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A new synthesis of 1,3-thiazines and their transformation into 1-substituted-6-alkyluracils by extrusion of carbonyl sulfide

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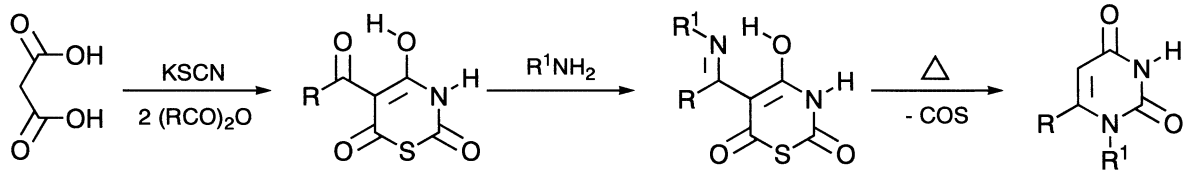
Abstract—A simple synthesis of 5-acyl-4-hydroxy-3,6-dihydro-2*H*-1,3-thiazine-2,6-diones from malonic acid, potassium thiocyanate and acid anhydrides is described. A new, general, regioselective method for the synthesis of 1-substituted-6-alkyluracils by the reaction of these thiazines with primary alkyl and arylamines is reported. © 2003 Elsevier Science Ltd. All rights reserved.

The purpose of the work described in this letter was to investigate the approaches to the synthesis of 1,3-thiazines. In our study of synthetic routes to 1,3-thiazines,[1] we decided to use thiocyanate as a building block for the construction of the 1,3-thiazine ring. When malonic acid, KSCN and acetic anhydride were allowed to react in acetic acid at room temperature for 24 h, 5-acetyl-4-hydroxy-3,6-dihydro-2*H*-1,3-thiazine-2,6-dione[2] **1a**, mp 198–200°C (benzene) was formed in 46% yield. (Scheme 1). Using propionic anhydride and propionic acid we were able to obtain 4-hydroxy-5-propionyl-3,6-dihydro-2*H*-1,3-thiazine-2,6-dione **1b**, mp 139–140°C (benzene/hexane), in 30% yield, while with butyric anhydride and butyric acid, 5-butyryl-4-hydroxy-3,6-dihydro-2*H*-1,3-thiazine-2,6-dione **1c**, mp 128–129°C (acetone/water) was obtained in 20% yield.

We next investigated the reaction of thiazine **1a** with different primary amines. Thus heating **1a** in dioxane or ethanol gave the corresponding Schiff bases **2a–b**.[3] We also carried out the reaction with a large excess of amine, without solvent and under reflux. In the case of aniline, evolution of carbonyl sulfide was observed and 1-phenyl-6-methyluracil **3a** was isolated, mp 284–285°C, (lit.[4] 280°C), in 75% yield. However, benzylamine afforded a mixture of 1-benzyl-6-methyluracil **3b** mp 231–232°C (lit.[5] 230–231°C) and 1,3-dibenzylurea, mp 170–171°C (lit.[6] 170–171°C), under the same conditions. The mixture was readily separated by treatment with aqueous NaOH, filtration and reprecipitation of the uracil by HCl. Formation of 1,3-substituted ureas from amines and carbonyl sulfide is well known.[7] When thiazine **1a** and 1,2-phenylenediamine were refluxed in



Scheme 1.

Keywords: 1,3-thiazine; 6-methyluracil; thiocyanate; malonic acid; carbonyl sulfide; 1,3-disubstituted urea.

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DMF for 30 min, 1-(2-aminophenyl)-6-methyluracil[8] **3d** was formed, mp 275–276°C, in 67% yield. Thiazine **1a** with monoethanolamine gave 1-(2-hydroxyethyl)-6-methyluracil[9] **3c**, mp 234–235°C (55%). While thiazine **1b** and aniline gave 1-phenyl-6-ethyluracil,[10] **3e** mp 274–275°C (73%). Uracils **3a–e** may also be prepared from the corresponding Schiff bases by refluxing in DMF for 1–3 h.

