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THE CONDENSATION OF (CHLOROCARBONYL)PHENYLKETENE WITH 1,3-DINUCLEOPHILES. II. PREPARATION OF 2-HYDROXY-3-PHENYL-4H-PYRIMIDO[2,1-*b*][1,3]BENZOTHIAZOL-4-ONES AND THIOXO DIHYDRO-4,6(1*H*,5*H*)-PYRIMIDINONES

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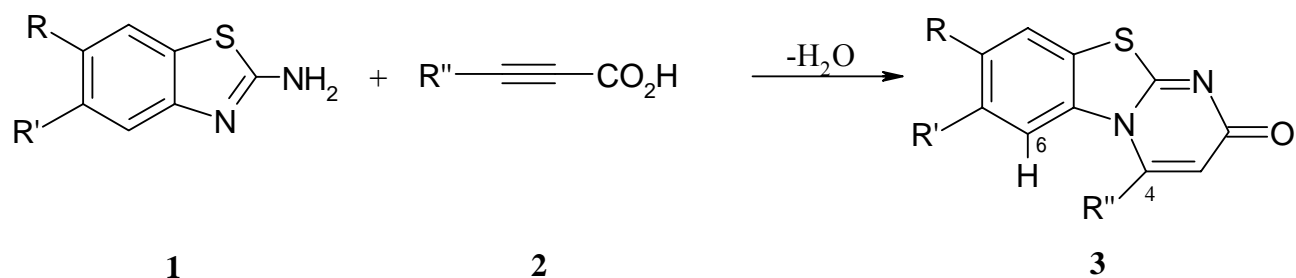
Abstract – A simple one-pot and efficient method is described for the synthesis of 2-hydroxy-3-phenyl-4*H*-pyrimido[2,1-*b*][1,3]benzothiazol-4-one and thioxo-dihydro-4,6(1*H*,5*H*)-pyrimidinone derivatives via the reaction of (chlorocarbonyl)-phenylketene with 1,3- dinucleophiles such as 2-aminobenzothiazoles and *N*-arylthioureas respectively. This method offers a simple and convenient route to prepare the title compounds in good to excellent yields in a short reaction time.

Phenylmalonic acid derivatives such as activated diesters and the diacyl chloride have often been described as versatile bifunctional reagent for the synthesis of numerous heterocycles. (Chlorocarbonyl)-phenylketene **2**, was first described by Nakanishi and represents as a highly reactive equivalent of phenylmalonic acid.¹ This ketene has been found to be a very effective 1,3-bielectrophile reagent and reacts with a wide variety of nucleophiles under a mild experimental conditions, and has been used mainly for the synthesis of five- and six-membered heterocycles functionalized with oxo and hydroxyl groups in 1,3-positions.²⁻⁷ More recently we have reported the reaction of (chlorocarbonyl)phenylketene with 1,3-dinucleophiles such as Schiff bases which were prepared from acetophenone and aryl amides led to the discovery of a new synthetic pathways towards 4-hydroxy-3,6-disubstituted-2(1*H*)-pyridinones and 2,5-diaryl-6-oxo-5-phenyl-6*H*-1,3-oxazin-3-ium-4-olates, respectively.⁸

The development of efficient and mild methods for the synthesis of heterocyclic compound represents a broad area of organic chemistry. Structures containing such units often play an essential role due to their biological activity, particularly in cancer and virus researches.^{9,10} Therefore, it is important to find new efficient methods to synthesize new hetero-polycyclic frameworks. Different synthetic methods such as

