Unusual Ring-Opening Reaction of 6,7-Dihydrothieno[3,2-*d*]pyrimidine-2,4-dione Derivatives Leading to 5-(Alkylthio)-6-vinyluracils

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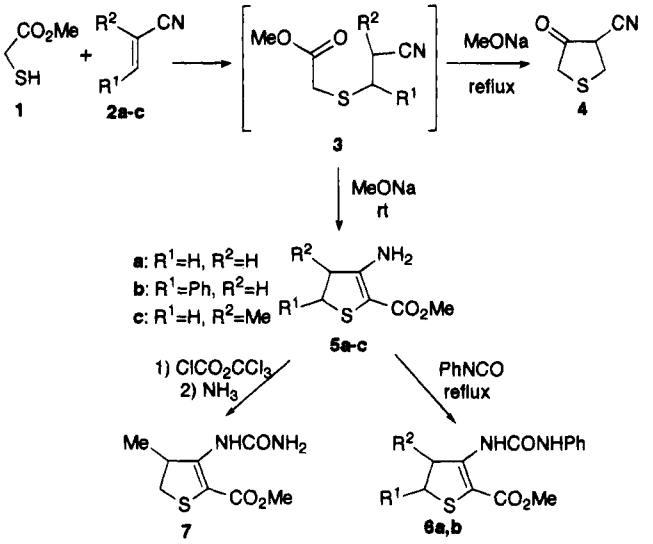
Received October 24, 1994

Our previous studies on 4-cyano- and 4-(methoxycarbonyl)thiolan-3-one, two sulfur-containing heterocycles usually utilized for the preparation of heteropolycyclic systems, led us to discover that their anions serve efficiently as synthetic equivalents of α-acrylate and α-acrylonitrile anions, respectively, allowing interesting synthetic applications.[1-3]

In an ongoing project aimed at further illustrating the potentiality of the thiolane ring system as latent functionality in organic synthesis, we report here an unusual transformation of the 6,7-dihydrothieno[3,2-*d*]pyrimidine-2,4-dione ring system which allows one to obtain 6-vinyluracils bearing a thioether moiety at position 5. To the best of our knowledge, this represents a new entry to pyrimidine derivatives, a class of compounds which continues to gain interest in view of their interesting pharmacological properties.[4] It is well known that C-5 and C-6-substituted uracils contained as the heteroaromatic base components in nucleosides have been found to be important pharmacophore for antiviral activity with possible application for treatment of acquired immunodeficiency syndrome (AIDS).[5,6] As a consequence, the synthesis of pyrimidine and uracil derivatives continue to represent a topical issue for the organic and medicinal chemistry community, and a number of different approaches have been appeared in the recent literature.[7,8]

The starting 4-cyano-3-oxotetrahydrothiophene[3] (**4**) is easily prepared by tandem Michael–Dieckmann reactions between acrylonitrile and methyl thioglycolate in the presence of sodium methoxide in refluxing methanol. In order to gain more information about this ring cyclization and bearing in mind the preparation of

Scheme 1



derivatives such as **5a–c** and **8a–c** we decided to perform the reaction under milder conditions in order to favor a Thorpe–Ziegler-like cyclization versus Dieckmann cyclization of the Michael adduct **3**. The importance of a careful choice of experimental conditions for controlling the cyclization of similar adducts, possessing dual potentiality to undergo cyclization, has been already observed.[9,10]

As expected, on treatment with sodium methoxide at room temperature, the initially formed Michael adduct **3** underwent intramolecular Thorpe–Ziegler-like cyclization involving the addition of the carbanion generated in α position to the carbomethoxy group on the cyano moiety leading to the formation of the enaminonitriles **5a–c** in appreciable to good yields (Scheme 1). Enamino esters **5a,b** were easily transformed into the corresponding 3-phenyl-6,7-dihydrothieno[3,2-*d*]pyrimidine-2,4-dione heterocycles **8a,b** by reaction with phenyl isocyanate followed by cyclization of the carbamate intermediate **6a,b**.

