10. $C_{26}H_{20}N_3O_3S_2$ (486.60): requires C, 64.18; H, 4.14; N, 8.64; S, 13.18.

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