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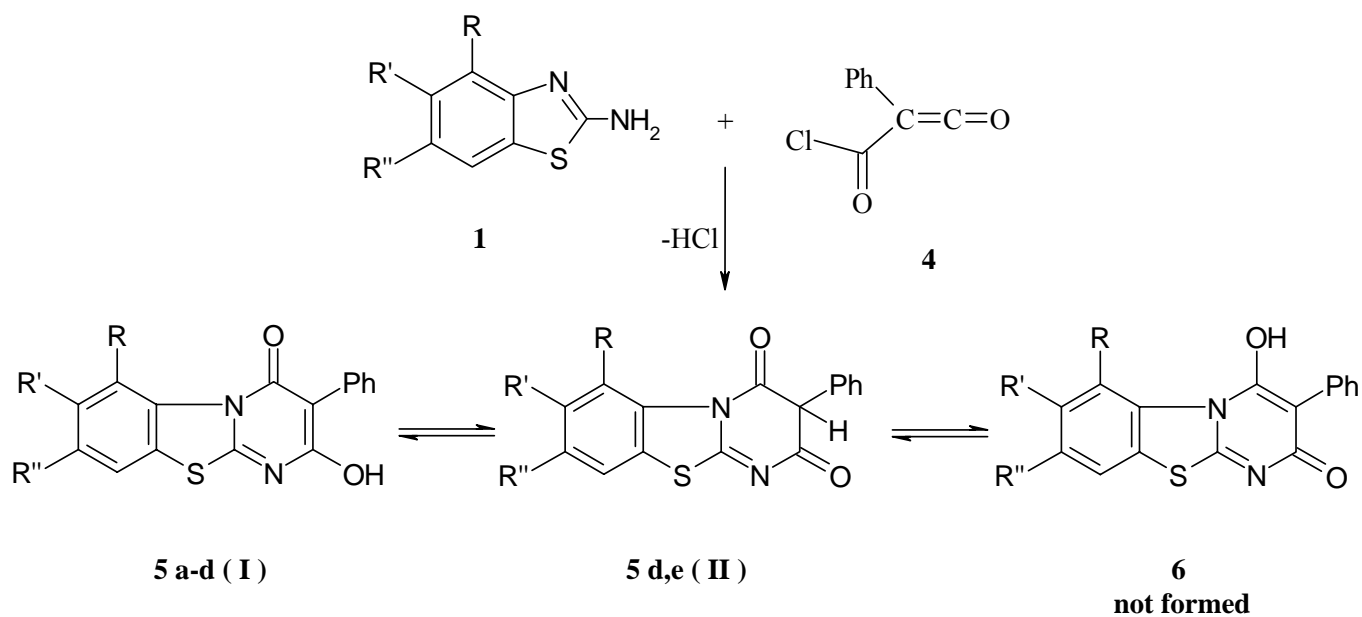
cyclization via reaction of amino-heterocycles with acetylenic compounds¹¹ and intramolecular nucleophilic acyl substitution¹² are known for such purpose. Condensed pyrimidine compounds with five-membered aromatic ring consisting of two heteroatoms such as thiazoles or oxazoles have been shown to exhibit interesting pharmacological properties¹³ and a number of synthetic methods has been reported for their preparation.¹⁴ Doepp et al. have reported the synthesis of substituted and unsubstituted 2*H*-pyrimido[2,1-*b*]benzothiazol-2-ones **3** from the conjugate addition of 2-aminobenzothiazoles **1** to the acetylenic acids **2**, followed by cyclocondensation. The shielding effects observed for the 6-H in the 4-phenyl-2*H*-pyrimido[2,1-*b*]benzothiazol-2-one derivatives (R'' = Ph) is due to the diamagnetic effect of the phenyl group attached to C₄¹⁵ (Scheme 1).



Scheme 1

The chemical importance and diversity of pyrimido[2,1-*b*]benzothiazolones have made these compounds important synthetic goals and have stimulated new methods and reagents for the preparation of these heterocyclic compounds.¹⁶ As a continuation of our study on the development of new synthetic routes to heterocyclic compounds, we now wish to describe the condensation of (chlorocarbonyl)phenylketene **4** with 1,3-dinucleophiles such as 2-aminobenzothiazoles **1** and *N*-arylthioureas **10a-d** to afford 2-hydroxy-3-phenyl-4*H*-pyrimido[2,1-*b*][1,3]benzothiazol-4-one **5a-e** and thioxodihydro-4,6(1*H*,5*H*)-pyrimidinone **11** and **12** derivatives, respectively.