Derivative **8c** was simply obtained through a three-step sequence involving (a) reaction of **5c** with trichloromethyl chloroformate to obtain the corresponding isocyanate, (b) reaction of the latter with ammonia, and (c) cyclization of the carbamate intermediate **7** to the desired thieno[3,2-*d*]pyrimidine derivatives **8c**. To our surprise, attempts to perform alkylation of derivatives **8a–c** by reaction with benzyl bromide in a 5% sodium hydroxide/Et_2O bilayer gave only traces of the desired **9**,[11] while an appreciable amount of the unexpected vinyl derivatives **11a–c** could be detected in the reaction mixture (Scheme 2).

Therefore, in view of the increasing interest of substituted uracils derivatives as pharmacophores for antiviral activity we decided to investigate a possible general application for this transformation. Different experimental conditions as well as different halides and bases were studied. In summary, we found that by stirring a suspension of the thienopyrimidine **8a–c** (4 mmol), the appropriate alkylating agent (4.4 mmol), and 5% sodium

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(11) **9**: pale yellow solid; mp 210–211 °C (EtOH); ^{1}H NMR ($CDCl_3$) δ 3.1–3.5 (m, 4H), 5.35 (s, 2H), 7.1–7.7 (m, 10H).

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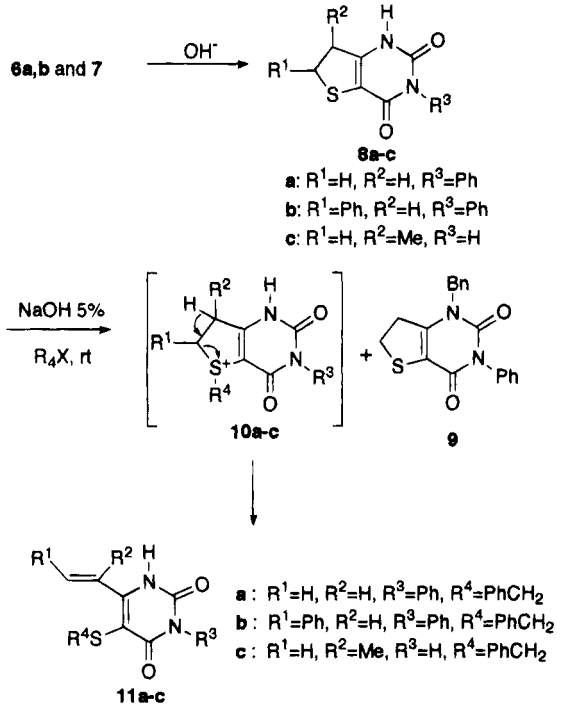
Scheme 2



hydroxide (12 mL) at room temperature for 12 h, a clean transformation took place affording the vinylpyrimidine **11a–c**. Although the interpretation of this result is not easy, we may advance the hypothesis that the initial formation of the sulfonium salts **10a–c**, generated *in situ* by interaction of the alkylating agent and the sulfur moiety, represents the activating step which is followed by the abstraction of α proton at position 7 of the thienopyrimidine. The overall process may be considered as a base-catalyzed β-sulfonium elimination reaction (Scheme 2).

The structures of synthesized vinylpyrimidines were unambiguously assigned on the basis of the IR and ^{1}H- and ^{13}C-NMR spectra.

In conclusion, we have developed a flexible approach to 6-vinylpyrimidines through a protocol easily amenable for large scale preparation. The mild conditions involved and the good overall yields make this sequence a novel and convenient route to this class of compounds. Further elaboration of this strategy toward the synthesis of natural and acyclic nucleosides is currently under way in our laboratories.

