Synthesis of Novel Dihydrothiazolo[3,2-*a*]pyrimidinone Derivatives

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Dedicated to Professor Ernest Campaigne on the occasion of his 75th birthday

Condensation of 2-amino-4-hydroxy-2-mercaptopyrimidine (**2**) hydrate and ethyl 4-bromocrotonate gave a mixture of ethyl 7-amino-2,3-dihydro-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-3-acetate (**4**) and 2a,3-dihydro-1-thia-5,8,8b-triazaacenaphthylene-4,7(2*H*)-dione (**5**) whereas reaction of **2** with 4-bromocrotononitrile afforded only 7-amino-2,3-dihydro-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-3-acetonitrile. Reaction of the tricycle **5** (which was isolated as a hemihydrate) with excess methyl iodide/potassium carbonate in dimethylformamide resulted in both ring hydrolysis and methylation to give 3,4-dihydro-1,7-dimethyl-4-[(methylthio)methyl]-2*H*-pyrimido[1,6-*a*]pyrimidine-2,6,8(1*H*,7*H*)-trione (**10**). Methylating **5** with excess methyl iodide/sodium methoxide in methanol also resulted in ring fragmentation and methylation but instead afforded methyl 7-methylamino-2,3-dihydro-5-oxo-7*H*-thiazolo[3,2-*a*]pyrimidine-3-acetate. The mechanistic aspects of these reactions are discussed.

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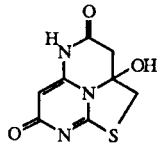
In a previous effort to prepare thiazolo[3,2-*a*]pyrimidinone derivatives, Campaigne and co-workers reported that the tricyclic carbinolamine **1** can be synthesized by reaction of 4-amino-6-hydroxy-2-mercaptopyrimidine (**2**) hydrate with ethyl 4-chloroacetoacetate [1,2]. Compound **1** was subsequently used as a key intermediate by this laboratory in the synthesis of planar "fully aromatized" thiadiazacyclazine **3** [3].



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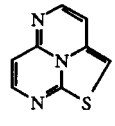
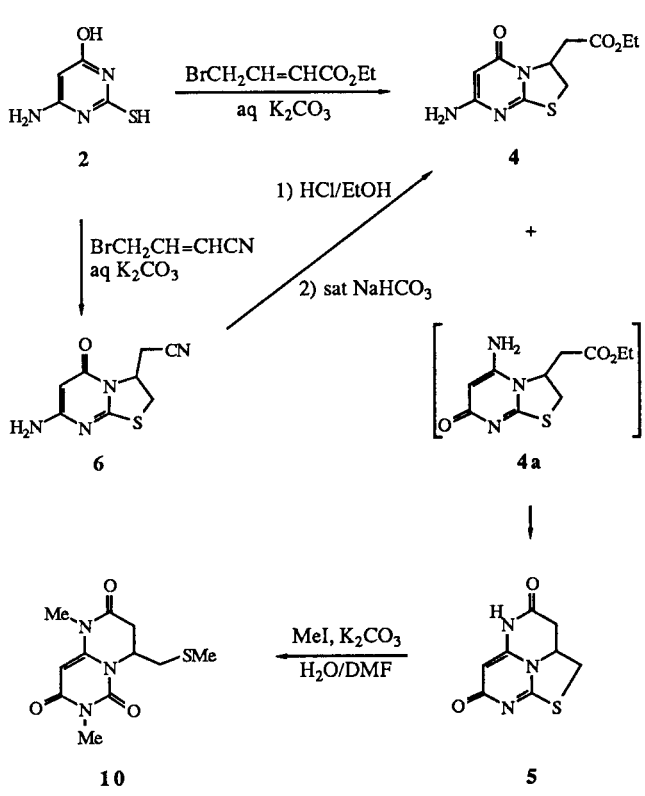


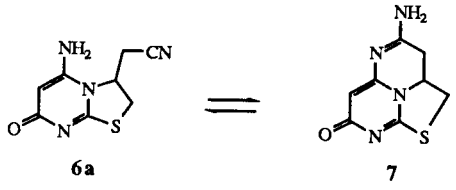
3

In honor of Professor Ernest Campaigne [4] for his many years of dedication to the field of synthetic heterocyclic chemistry and his years of service on the editorial staff of this journal, we wish to report now on the synthesis of related novel heterocycles by reaction of 4-amino-6-hydroxy-2-mercaptopyrimidine (**2**) with ethyl 4-bromocrotonate and 4-bromocrotononitrile [6,7].