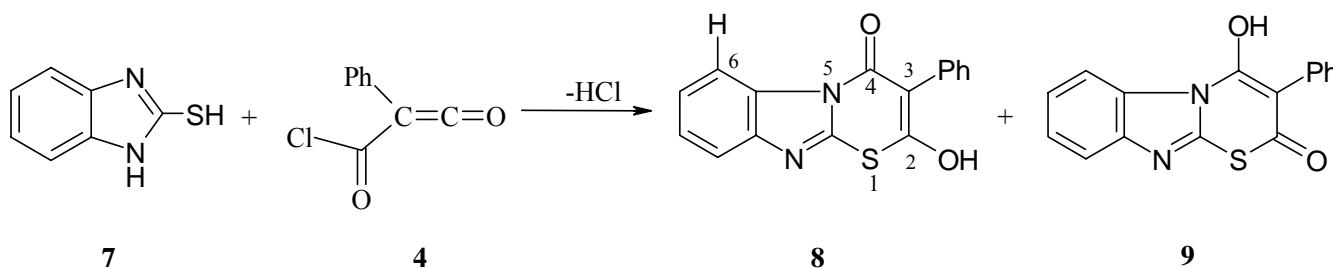
Scheme 2 summarizes the general synthetic approach which was employed for the synthesis of 3-phenyl-4*H*-pyrimido[2,1-*b*]benzothiazolones **5a-e**. These compounds have also been prepared by condensation of (chlorocarbonyl)phenylketene **4** with 2-aminobenzothiazoles **1** in boiling dry toluene in excellent yields in a short experimental time. Only one tautomer was formed by reaction of 2-aminobenzothiazoles **1a-c** with ketene **4** while in the IR and ¹H-NMR spectra of compounds **5d** and **5e** two tautomers **I** and **II** were observed. On basis of ¹³C-NMR spectrum of compound **5d**, tautomer **Id** is unstable and was converted to tautomer **IId**.



- 5a:** R= R' = R'' = H
5b: R= R' = H, R'' = Me
5c: R= R' = H, R'' = OMe
5d: R= R' = Me, R'' = H
5e: R= R' = H, R'' = Cl

Scheme 2

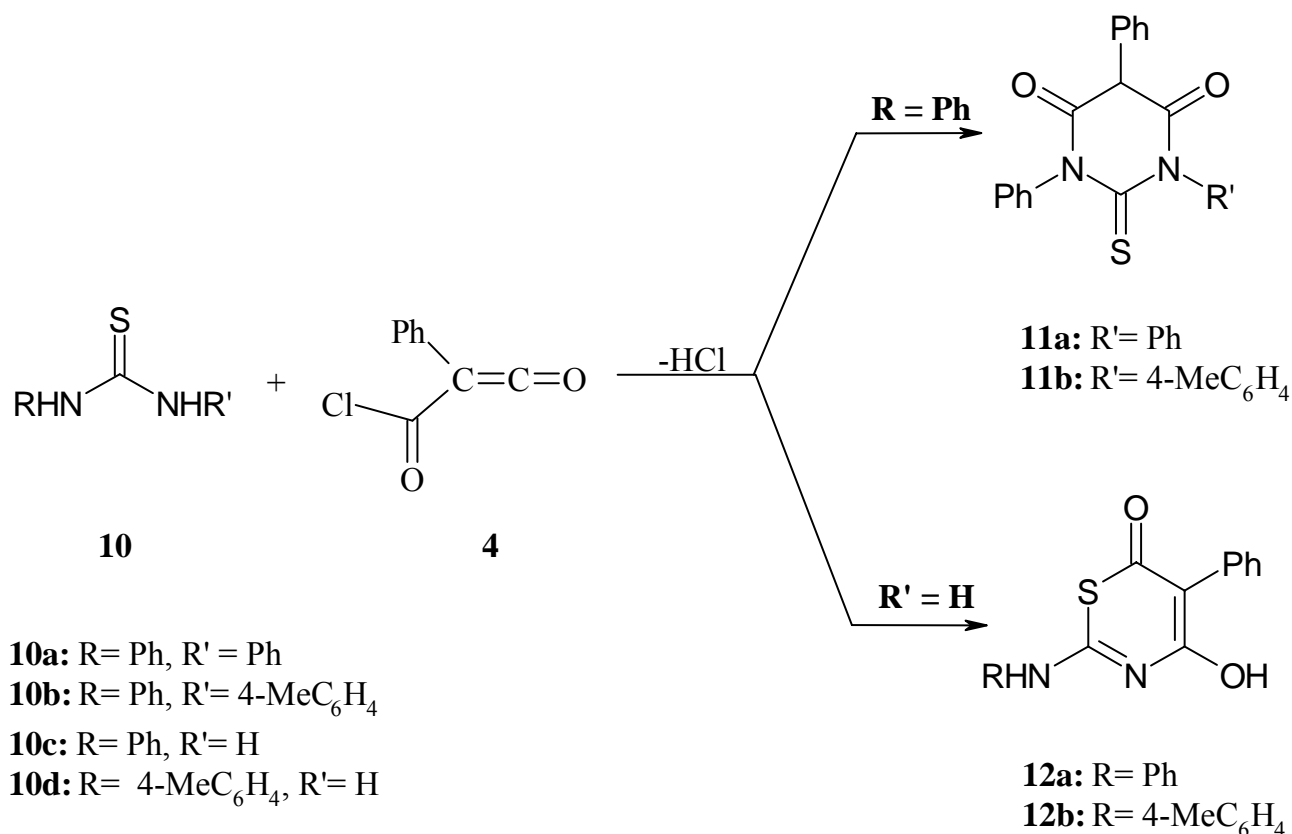
Potts and coworkers have reported the synthesis of 2-hydroxy-3-phenyl[1,3]thiazino[3,2-*a*][1,3]benzimidazol-4-one by treating (chlorocarbonyl)phenylketene and triethyl amine with 2(3*H*)-benzimidazolethione in refluxing anhydrous dioxane. The ¹H-NMR spectrum of this compound exhibited chemical shift of the proton on C₆ at δ 8.70 that this proton was deshielded, in this instance by the carbonyl group (C₄). On the bases of these informations the tautomer **8** was reported as the only product.¹⁷