Experimental Section

General. Melting points are uncorrected. Reactions were routinely monitored by thin-layer chromatography (TLC) on silica gel coated plates F_{254} (Merck) and visualized with iodine or aqueous potassium permanganate. UV absorption spectra were recorded with a Perkin-Elmer λ 19 spectrophotometer. Nuclear magnetic resonance (^{1}H NMR) spectra were recorded in $CDCl_3$ unless otherwise noted; peak positions are given in parts per million downfield from tetramethylsilane as an internal standard, and J values are given in Hz. Organic solutions were dried over anhydrous magnesium sulfate and evaporated with a rotary evaporator. Petroleum ether refers to the fractions boiling in the range 40–60 °C. Flash chromatography was carried out with Merck silica gel (230–400 mesh). Where necessary reactions were carried out under N_2. Elemental analyses were performed by the microanalytical laboratory of Dipartimento di Chimica, University of Ferrara.

General Procedure for the Preparation of 3′- or 4′-Substituted 3-Amino-2-(methoxycarbonyl)-4,5-dihydrothiophene Derivatives 5a–c. To a cooled (0 °C) and well-stirred solution of sodium methoxide (0.46 g, 0.02 mol) in methanol (10 mL), were added methyl thioglycolate (1.6 mL, 0.017 mol) and the appropriate acrylonitrile (0.02 mol). The reaction was allowed to warm at room temperature and stirred additionally for 2 days. The mixture was cooled at 0 °C, quenched with water, and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried and concentrated *in vacuo* at reduced pressure. The residue solid was purified by flash chromatography.

5a: yellow solid, 1.89 g (70%); mp 100–102 °C (ether); IR (KBr) 3500, 3300, 1670, 1620, 1545 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.7–3.2 (m, 4H), 3.75 (s, 3H), 6.0 (bs, 2H). Anal. Calcd for $C_6H_9NO_2S$: C, 45.27; H, 5.7; N, 8.8. Found: C, 45.41; H, 5.64; N, 8.87.

5b: yellow solid, 3.07 g (77%); mp 93–95 °C (ether); IR (KBr) 3350, 1670, 1610, 1540 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.22 (dd, 2H, J = 8, 10), 3.25 (s, 3H), 4.2 (dd, 1H, J = 8, 2), 5.9 (bs, 2H), 7.2–7.45 (m, 5H). Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95. Found: C, 61.18; H, 5.50; N, 5.87.

5c: colorless solid, 2.49 g (85%); mp 55–57 °C (ether); IR (KBr) 3350, 1710, 1640, 1490 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.27 (d, 3H, J = 7), 2.71 (dd, 1H, J = 8, 11), 3–3.2 (m, 1H), 3.25 (dd, 1H, J = 8, 11), 3.35 (s, 3H), 5.9 (bs, 2H). Anal. Calcd for $C_7H_{11}NO_2S$: C, 48.53; H, 6.4; N, 8.09. Found: C, 48.71; H, 6.48; N, 7.99.

***N*-[2-(Methoxycarbonyl)-4-methyl-4,5-dihydrothiophen-3-yl]urea (7).** To a stirred and cooled solution of the enamino ester **5c** (1 g, 5.8 mmol) dissolved in dry dioxane (20 mL) was added trichloromethyl chloroformate (0.7 mL, 5.8 mmol) in one portion. The reaction course was monitored by TLC analyses (about 8 h was necessary to complete the reaction). The mixture was concentrated *in vacuo*, and the residue, dissolved in dry $CHCl_3$ (30 mL), was bubbled with ammonia gas for 10 min. Finally, the solution was concentrated again *in vacuo* affording **7** as a white solid material which was further purified by crystallization from MeOH: 1.16 g (89% yield); mp 230–231 °C (MeOH); IR (KBr) 3400–3250, 1720, 1650, 1580, 1430 cm^{-1}; ^{1}H NMR (DMSO) δ 1.26 (d, 3H, J = 7), 2.73 (dd, 2H, J = 7, 11), 3.1–3.25 (m, 1H), 3.28 (s, 3H), 3.38 (dd, 1H, J = 8, 11), 7.8 (bs, 2H), 8.9 (bs, 1H). Anal. Calcd for $C_8H_{12}N_2O_3S$: C, 44.43; H, 5.59; N, 12.95. Found: C, 44.29; H, 5.68; N, 12.71.

