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An Efficient Synthesis of Thioisomünchnones Derived from Uracils and Uridine: Novel Type of Mesoionic Nucleosides[1]

Heinrich Wamhoff,*,† Christof Höhmann,† and Pál Sohár‡

Kekulé-Institut für Organische Chemie und Biochemie, Universität Bonn, Gerhard-Domagk-Strasse 1, D-53121 Bonn, Germany, and Institute of Inorganic and General Chemistry, Eötvös-Loránd University, Pázmány sétany 2, H-1117 Budapest, Hungary

wamhoff@uni-bonn.de

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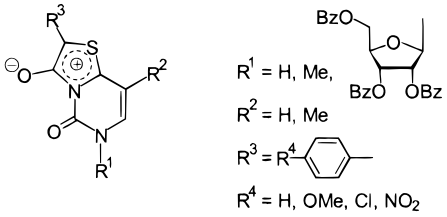
ABSTRACT



Synthetic approaches to a variety of thioisomünchnones derived from uracils and uridine are described, as well as their properties and cycloaddition tendencies. The *anhydro*-3-hydrocy-2-phenyl-6-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)thiazolo[3,2-*c*]pyrimidine-5(6*H*)-on-4-ium hydroxide represents a novel class of mesoionic nucleosides.

In 1951 Duffin and Kendall[2] postulated for the first time a mesoionic thioisomünchnone structure for the product formed from *S*-(2-pyridyl)thioglycolic acid and acetanhydride.[3] Recently, several derivatives of thiosiomünchnone, or *anhydro*-4-hydroxy-1,3-thiazolium hydroxide, structure **1** (Figure 1), have been prepared.[4]

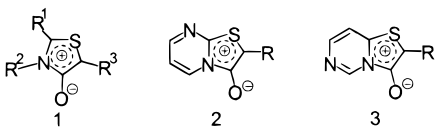


Figure 1. Some thioisomünchnones.

Thiazolo[3,2-*a*]- (**2**) and thiazolo[3,2-*c*]pyrimidines (**3**) represent condensed mesoionic systems.[5] In most cases, R represents an aryl residue which is needed for stabilization.

As thioisomünchnones based upon uracils[5] are unknown in the literature hitherto, we report here a short and efficient synthesis of this novel class of compounds. In the first step, the uracil derivatives were smoothly transformed with the aid of Lawesson's reagent into the 4-thioxo derivatives **4**.[6] Upon treatment with DL-α-bromoarylacetyl chloride **5** under mild conditions, these thiouracils are converted to afford the

† Universität Bonn.
‡ Eötvös-Loránd University.

(1) Reactions of Uracils, 25. For part 24, see: Wamhoff, H.; Sattler, C.; Sohár, P.; Rohonczy, J. *Synth. Commun.* **1999**, *29*, 3919−3937.
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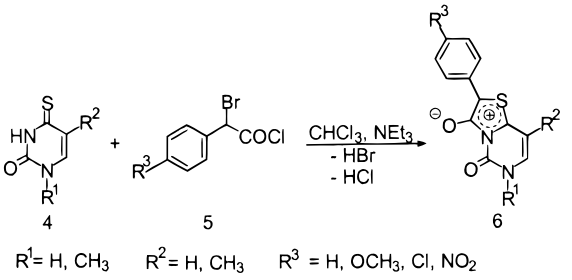
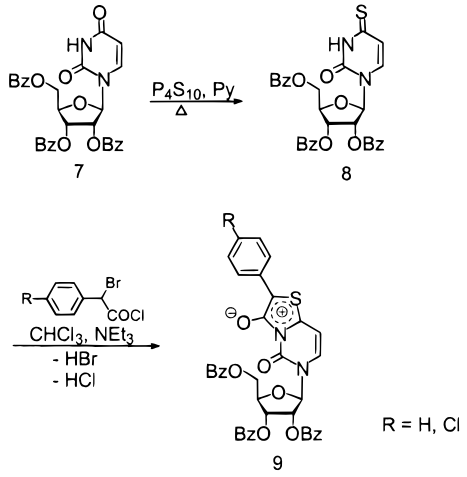
anhydro-2-aryl-3-hydroxythiazolo[3,2-*c*]pyrimidin-5(6*H*)-on-4-ium hydroxides **6** in moderate to good yields (21−83%) (Scheme 1).[7] Suprisingly, this synthesis was not transferable to the isomeric 2-thiouracils.