Scheme 3

The structure of the compounds **5a-e** were evident from the spectral data, especially the aromatic protons (δ 7.00-8.77) in the ¹H-NMR spectra, the proton on C₆ was shifted downfield to δ 8.45-8.77 by the deshielding effect of the carbonyl group at C₄. We have reported the synthesis of a specific tautomer of 1,3-thiazinones from the reaction of chlorocarbonylketenes (CCKs) with thioamides such as thiobenzamide and thioacetamide as 1,3-dinucleophiles.¹⁸ In our investigation it was found that the

reaction of thioureas **10a** and **10b** with (chlorocarbonyl)phenylketene gave 1,3,5-triphenyl-2-thioxodihydro-4,6(1*H*,5*H*)-pyrimidinediones **11a** and **11b** as the only product. Similarly, *N*-arylthioureas **10c** and **10d** reacted with ketene **4** to give a specific tautomer of 6-hydroxy-2-(arylamino)-5-phenyl-6*H*-1,3-thiazin-6-ones **12a** and **12b**, respectively (Scheme 4).



Scheme 4

2-Hydroxy-3-phenyl-4*H*-pyrimido[2,1-*b*][1,3]benzothiazol-4-ones **5a-e** and compounds **11a, b** and **12a, b** were characterized by their microanalyses, spectroscopic, and mass spectrometric data. The spectral data of compounds **5a-c** exhibited only one tautomer (**I**), while the spectroscopic data of compounds **5d, e** showed a mixture of two tautomers (**I, II**). The IR spectra of compounds **5a-e** showed a strong absorption at 3200-2850 cm⁻¹ attributed to the OH group tautomer **I** and in the ¹H-NMR spectra, the OH proton appears at 11-12 ppm as a singlet peak. So the structure of tautomer **I** was evident from ¹H-NMR spectral data, especially the aromatic protons such as the proton on C₆ was shifted downfield to δ 8.45- 8.77 by the carbonyl group at C₄. The ¹H-NMR spectra of the compounds **5d** and **5e** showed a singlet at δ 12.7 and 12.3 ppm, respectively, attributed to enolic proton of tautomer **I**, and a singlet at δ 5.2 and 4.6 ppm for malonyl-H on C₃ in the tautomer **II**.

EXPERIMENTAL

General Procedures. (Chlorocarbonyl)phenylketene **4** was prepared according to a literature procedure.¹ The 2-aminobenzothiazoles **1** and *N*-arylthioureas were known and prepared according to a general procedure.¹⁹ Toluene and THF were dried over sodium and distilled prior to use. Melting points were determined on an Gallenkamp melting point apparatus and are uncorrected. IR spectra were measured on a Mattson 1000 FT-IR spectrophotometer. ¹H-NMR and ¹³C-NMR spectra were determined on a BRUKER DRX-500 AVANCE spectrometer at 500 and 125.77 MHz, respectively. MS spectra were recorded on a Shimadzu QP 1100EX mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

