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

Hassan Sheibani* and Mahboobeh Zahedifar

Department of Chemistry, Shahid Bahonar University of Kerman, Kerman 76169, Iran, E-mail: hsheibani@mail.uk.ac.ir

Abstract – A simple one-pot and efficient method is described for the synthesis of 2-hydroxy-3-phenyl-4\(\text{H}\)-pyrimido[2,1-\(b\)][1,3]benzothiazol-4-one and thioxodihydro-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. 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. 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.

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. Therefore, it is important to find new efficient methods to synthesize new hetero-polycyclic frameworks. Different synthetic methods such as

* Corresponding author. Tel.: + 98-341-322-1451; fax: +98-341-322-1452;
e-mail: hsheibani@mail.uk.ac.ir
cyclization via reaction of amino-heterocycles with acetylenic compounds\textsuperscript{11} and intramolecular nucleophilic acyl substitution\textsuperscript{12} 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 properties\textsuperscript{13} and a number of synthetic methods has been reported for their preparation.\textsuperscript{14} Doepp et al. have reported the synthesis of substituted and unsubstituted 2\textit{H}-pyrimido[2,1-\textit{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\textit{H}-pyrimido[2,1-\textit{b}]benzothiazol-2-one derivatives (\textit{R}'' = \text{Ph}) is due to the diamagnetic effect of the phenyl group attached to C\textsubscript{4}\textsuperscript{15} (Scheme 1).

\begin{center}
\includegraphics[width=\textwidth]{Scheme1.png}
\end{center}

\textbf{Scheme 1}

The chemical importance and diversity of pyrimido[2,1-\textit{b}]benzothiazolones have made these compounds important synthetic goals and have stimulated new methods and reagents for the preparation of these heterocyclic compounds.\textsuperscript{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 \textit{N}-arylthioureas 10\textit{a-d} to afford 2-hydroxy-3-phenyl-4\textit{H}-pyrimido[2,1-\textit{b}][1,3]benzothiazol-4-one 5\textit{a-e} and thioxodihydro-4,6(1\textit{H},5\textit{H})-pyrimidinone 11 and 12 derivatives, respectively.

Scheme 2 summarizes the general synthetic approach which was employed for the synthesis of 3-phenyl-4\textit{H}-pyrimido[2,1-\textit{b}]benzothiazolones 5\textit{a-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 1\textit{a-c} with ketene 4 while in the IR and \textsuperscript{1}H-NMR spectra of compounds 5\textit{d} and 5\textit{e} two tautomers \textit{I} and \textit{II} were observed. On basis of \textsuperscript{13}C-NMR spectrum of compound 5\textit{d}, tautomer \textit{Id} is unstable and was converted to tautomer \textit{IId}. 
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(3H)-benzimidazolethione in refluxing anhydrous dioxane. The $^1$H-NMR spectrum of this compound exhibited chemical shift of the proton on C$_6$ at $\delta$ 8.70 that this proton was deshielded, in this instance by the carbonyl group (C$_4$). On the bases of these informations the tautomer 8 was reported as the only product.$^{17}$

The structure of the compounds 5a-e were evident from the spectral data, especially the aromatic protons ($\delta$ 7.00-8.77) in the $^1$H-NMR spectra, the proton on C$_6$ was shifted downfield to $\delta$ 8.45-8.77 by the deshielding effect of the carbonyl group at C$_4$. We have reported the synthesis of a specific tautomer of 1,3-thiazinones from the reaction of chlorocarbonylketen (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-6,6(1H,5H)-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-6H-1,3-thiazin-6-ones 12a and 12b, respectively (Scheme 4).

Scheme 4

2-Hydroxy-3-phenyl-4H-pyrimido[2,1-b][1,3]benzothiazol-4ones 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-e 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 \(^1\)H-NMR spectra, the OH proton appears at 11-12 ppm as a singlet peak. So the structure of tautomer I was evident from \(^1\)H-NMR spectral data, especially the aromatic protons such as the proton on C\(_6\) was shifted downfield to \(\delta\) 8.45-8.77 by the carbonyl group at C\(_4\). The \(^1\)H-NMR spectra of the compounds 5d and 5e showed a singlet at \(\delta\) 12.7 and 12.3 ppm, respectively, attributed to enolic proton of tautomer I, and a singlet at \(\delta\) 5.2 and 4.6 ppm for malonyl-H on C\(_3\) 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.10 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-4H-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; \( \nu_{\text{max}}(\text{KBr}): 3150-2850 \) (broad, OH), 1666 (C=O), 1592, 1517 (Ar) cm\(^{-1}\); \( \delta_H \) (500 MHz, DMSO-\( d_6 \)): 11.89 (1H, s, OH), 8.84 (1H, d, \( J_{HH} = 8.67 \) Hz, proton on C6), 7.93 (1H, d, \( J_{HH} = 8.72 \) Hz, arom), 7.45-7.15 (7H, m, arom); \( \delta_C \) (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 C\(_{16}\)H\(_{10}\)N\(_2\)O\(_2\)S: 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-4H-pyrimido[2,1-b][1,3]benzothiazol-4-one (5b): A 0.56 g pale of yellow crystals, yield 91%; mp 260-263 °C; \( \nu_{\text{max}}(\text{KBr}): 3100-2850 \) (broad, OH), 1641 (C=O), 1617, 1517 (Ar) cm\(^{-1}\); \( \delta_H \) (500 MHz, DMSO-\( d_6 \)): 11.84 (1H, s, OH), 8.68 (1H, d, \( J_{HH} = 8.45 \) Hz, proton on C6), 7.70( 1H, s, arom), 7.40-7.15 (6H, m, arom), 2.31(3H, s, CH\(_3\)); \( \delta_C \) (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 C\(_{17}\)H\(_{12}\)N\(_2\)O\(_2\)S: C, 65.29; H, 3.42; N, 9.52 %. Found : C, 65.03; H, 3.35; N, 9.20 %.