In conclusion, we have reported a new method for the synthesis of 1,3-thiazines from simple starting substances and have developed a new, general, regioselective method for the synthesis of 1-substituted-6-alkyluracils from 1,3-thiazines by a hitherto unknown extrusion reaction of carbonyl sulfide.

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2. Ziegler, E.; Steiner, E. *Monatsh. Chem.* **1964**, *95*, 495–500. The authors described the synthesis of compound **1a** starting from xantogenamid, malonic acid and PCl_3. They reported an mp of 184°C for this product. We have repeated this reaction and obtained the product with mp 198–200°C, which has exactly the same spectral characteristics as **1a** obtained by our method: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 17.67 (s, 1H), 8.43 (br s, 1H), 2.69 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 198.4, 180.3, 173.4, 163.2, 101.2, 26.8; MS (70 eV): m/e 187 (M^+, 28%), 127 (28), 99 (30), 84 (22), 69 (25), 43 (100).
3. Selected spectroscopic data: **4-Hydroxy-5-(1-phenyliminoethyl)-3,6-dihydro-2*H*-1,3-thiazine-2,6-dione, 2a**. Mp 244–245°C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 14.14 (s, 1H), 11.87 (s, 1H), 7.38–7.54 (m, 5H), 2.47 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 180.6, 173.4, 168.4, 163.0, 135.7, 129.5, 128.3, 125.9, 97.6, 20.7; MS (70 eV): m/e 262 (M^+, 100%), 234 (15), 201 (23), 163 (27), 158 (65), 130 (69), 118 (42), 77 (100), 67 (38), 51 (54), 39 (42).
5-(1-Benzyliminoethyl-4-hydroxy-3,6-dihydro-2*H*-1,3-thiazine-2,6-dione, 2b. Mp 187–188°C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 12.93 (br s, 1H), 8.62 (s, 1H), 7.26–7.41 (m, 5H), 4.67 (d, 2H, $J=5$ Hz), 2.64 (s, 3H); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 12.88 (br s, 1H), 11.40 (s, 1H), 7.32–7.40 (m, 5H), 4.69 (d, 2H, $J=5$ Hz), 2.58 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 180.1, 174.1, 167.7, 163.1, 135.8, 128.9, 127.9, 127.5, 96.9, 47.3, 18.8; MS (70 eV): m/e 276 (M^+, 45%), 187 (25), 144 (35), 91 (100), 65 (27), 39 (15).
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8. **3d**: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.11 (s, 1H), 7.09 (t, 1H, $J=8$ Hz), 6.94 (d, 1H, $J=8$ Hz), 6.75 (d, 1H, $J=7$ Hz), 6.57 (t, 1H, $J=8$ Hz), 5.60 (s, 1H), 5.32 (s, 2H), 1.76 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 163.2, 154.1, 151.1, 145.5, 129.5, 129.4, 120.9, 115.9, 115.5, 101.2, 19.2. MS (70 eV): m/e 217 (M^+, 100%), 200 (12), 159 (52), 133 (88), 92 (16), 65 (32), 50 (12), 39 (24).
9. **3c**: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.99 (br s, 1H), 5.44 (s, 1H), 4.94 (br s, 1H), 3.77 (t, 2H, $J=5$ Hz), 3.56 (t, 2H, $J=5$ Hz), 2.26 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 162.5, 155.0, 151.5, 100.6, 58.4, 45.8, 19.8; MS (70 eV): m/e 170 (M^+, 20%), 127 (30), 126 (43), 96 (100), 55 (33), 39 (25).
10. **3e**: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.34 (s, 1H), 7.36–7.52 (m, 5H), 5.56 (s, 1H), 2.01 (q, 2H, $J=7$ Hz), 0.93 (t, 3H, $J=7$ Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 162.9, 158.4, 151.4, 136.3, 129.24, 129.19, 128.81, 98.7, 25.66, 10.96.