Scheme 1



This transformation could be easily transferred to uridine, after protection of the sugar moiety **7** and thionation with P_4S_{10} in pyridine[8] in 91−98% yield (Scheme 2). **9** represents

Scheme 2



the first nucleosidic thioisomünchnones, derived from uridine, a novel class of mesoionic nucleosides that have been characterized by spectroscopic methods, especially FAB-MS and MALDI-TOF.[9]

Although in the literature the term "mesoionic nucleosides" has been used for several years,[10] compounds **10** and **11** shown in Scheme 3 represent *zwitterionic* or *betainic* nucleosides according to the definition of Ollis and Ramsden,[11] where the term "mesoionic" is reserved for five-membered heterocycles and *anhydro*-5-(dimethylamino)-3-mercapto-4-methyl-1-*β*-D-ribofuranosyl-1,2,4-triazolium hydroxide **12** described by Yokoyama et al.[12] is the only real mesoionic nucleoside known hitherto (Figure 2).

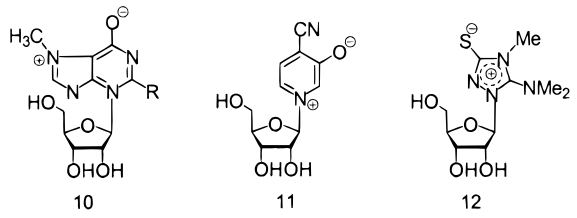


Figure 2.

While uracils are known to possess a weak solubility in common solvents generally (therefore 1,3-dialkylated derivatives serve as model compounds),[5] the thioisomünchnones derived from uracils show a similar behavior; the solubility can be effectively improved by substitution of the remaining lactamic NH by a methyl substituent or by a sugar moiety (Figure 3).

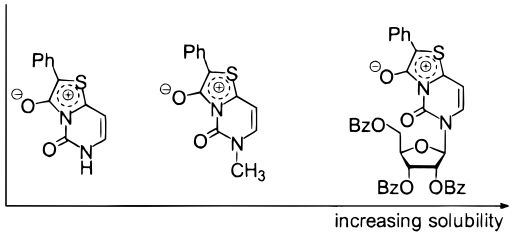


Figure 3. Substituent dependency of the solubility.

The thioisomünchnones **6** and **9** obtained form intense colored solids and exhibit typical and characteristic negative solvatochromism.[13] As shown in Table 1, the *N*-methylated mesoionic thiazolo[3,2-*c*]pyrimidine **6b** exhibits in its UV−vis spectrum the highest UV shift, $\Delta\lambda_{max} = 92$ nm, for the

(7) **Representative Procedure**. *anhydro*-3-Hydroxy-8-methyl-2-phenylthiazolo[3,2-*c*]pyrimidine-5(6*H*)-on-4-ium hydroxide **6** (R^1 = H, R^2 = Me, R^3 = H). To a suspension of 4-thiothymine (4 mmol, 510 mg) in absolute $CHCl_3$ (10 mL) is added dropwise a solution of acid chloride **5** (930 mg, 4 mmol) in absolute $CHCl_3$ (4 mmol). The mixture is stirred for 15 min; then absolute NEt_3 (1.12 mL, 8 mmol) is slowly added. The color of the suspension changes significantly from yellow-orange to deep violet in a slightly exothermic reaction. After the solution is stirred for an additional 3−4 h at ambient temperature, the precipitate is filtered off, washed with $CHCl_3$, dissolved in TFA, and precipitated again with H_2O. The product is stirred for 10 min in boiling H_2O and filterd hot, and the thioisomünchnone is washed with EtOH and ether and dried finally at 50 °C in vacuo. Yield: 650 mg (63%) of a ruby-red amorphous solid, mp 246−249 °C; FTIR (KBr) 3046, 2875, 1765, 1622, 1577, 1368, 1230, 1169 cm^{-1}; UV (MeCN) λ (log ϵ) = 503 (3.21), 404 (3.42), 301 (3.37); ^{1}H NMR (250.13 MHz, TFA-*d*) δ 2.46 (s, 3H), 7.54−7.57 (m, 3H), 7.76−7.80 (m, 3H); ^{13}C NMR (100.62 MHz, TFA-*d*) δ 13.99, 112.49, 114.65, 127.63, 128.78, 131.37, 132.27, 137.23, 148.26, 150.59, 161.40; MS (EI, 70 eV) *m/z* (rel intensity) 258.0 (M^+, 54%); HR-MS calcd for $C_{13}H_{10}N_2O_2S$ 258.0463, found 258.0468. Anal. Calcd for $C_{13}H_{10}N_2O_2S$: C, 60.45; H, 3.90; N, 10.85; S, 12.41. Found: C, 60.06; H, 3.88; N, 10.86; S, 12.38.