As shown in Scheme 1, reaction of ethyl 4-bromocrotonate with 4-amino-6-hydroxy-2-mercaptopyrimidine hydrate (**2**) in aqueous potassium carbonate gave two products: the dihydrothiazolo[3,2-*a*]pyrimidinone acetate **4** in 11% yield and the thiatriazaacenaphthylenedione derivative **5**, which was isolated as a hemihydrate, in 50% yield. Stirring **4** in aqueous potassium carbonate at room temperature or on warming did not yield the tricyclic heterocycle **5** and confirmed that this dihydrothiazolopyrimidinone was not intermediate **4a**. Reaction of the mercaptopyrimidine **2** with 4-bromocrotononitrile in aqueous potassium carbonate gave only one product, the dihydrothiazolopyrimidinone **6** in 79% yield. A cyano absorption at 2240 cm^{-1} in the ir indicated that formation of the tricycle **7**, resulting from initial formation of **6a**, had not occurred. Also, structure **6a** was ruled out since heating the compound in ethanolic hydrogen chloride followed by neutralization with saturated sodium bicarbonate gave a 57% yield of **4** rather than **4a** or **5**.

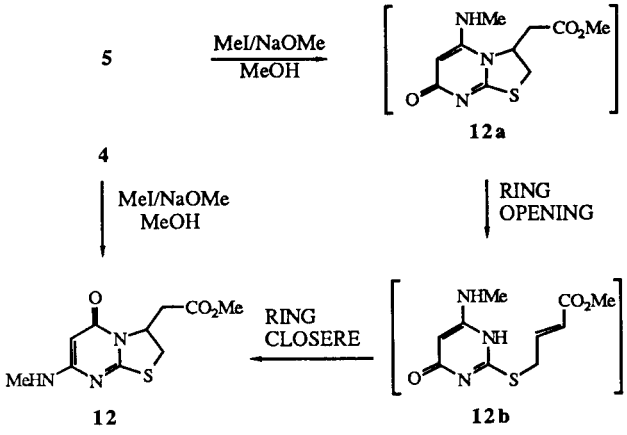
Scheme 1



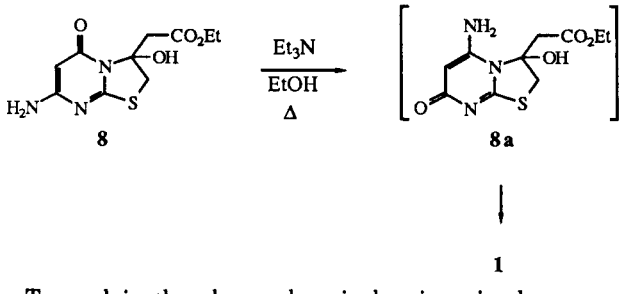


6a 7

Scheme 2

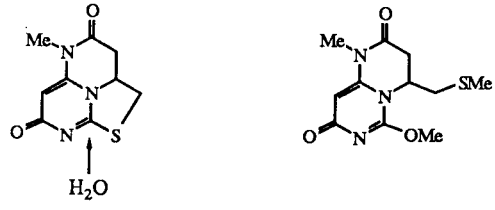


Campaigne, *et al.* [1] had also reported that reaction of **2** with ethyl 4-chloroacetoacetate under mild reaction conditions (aqueous potassium bicarbonate) gave the bicyclic carbinolamine **8**, the structure of which was proven by X-ray. Subsequent heating of **8** in triethylamine/ethanol resulted in ring opening followed by ring reclosure to give **8a** which was also trapped in this regiochemistry by further cyclization to **1**.