2-Hydroxy-3-phenyl-4*H*-pyrimido[2,1-*b*][1,3]benzothiazol-4-one (5a): *General procedure (5a-e).* A solution of (chlorocarbonyl)phenylketene **4** (361 mg, 2 mmol) in anhydrous THF (10 mL) was added to a stirred boiling solution of 2-aminobenzothiazole **1a** (446 mg, 2 mmol) in 20 mL of anhydrous toluene under N₂. The compound **5a** was formed immediately as a pale yellow precipitate. The reaction mixture was cooled and the solid product was collected and washed with 20 mL of anhydrous THF. The solid product was recrystallized from ethanol. 0.53 g. yield 90%; mp 268-270 °C; ν_{\max} (KBr): 3150-2850 (broad, OH), 1666 (C=O), 1592, 1517(Ar) cm⁻¹; δ_{H} (500 MHz, DMSO-*d*₆): 11.89 (1H, s, OH), 8.84 (1H, d, ³*J*_{HH} = 8.67 Hz, proton on C₆), 7.93 (1H, d, ³*J*_{HH} = 8.72 Hz, arom), 7.45-7.15 (7H, m, arom); δ_{C} (125 MHz, DMSO-*d*₆): 164.58, 162.05, 160.93, 137.21, 133.36, 131.67, 128.25, 127.67, 127.40, 127.25, 124.55, 123.86, 119.40, 99.16; MS, *m/z* (%): 294 (M⁺, 75), 242 (15), 177 (100), 118 (36), 71 (80), 57 (40), 43 (31). Anal. Calcd For C₁₆H₁₀N₂O₂S: C, 65.29; H, 3.42; N, 9.52 %. Found : C, 65.03; H, 3.35; N, 9.20 %.

2-Hydroxy-8-methyl-3-phenyl-4*H*-pyrimido[2,1-*b*][1,3]benzothiazol-4-one (5b): A 0.56 g pale of yellow crystals, yield 91% ; mp 260-263 °C; ν_{\max} (KBr): 3100-2850 (broad, OH), 1641 (C=O), 1617, 1517 (Ar) cm⁻¹; δ_{H} (500 MHz, DMSO-*d*₆): 11.84 (1H, s, OH), 8.68 (1H, d, ³*J*_{HH} = 8.45 Hz, proton on C₆), 7.70(1H, s, arom), 7.40-7.15 (6H, m, arom) ,2.31(3H, s, CH₃); δ_{C} (125 MHz, DMSO-*d*₆): 164.52, 161.87, 160.70, 137.19, 135.02, 133.39, 131.66, 128.51, 128.23, 127.23, 124.45, 123.61, 119.05, 99.13, 21.72; MS, *m/z* (%): 308(M⁺, 70), 256(10), 191(100), 164 (42), 118(42), 97(23), 83(18), 71(74), 57(36), 43(26). Anal. Calcd For C₁₇H₁₂N₂O₂S: C, 66.22; H, 3.92; N, 9.08 %. Found : C, 65.89; H,3.78; N, 8.70 %.

2-Hydroxy-8-methoxy-3-phenyl-4*H*-pyrimido[2,1-*b*][1,3]benzothiazol-4-one (5c): A 0.56 g of pale yellow crystals, yield 87% ; mp 283-286 °C; ν_{\max} (KBr): 3131-2850 (broad, OH), 1666 (C=O), 1592, 1517(Ar) cm⁻¹; δ_{H} (500 MHz, DMSO-*d*₆): 11.80 (1H, s, OH), 8.71 (1H, d, ³*J*_{HH} = 9.20 Hz, proton on C₆), 7.55(1H, d, ⁴*J*_{HH} = 2.36 Hz, arom), 7.39(2H, d, ³*J*_{HH} = 7.74 Hz, arom), 7.26(2H, t, ³*J*_{HH} = 8.00 Hz, arom), 7.15(1H, t, ³*J*_{HH} = 7.32 Hz, arom), 7.02(1H, d, ³*J*_{HH} = 7.74 Hz, arom), 3.73(3H, s, CH₃); δ_{C} (125 MHz, DMSO-*d*₆): 164.37, 161.69, 160.41, 158.41, 133.43, 131.67, 130.90, 128.21, 127.19, 125.96, 120.22, 114.56, 108.09, 99.15, 56.59; MS, *m/z* (%): 324 (M⁺, 40), 207 (100), 192 (17), 89 (40), 63 (18). Anal.