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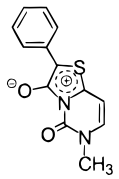
(9) **Representative Procedure**. *anhydro*-3-Hydroxy-2-phenyl-6-(2′,3′,5′-tri-*O*-benzoyl-*β*-D-ribofuranosyl)thiazolo[3,2-*c*]pyrimidine-5(6*H*)-on-4-ium hydroxide **9** (R = H). To a solution of 1-(2′,3′,5′-tri-*O*-benzoyl-*β*-D-ribofuranosyl)-4-thiouracil (2.29 g, 4 mmol) in absolute $CHCl_3$ (10 mL) is added dropwise a solution of freshly distilled acid chloride **5** (930 mg, 4

Table 1. Dependency of the λ_{max} from the Polarity of the Solvent

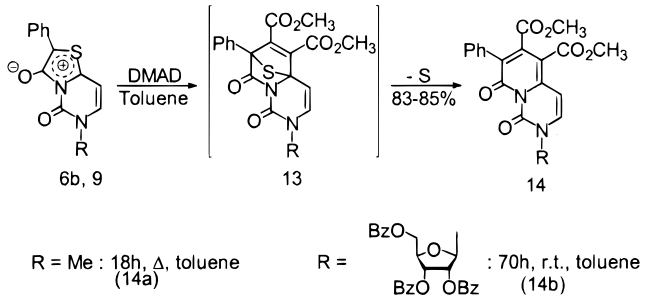


Solvent	E_T^N-Value [13]	λmax [nm]
Toluene	0.099	559
Chloroform	0.259	538
Acetone	0.355	532
Acetonitrile	0.460	507
Methanol	0.762	494
2,2,2-Trifluorethanol	0.898	470
Water	1.000	467

CT band; these measurements parallel the earlier findings of Ishchenko[14] for a related pyrimidine derivative.

As mesoionic heterocycles of the type A[15] contain masked or latent 1,3-dipole moieties,[11] thioisomünchnones may be considered as latent thiocarbonylylides; Potts et al.[16] have systematically investigated the cycloaddition tendency of dipolarophiles toward thioisomünchnones and found that reactive acetylene derivatives can lead in a cycloaddition−extrusion sequence either to pyrimidones (S-extrusion) or thiophenes (isocyanate extrusion), directed more by steric than electronic effects.[16] We have found that in reacting soluble methylated (**6b**) or glycosylated (**9**) thioisomünchnones with acetylenedicarboxylates (DMAD), after 1,3-dipolar cycloaddition, the intermediary adducts underwent a sulfur extrusion reaction to form 1,8-dioxo-2*H*,8*H*-pyrido-[1,2-*c*]pyrimidinedicarboxylates **14a**,**b**.

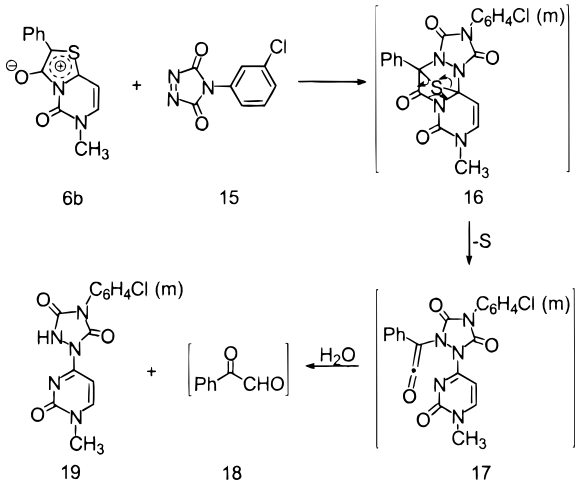
Scheme 3



6b had to be heated for 18 h while nucloside **9** was converted after 70 h of standing at room temperature; however, the product **14b** formed could only be purified with difficulty.[17]

Then, we reacted thioisomünchnone **6b** with 4-(3′-chlorophenyl)-1,2,4-triazoline-3,5-dione **15**[18] for the first time at temperatures lower than and up to room temperature (accompanied by intense color changes). The colorless compound precipitating from the solution was not the expected reaction product; MS revealed that subsequent fragmentations took place.[19]

Scheme 4. Suggested Cycloaddition Extrusion Mechanism



The molecular formula of **19** derived from the HMQC (CH−COSY) and HMBC (CH−COLOC) experiments leads