To explain the observed regiochemistry in these reactions, the following explanation is proposed. The adducts **4a**, **6a** and **8a** are kinetically formed in the aqueous base media but prefer to quickly isomerise to the more thermodynamically stable regioisomers **4**, **6** and **8**. Isomerization would occur by reopening of the thiazoline ring to give back the open chain intermediate which could then recyclize by way of the other pyrimidine ring nitrogen. Only in the case of **4a** is the kinetic adduct trapped under the reaction conditions by conversion to the tricycle **5** (**8** cyclized to **1** only on further heating). Key to this argument is that isomerization of **4** to **4a** (followed by subsequent conversion to **5**) does not occur and that **4** is a minor adduct from the cyclization whereas **6** and **8**, which have the same regiochemistry, are major products. Compounds **6** and **8** are formed in good yield since the kinetic adducts **6a** and **8a** are not trapped as the tricycles. Formation of the tricycle **7** is either not preferred or is reversible.

Methylation of the hemihydrate **5** by warming at 70° for 15 minutes with excess methyl iodide/potassium carbonate in dimethylformamide did not give the expected *N*-methylated adduct **9** but instead gave the bicyclic heterocycle **10** in rather low yield (28%), Scheme 1. Formation of **10** most likely resulted from hydrolysis of adduct **9** along with subsequent methylation. In an attempt to improve on the hydrolysis step (and since **5** was analyzed as only a hemihydrate), water (~3 equivalents) was added to the reaction but only a modest improvement in yield (37%) was observed. Stirring this reaction (without adding water) at room temperature 24 hours in an attempt to isolate **9** only resulted in a lower and more impure yield of **10**.



9 11

In an attempt to determine whether ring fragmentation of **9** by sodium methoxide might compete with hydrolysis, **5** was stirred with excess methyl iodide/sodium methoxide in methanol at room temperature for 24 hours. The expected adduct **11** was not obtained however and the bicyclic adduct **12** was isolated in 30% yield instead, Scheme 2. Formation of **12** most likely resulted from methoxide attack at the amide carbonyl of **9** (rather than at the site of hydrolysis) to give the intermediate **12a** which then underwent ring opening to give **12b** which recyclized to afford **12**. Methylation of **4** with a large excess of methyl iodide/sodium methoxide in methanol also gave the same compound, thus verifying the structure of **12**. The methylation of **4** went very slowly however. Based on the above mechanistic argument, **12a** would correspond to the suggested kinetic adducts **4a**, **6a** and **8a**. It would also be expected to isomerize to the more thermodynamically stable regioisomer **12** and experimently this was observed.

In summary, these results continue to demonstrate that interesting and novel heterocycles can be obtained by reaction of 4-amino-6-hydroxy-2-mercaptopyrimidine (**2**) with suitably chosen alkylating agents. Regarding the regiochemistry, these results are in agreement with the previous finding of Campaigne, *et al.* [1], and further ex-

emplify the mechanistic aspects of the cyclization reaction as well.

EXPERIMENTAL

All melting points were determined on a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 783 spectrophotometer and nmr/cmr spectra were recorded on a VARIAN XL-200 spectrometer. Chemical shifts are expressed in parts per million downfield from TMS and the cmr spectra were proton decoupled. Mass spectra were obtained on DuPont Model 21-492 spectrometer and elemental analyses were carried out by Micro-Analysis Inc., Wilmington, Delaware.

Ethyl 7-Amino-2,3-dihydro-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-3-acetate (**4**) and 2a,3-Dihydro-1-thia-5,8,8b-triazaacenaphthylene-4,7(2*H*)-dione (**5**).

To a stirred solution of 10.0 g (62.1 mmoles) of 4-amino-6-hydroxy-2-mercaptopyrimidine (**2**) hydrate (Aldrich) and 15.0 g (108.7 mmoles) of potassium carbonate in 110 ml of water, 20.0 ml of ethyl 4-bromocrotonate [5] was added and the mixture stirred at room temperature for 1 hour. The *p*H of the reaction mixture was adjusted to 7 by addition of concentrated hydrochloric acid. The insoluble white solid was filtered, washed thoroughly with water and ethyl acetate followed by oven drying to give 6.8 g (50%) of **5**. Recrystallization from aqueous dimethyl sulfoxide gave an analytically pure sample of the hemihydrate, mp >250°; ir (Nujol): 3490 (NH), 1700 (C=O), 1640, 1585 (C=N) cm^{-1}; ms: (EI) 209 (M^+); ^1H nmr (DMSO-d_6): δ 2.75-3.10 (m, 2H), 3.20-3.45 (m, 1H-H_2O), 3.62 (dd, J = ~6, 11 Hz, 1H), 4.75-4.97 (m, 1H), 5.10 (s, 1H), 11.12 (broad s, 1H); ^{13}C nmr (DMSO-d_6): δ 170.0, 165.8, 164.1, 145.8, 86.4, 57.9, 36.0, 33.2.