2-Hydroxy-8-methoxy-3-phenyl-4H-pyrimido[2,1-b][1,3]benzothiazol-4-one (5c): A 0.56 g of pale yellow crystals, yield 87%; mp 283-286 °C; \( \nu_{\text{max}}(\text{KBr}): 3131-2850 \) (broad, OH), 1641 (C=O), 1617, 1517 (Ar) cm\(^{-1}\); \( \delta_H \) (500 MHz, DMSO-\( d_6 \)): 11.80 (1H, s, OH), 8.71 (1H, d, \( J_{HH} = 9.20 \) Hz, proton on C6), 7.55(1H, d, \( J_{HH} = 2.36 \) Hz, arom), 7.39(2H, d, \( J_{HH} = 7.74 \) Hz, arom), 7.26( 2H, t, \( J_{HH} = 8.00 \) Hz, arom), 7.15( 1H, t, \( J_{HH} = 7.32 \) Hz, arom), 7.02(1H, d, \( J_{HH} = 7.74 \) Hz, arom), 3.73(3H, s, CH\(_3\)); \( \delta_C \) (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.
Caled For C_{17}H_{12}N_{2}O_{3}S: C, 62.95; H, 3.73; N, 8.64%. Found: C, 62.59; H, 3.54; N, 8.28 %.

6,7-Dimethyl-3-phenyl-2\(H\)-pyrimido[2,1-b][1,3]benzothiazolone (5d): A 0.55 g of pale yellow crystals, yield 85%; mp 137-140 °C; ν\(_{\text{max}}\) (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, \(^3J_{\text{HH}} = 8.03\) Hz, arom)*, 7.35-7.24 (4H, m, arom)*, 7.01 (1H, d, \(^3J_{\text{HH}} = 8.03\) Hz, arom) *, 5.22 (1H, s, malonyl-H on C\(_3\))b, 2.39 (3H, s, CH\(_3\))*; 184 \(\delta\)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\(_2\)O\(_2\)S: 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-4\(H\)-pyrimido[2,1-b][1,3]benzothiazol-4-one.
b For tautomer 5d II: 6,7-dimethyl-3-phenyl-2\(H\)-pyrimido[2,1-b][1,3]benzothiazol-2,4(3\(H\))-dione.
* For two tautomers.

8-Chloro-3-phenyl-2\(H\)-pyrimido[2,1-b][1,3]benzothiazolone (5e): A 0.5 g of yellow crystals, yield 82 %; mp 135-137°C; ν\(_{\text{max}}\) (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 C\(_3\)) b; 184 \(\delta\)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), 254 (15), 180 (4), 145 (100), 135 (10), 118 (24), 90 (27), 77 (27), 63 (5), 51 (10). Anal. Calcd For C\(_{16}\)H\(_9\)ClN\(_2\)O\(_2\)S: 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-4\(H\)-pyrimido[2,1-b][1,3]benzothiazol-4-one. b For tautomer 5e II: 8-chloro-3-phenyl-2\(H\)-pyrimido[2,1-b][1,3]benzothiazol-2,4(3\(H\))-dione. * For two tautomers.

1,3,5-Triphenyl-2-thioxodihydro-4,6(1\(H\),5\(H\))-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\(_{\text{max}}\) (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 C\(_5\))b; 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\(_{14}\)N\(_2\)O\(_2\)S: C, 70.95; H, 4.33; N, 7.52 %. Found: C, 70.83; H, 4.22; N, 7.35 %.

1-(4-Methylphenyl)-3-diphenyl-2-thioxodihydro-4,6(1\(H\),5\(H\))-pyrimidinedione (11b): A 0.7 g of yellow crystals, yield 90%; mp 120 °C (decomp); ν\(_{\text{max}}\) (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 C\(_5\)), 2.3 (3H, s, CH\(_3\)); 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, 128.7, 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 C$_{23}$H$_{18}$N$_2$O$_2$S: 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-6$H$-1,3-thiazin-6-one (12a): A 0.50 g of white crystals, yield 85%; mp 144-146 °C; $\nu_{\text{max}}$(KBr): 3270-2850 (broad, OH and NH), 1641 (C=O), 1617, 1517 cm$^{-1}$; $\delta$H (500 MHz, DMSO-$d_6$): 12.29 (1H, s, OH), 7.41-7.11(10H, m, arom), 5.11(1H, broad, NH); $\delta$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 C$_{16}$H$_{12}$N$_2$O$_2$S: 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)-6$H$-1,3-thiazin-6-one(12b): A 0.51 g of white crystals, yield 82%; mp 157-160 °C; $\nu_{\text{max}}$(KBr): 3385 (NH), 3100-2850 (broad, OH), 1666 (C=O), 1617, 1542 cm$^{-1}$; $\delta$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, CH$_3$); $\delta$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 C$_{17}$H$_{14}$N$_2$O$_2$S: C, 65.79; H, 4.55; N, 9.03 %. Found : C, 65.53; H, 5.37; N, 8.78 %.

ACKNOWLEDGEMENTS
The authors express appreciation to the Shahid Bahonar University of Kerman Faculty Research Grant for its support of this investigation.

REFERENCES