General Procedure for Preparation of 3′- or 4′-Substituted *N*^{1}-Phenyl-*N*^{2}-[2-(methoxycarbonyl)-4,5-dihydrothiophen-3-yl]urea Derivatives 6a,b. To a solution of enamino esters **5a,b** (0.017 mol) in dry toluene (20 mL) was added phenyl isocyanate (1.85 mL, 0.017 mol) dissolved in toluene (3 mL) dropwise and the reaction allowed to proceed with stirring at room temperature for 12 h. After removal of the solvent under reduced pressure, **6a,b** were obtained as solid materials which were crystallized from an appropriate solvent.

6a: colorless solid, 3.54 g (75%); mp 160–162 °C (EtOH); IR (KBr) 3250, 1730, 1660, 1590, 1540 cm^{-1}; ^{1}H NMR (DMSO) δ 3–3.3 (m, 2H), 3.5–3.75 (m, 2H), 3.75 (s, 3H), 7.2–7.6 (m, 5H), 9.5 (bs, 1H), 9.9 (bs, 1H). Anal. Calcd for $C_{13}H_{14}N_2O_3S$: C, 56.10; H, 5.07; N, 10.06. Found: C, 56.15; H, 5.08; N, 9.99.

6b: colorless solid, 4.69 g (78%); mp 172–173 °C (MeOH); IR (KBr) 3260, 1720, 1640, 1540 cm^{-1}; ^{1}H NMR (DMSO) δ 3.2 (dd, 2H, J = 8, 11), 3.27 (s, 3H), 4.2 (dd, 1H, J = 8, 1.5), 7.2–7.6 (m, 10H), 8.9 (bs, 1H), 9.5 (bs, 1H). Anal. Calcd for $C_{19}H_{18}N_2O_3S$: C, 64.39; H, 5.12; N, 7.9. Found: C, 64.25; H, 5.18; N, 7.99.

General Procedures for the Preparation of 6,7-Dihydrothieno[3,2-*d*]pyrimidine-2,4-dione Derivatives 8a–c. Compounds **6a,b** and **7** (0.02 mol) were dissolved in aqueous NaOH (60 mL, 5%) and warmed at reflux for 30 min. After the mixture was cooled at 0 °C, aqueous 5% HCl was added dropwise to pH 3. The precipitated product was filtered and crystallized from an appropriate solvent.

8a: colorless solid, 4.2 g (87%); mp 260–263 °C (EtOH); IR (KBr) 3180, 3080, 1720, 1630, 1580 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.1–3.5 (m, 4H), 7.1–7.45 (m, 10H), 9.8 (bs, 1H). Anal. Calcd for $C_{12}H_{10}N_2O_2S$: C, 58.52; H, 4.09; N, 11.37. Found: C, 58.45; H, 4.14; N, 11.45.

8b: colorless solid, 5.98 g (93%); mp 248–250 °C (EtOH); IR (KBr) 3350–3150, 1710, 1580, 1430 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.25 (dd, 2H, J = 8, 12), 4.31 (dd, 1H, J = 8, 2), 7.2–7.5 (m, 10H), 9.4 (bs, 1H). Anal. Calcd for $C_{18}H_{14}N_2O_2S$: C, 67.06; H, 4.38; N, 8.69. Found: C, 67.11; H, 4.29; N, 8.77.

8c: colorless solid, 2.5 g (68%); mp 188–190 °C (MeOH); IR (KBr) 3400–3200, 1690, 1670, 1590, 1430 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (d, 3H, J = 7), 3.15 (dd, 1H, J = 4, 11), 3.21–3.35 (m, 1H), 3.48 (dd, 1H, J = 8, 11), 6.8 (bs, 1H), 9.5 (bs, 1H). Anal. Calcd for $C_7H_8N_2O_2S$: C, 45.64; H, 4.38; N, 15.21. Found: C, 45.55; H, 4.46; N, 15.09.