Calcd For $C_{17}H_{12}N_2O_3S$: C, 62.95; H, 3.73; N, 8.64%. Found : C, 62.59; H, 3.54; N, 8.28 %.

6,7-Dimethyl-3-phenyl-2H-pyrimido[2,1-*b*][1,3]benzothiazolone (5d): A 0.55 g of pale yellow crystals, yield 85%; mp 137-140 °C; ν_{\max} (KBr): 3100-2850 (broad, OH), 1691, 1637 (C=O), 1542 (C=N) cm^{-1} ; δ_H (500 MHz, DMSO-*d*₆): 12.70 (1H, s, OH)^a, 7.56 (1H, d, $^3J_{HH} = 8.03$ Hz, arom)^{*}, 7.35-7.24 (4H, m, arom)^{*}, 7.01 (1H, d, $^3J_{HH} = 8.03$ Hz, arom)^{*}, 5.22 (1H, s, malonyl-H on C₃)^b, 2.39 (3H, s, CH₃)^{*}, 2.23 (3H, s, CH₃)^{*}; δ_C (125 MHz, DMSO-*d*₆): 167.85, 157.68, 148.89, 134.51, 134.21, 130.68, 130.24, 129.34, 129.29, 129.13, 128.78, 126.60, 119.08, 59.06 (C₃), 20.18, 15.12; MS, *m/z* (%): 322 (M⁺, 30), 205 (100), 189 (8), 178 (68), 163 (30), 150 (8), 135 (6), 118 (52), 91 (19), 89 (33), 77 (12), 63 (11), 51 (9). Anal. Calcd For $C_{18}H_{14}N_2O_2S$: C, 67.06; H, 4.38; N, 8.69 %. Found : C, 66.73; H, 4.16; N, 8.34 %. ^a For tautomer **5d I**: 2-hydroxy-6,7-dimethyl-3-phenyl-4H-pyrimido[2,1-*b*][1,3]benzothiazol-4-one. ^b For tautomer **5d II**: 6,7-dimethyl-3-phenyl-2H-pyrimido[2,1-*b*][1,3]benzothiazol-2,4(3H)-dione. * For two tautomers.

8-Chloro-3-phenyl-2H-pyrimido[2,1-*b*][1,3]benzothiazolone (5e): A 0.5 g of yellow crystals, yield 82 %; mp 135-137 °C; ν_{\max} (KBr): 3230-2800 (broad, OH), 1705, 1691 (C=O), 1617 (C=N) cm^{-1} ; δ_H (500 MHz, DMSO-*d*₆): 12.3 (1H, s, OH)^a, 7.6-7.2 (8H, m, arom)^{*}, 4.6 (1H, s, malonyl-H on C₃)^b; δ_C (125 MHz, DMSO-*d*₆): 175.6, 173.5, 170.6, 164.2, 163.0, 158.0, 139.7, 135.0, 131.9, 131.6, 130.7, 130.2, 129.7, 129.6, 129.0, 128.4, 126.3, 126.2, 127.4, 127.2, 126.1, 97.2 (C₃)^a, 58.4 (C₃)^b; MS, *m/z* (%): 328 (M⁺, 5), 169 (15), 145 (8), 118 (100), 111 (15), 90 (45), 75 (12), 63 (15), 51 (9). Anal. Calcd For $C_{16}H_9ClN_2O_2S$: C, 58.45; H, 2.76; N, 8.52 %. Found : C, 58.12; H, 2.57; N, 8.24 %. ^a For tautomer **5e I**: 8-chloro-2-hydroxy-3-phenyl-4H-pyrimido[2,1-*b*][1,3]benzothiazol-4-one. ^b For tautomer **5e II**: 8-chloro-3-phenyl-2H-pyrimido[2,1-*b*][1,3]benzothiazol-2,4(3H)-dione. * For two tautomers.