mmol) within 10 min, which causes a color change from orange to red. Then absolute NEt_3 (1.12 mL, 8 mmol) is slowly added, while the solution changes from red to deep violet in a slightly exothermic reaction. The suspension formed is stirred for 3−4 h at ambient temperature, and the ammonium salts formed are removed by treatment with a saturated $NaHCO_3$ solution and 2-fold extraction with H_2O. After drying (Na_2SO_4) the solvent is evaporated and the residue is dried at 50 °C in vacuo: yield 2.70 g (98%) of a deep violet amorphous solid of mp 106−110 °C; FTIR (KBr) ν 3067, 2967, 1726, 1624, 1593, 1266, 1094 cm^{-1}; UV (MeCN) λ (log ϵ) = 529 (4.11), 281 (4.14), 227 (4.86); ^1H NMR (400, 13 MHz, DMSO-d_6) δ 4.78 (m, 2H), 4.92 (dt, 1H, J = 7.25, 3.94 Hz), 6.05 (pt, 1H, J = 6.65 Hz), 6.15 (dd, 1H, J = 6.15, 3.20 Hz), 6.41 (d, 1H, 2.96 Hz), 7.11 (t, 1H, J = 7.38 Hz), 7.20(d, 1H, J = 7.63 Hz), 7.38 (dd, 2 Hz, J = 8.37, 7.38 Hz), 7.47 (dd, 2H, J = 8.13, 7.51 Hz), 7.56 (m, 4H), 7.66−7.76 (m, 4H), 7.89 (m, 3H), 7.97 (d, 1H, J = 7.38 Hz), 8.01 (dd, 2H, J = 8.36, 1.23 Hz), 8.09 (dd, 2H, J = 8.36 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 63.85, 71.74, 74.28, 80.73, 90.28, 94.31, 101.19, 124.27−133.82, 145.01, 146.75, 156.66, 165.25−166.09; MS (FAB) *m*/*z* (rel intensity) 689.1 (M^+, 6.5%); MALDI-TOF Da/e (rel intensity) (688.8 (M^+, 100%) 689.8 (M + H^+, 41%), 44.59 (M^+ − aglycone).

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(17) **14b** was enriched after 2-fold column chromatography (silica gel; EE/PE 3:2 and 1:1); the ^1H NMR displays all relevant signals, especially the protons of the sugar moiety, and both the methyl ester groups; MS-(FAB) *m*/*z* 799.1 (M^+), 663.3 (M^+ − CO), 445.1 (M^+ − aglycon). A complete purification could not be achieved, as each chromatography leads to a partial decomposition of the product.

to the unambiguous identification of the methine C and the Me group as well as single atoms of the pyrimidine and aromate moieties; further information follows from the fragmentation pattern in MS and HR-MS.

On the basis of thess data, we suggest the following cycloaddition−extrusion mechanism: After cycloaddition to intermediate **16**, sulfur is extruded by ring cleavage of the central triazinone ring to **17** which by moisture loses "phenylglyoxal" **18** to form the final urazolylpyrimidine **19**. However, a radical attack of the triazolyl radical (via disproportion reaction always concomitant with the triazolinediones)[18] could be discussed as well leading to an alternative fragmentation of the thioisomünchnone ring (Scheme 4).

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(19) Preparation of **19**: A suspension of **6b** (129 mg, 0.5 mmol) in CH_2Cl_2 (10 mL) is cooled to −30 °C and a solution of **15** (105 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) is slowly added, and intense and reversible color changes are observed. After addition, the reaction mixture is stirred for additional 2 h at −30 °C and for the same time after warming to ambient temperature. After standing for 2 d in the dark for completion of the reaction, the colorless precipitated product is filtered off, washed with CH_2Cl_2, and dried at 50 °C in vacuo to give 73 mg (46%) of **19** as colorless amorphous solid: mp 254 °C (dec); IR (KBr) ν = 3436, 3134, 3087, 2967, 1779, 1735, 1697, 1651, 1627 cm^{-1}; UV (DMSO) λ_{max} (log ϵ) = 350 (4.01), 327 (3.93); ^1H NMR (500.13 MHz, DMSO-d_6) δ = 3.43 (s, 3H), 7.13 (d, 1H, J = 7.24 Hz), 7.51 (dpt, 1H, J = 7.46, 1.80 Hz), 7.54 (dpt, 1H, J = 8.16, 1.84 Hz), 7.57 (ptd, 1H, J = 7.52, 0.49 Hz), 7.64 (ptd, 1H, J = 1.94, 0.51 Hz), 8.20 (d, 1H, J = 7.58 Hz); ^{13}C NMR (125.76 MHz, DMSO-d_6) δ = 38.50, 93.36, 126.47, 127.60, 129.32, 131.47, 133.19, 133.80, 148.62, 150.29, 152.08, 155.88, 156.59; MS (EI, 70 eV) *m*/*z* (rel intensity) 319.1 (M^+, 0.9%), 211.0 ($M^+ - C_5H_4N_2O$, 0.2%), 166.1 ($M^+ - C_7H_4ClNO$, 100%), 125.0 ($M^+ - C_7H_6N_4O_3$, 47%); HR-MS (FAB) calcd for $C_{13}H_{10}ClN_5O_3$ 319.0472, found 319.0481; calcd for $C_8H_6ClN_3O_2$ 211.048, found 211, 0147; calcd for $C_6H_6N_4O_2$ 166.0491, found 166.0493; calcd for C_6H_4ClN 125.0033, found 125.0035.