General Procedure for the Preparation of 5-(Alkylthio)-6-vinylpyrimidine-2,4-dione Derivatives 11a–c. Benzyl bromide (1.78 mL, 0.015 mol) was added to a solution of **8a–c** (0.01 mol) in aqueous NaOH 1N (50 mL). The mixture was stirred at room temperature and the course of the reaction monitored by TLC analyses (about 24 h was necessary to complete the reaction). The aqueous basic solution was sequentially extracted with Et_2O (3 × 30 mL), acidified to pH 3 with HCl (10%), and extracted again with CH_2Cl_2 (3 × 30 mL). The methylene chloride organic layers were recombined, dried, and concentrated *in vacuo* to give the crude **11a–c** as solid materials which were further purified by flash chromatography (petroleum ether–EtOAc 1:1).

11a: colorless solid, 2.68 g (80%); mp 186–188 °C (MeOH–toluene); UV (MeOH) λ 207 (ϵ 28 238), λ 301 (ϵ 5922); IR (KBr) 3200, 1720, 1650, 1580, 1400 cm^{-1}; ^1H NMR (DMSO) δ 4.0 (s, 2H), 5.35 (d, 1H, J = 12), 5.8 (d, 1H, J = 18), 6.85–6.95 (m, 1H), 7.1–7.5 (m, 10H), 10.2 (bs, 1H); ^{13}C NMR (DMSO) δ 37.72, 103.27, 123.81, 126.34, 126.82, 127.73, 128.38, 135.02, 137.20, 149.84, 150.50, 161.50. Anal. Calcd for $C_{19}H_{16}N_2O_2S$: C, 67.84; H, 4.79; N, 8.33. Found: C, 67.76; H, 4.88; N, 8.51.

11b: colorless solid, 3.21 g (78%); mp 203–205 °C (MeOH); UV (MeOH) λ 206 (ϵ 33 410), λ 312 (ϵ 14 513); IR (KBr) 3250–3150, 1710, 1640, 1530, 1380 cm^{-1}; ^1H NMR (DMSO) δ 4.21 (s, 2H), 6.72 (d, 1H J = 14), 7.1 (d, 1H, J = 14), 7.1–7.7 (m, 15H), 10.45 (bs, 1H); ^{13}C NMR (DMSO) δ 37.17, 102.94, 117.88, 126.37, 126.96, 127.68, 128.38, 128.39, 129.40, 134.58, 135.13, 136.71, 137.55, 149.92, 151.31, 161.56. Anal. Calcd for $C_{25}H_{20}N_2O_2S$: C, 72.79; H, 4.89; N, 6.79. Found: C, 72.75; H, 4.81; N, 6.65.

11c: colorless solid, 2.46 g (90%); mp 172–174 °C (EtOH); UV (MeOH) λ 209 (ϵ 15 609), λ 237 (ϵ 14 515), λ 305 (ϵ 7459); IR (KBr) 3300–3200, 1720, 1640, 1410 cm^{-1}; ^1H NMR (DMSO) δ 2.11 (d, 3H, J = 7), 4.25 (s, 2H), 5.15 (d, 1H, J = 1.5), 5.5 (d, 1H, J = 1.7), 7.25–7.45 (m, 5H), 8.45 (bs, 1H), 9.4 (bs, 1H); ^{13}C NMR (DMSO) δ 17.05, 37.25, 102.51, 124.47, 125.41, 129.51, 132.77, 135.97, 137.14, 149.91, 156.79, 161.36. Anal. Calcd for $C_{14}H_{14}N_2O_2S$: C, 61.29; H, 5.14; N, 10.21. Found: C, 61.20; H, 5.05; N, 10.35.

Acknowledgment. Thanks are due to the Italian MURST (grant 40% and 60%) and CNR for financial support.

JO9417941