1,3,5-Triphenyl-2-thioxodihydro-4,6(1H,5H)-pyrimidinedione (11a): *General procedure (11a-b and 12a-b)*. To a boiling solution of *N,N*-diphenylthiourea **10a** (0.25 g, 2 mmol) in 15 mL of dry xylene was added (chlorocarbonyl)phenylketene (0.36 g, 2 mmol). The reaction mixture was cooled and a precipitate formed instantly and washed with 20 mL of anhydrous THF. The solid product was collected and recrystallized from ethanol. A 0.70 g of yellow crystals, yield 94%; mp 235-237 °C; ν_{\max} (KBr): 1741, 1641 (C=O), 1617 (Ar) cm^{-1} ; δ_H (500 MHz, DMSO-*d*₆): 7.53-7.12 (15H, m, arom), 5.05 (1H, s, malonyl-H on C₅); δ_C (125 MHz, DMSO-*d*₆): 181.18, 165.56, 138.68, 132.95, 129.85, 129.55, 129.23, 129.07, 128.82, 128.10, 127.22, 57.16; MS, *m/z* (%): 372 (M⁺, 18), 254 (16), 225 (6), 180 (4), 145 (100), 135 (10), 118 (24), 90 (27), 77 (27), 63 (5), 51 (10). Anal. Calcd For $C_{22}H_{16}N_2O_2S$: C, 70.95; H, 4.33; N, 7.52 %. Found : C, 70.83; H, 4.22; N, 7.35 %.

1-(4-Methylphenyl)-3,5-diphenyl-2-thioxodihydro-4,6(1H,5H)-pyrimidinedione (11b): A 0.7 g of yellow crystals, yield 90%; mp 120 °C (decomp); ν_{\max} (KBr): 1729, 1706 (C=O), 1659 (Ar) cm^{-1} ; δ_H (500 MHz, DMSO-*d*₆): 7.6-7.1 (14H, m, arom), 4.3 (1H, s, malonyl-H on C₅), 2.3 (3H, s, CH₃); δ_C (125 MHz,

DMSO-*d*₆): 185.2, 168.5, 160.6, 138.7, 137.2, 133.7, 131.6, 130.0, 129.5, 128.9, 128.7, 126.4, 124.0, 119.8, 115.7, 58.3, 21.2 ; MS, *m/z* (%): 386 (M⁺, 32), 268 (28), 251 (33), 236 (20), 159 (49), 145 (100), 118 (45), 90 (48), 77 (35), 65 (18), 44 (62). Anal. Calcd For C₂₃H₁₈N₂O₂S: C, 71.48; H, 4.69; N, 7.25 %. Found : C, 71.10; H, 4.52; N, 7.05 %.

2-Anilino-6-hydroxy-5-phenyl-6H-1,3-thiazin-6-one (12a): A 0.50 g of white crystals, yield 85%; mp 144-146 °C; ν_{\max} (KBr): 3270-2850 (broad, OH and NH), 1641 (C=O), 1617, 1517 cm⁻¹; δ_{H} (500 MHz, DMSO-*d*₆): 12.29 (1H, s, OH), 7.41-7.11(10H, m, arom), 5.11(1H, broad, NH); δ_{C} (125 MHz, DMSO-*d*₆): 175.79, 170.57, 162.52, 157.83, 132.69, 130.47, 129.87, 129.60, 129.07, 128.60, 126.18, 97.49; MS, *m/z* (%): 296(M⁺, 18), 179 (8), 150(9), 135 (7), 118(100), 90(60), 77(30), 63(18), 51(22). Anal. Calcd For C₁₆H₁₂N₂O₂S: C, 64.85; H, 4.08; N, 9.45 %. Found : C, 64.49; H, 3.82; N, 9.18 %.

6-Hydroxy-5-phenyl-2-(4-toluidino)-6H-1,3-thiazin-6-one(12b): A 0.51 g of white crystals, yield 82%; mp 157-160 °C; ν_{\max} (KBr): 3385 (NH), 3100-2850 (broad, OH), 1666 (C=O), 1617, 1542 cm⁻¹; δ_{H} (500 MHz, DMSO-*d*₆): 11.96 (1H, s, OH), 7.42-6.98 (9H, m, arom), 4.8 (1H, broad, NH), 2.29 (3H, s, CH₃); δ_{C} (125 MHz, DMSO-*d*₆): 175.32, 162.53, 158.46, 137.58, 131.47, 130.00, 129.79, 129.66, 129.29, 128.21, 126.58, 96.38, 21.61; MS, *m/z* (%): 310 (M⁺, 20), 132 (18), 118 (100), 106 (17), 91 (52), 77 (25), 58 (23), 51 (14). Anal. Calcd For C₁₇H₁₄N₂O₂S: C, 65.79; H, 4.55; N, 9.03 %. Found : C, 65.53; H, 5.37; N, 8.78 %.

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