Anal. Calcd. for $C_8H_7N_3O_2S \cdot \frac{1}{2}H_2O$: C, 44.03; H, 3.69; N, 19.26. Found: C, 44.29; H, 3.93; N, 19.22.

An additional 150 ml of ethyl acetate was added to the above filtrate. The organic layer was separated, washed with water, brine, dried over magnesium sulfate and evaporated *in vacuo* to give an oily yellow residue. Addition of *n*-butyl chloride and a minimal amount of ethanol to the residue and allowing to set overnight resulted in crystallization of a solid which was filtered to give 1.8 g (11%) of **4**, mp 128-129° (acetonitrile/*n*-butyl chloride); ir (Nujol): 3410, 3320, 3200 (NH), 1725, 1650-1610 (C=O, C=N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.26 (t, J = 7 Hz, 3H), 2.77-3.08 (m, 2H), 3.26 (d, J = 12 Hz, 1H), 3.74 (dd, J = 8, 12 Hz, 1H), 4.18 (q, J = 7 Hz, 2H), 4.72 (broad s, 2H), 5.14 (s, 1H), 5.23-5.38 (m, 1H); ^{13}C nmr (deuteriochloroform): δ 170.1, 164.5, 163.0, 161.3, 83.3, 61.1, 56.9, 34.7, 31.5, 14.1.

Anal. Calcd. for $C_{10}H_{13}N_3O_3S$: C, 47.05; H, 5.13; N, 16.46. Found: C, 47.38; H, 5.27; N, 16.56.

7-Amino-2,3-dihydro-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-3-acetonitrile (**6**).

To a solution of 10.0 g (62.1 mmoles) of 4-amino-6-hydroxy-2-mercaptopyrimidine (**2**) hydrate (Aldrich) and 15.0 g (108.7 mmoles) of potassium carbonate stirring in 120 ml of water at room temperature, 18.0 g of crude 4-bromocrotononitrile [6,7] was added. A solid soon precipitated and the resulting dark suspension stirred 1.5 hours. The insoluble material was filtered and washed thoroughly with water followed by ethyl acetate to give after oven drying 10.2 g (79%) of gray colored **6**. Recrystallizing twice from aqueous dimethyl sulfoxide gave light brown crystals, mp 238-244° dec; ir (Nujol): 3310, 3115 (NH), 2240 (C≡N) 1660, 1630 (C=O, C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.92-3.45 (m, 3H-H_2O), 3.82 (dd, J = ~7, 11 Hz, 1H), 4.83 (s, 1H), 4.95-5.10 (m, 1H), 6.64 (broad s, 2H); ms: (CI) 209 (M+1); ^{13}C nmr (DMSO-d_6): δ 164.1, 163.9, 160.2, 117.3, 80.3, 55.7, 30.2, 20.4.

Anal. Calcd. for $C_8H_8N_4OS$: C, 46.15; H, 3.87; N, 26.91. Found: C, 46.13; H, 3.85; N, 26.55.

3,4-Dihydro-1,7-dimethyl-4-[(methylthio)methyl]-2*H*-pyrimido-[1,6-*a*]pyrimidine-2,6,8(1*H*,7*H*)-trione (**10**).

To a mixture of 1.2 g (5.5 mmoles) of **5** (hemihydrate) and 2.5 g (18 mmoles) of potassium carbonate stirring in 15 ml of dimethylformamide at room temperature, 0.3 ml of water and 2.5 ml of methyl iodide were added. The mixture was stirred and heated at 70° for 15 minutes. Excess water and 150 ml of ethyl acetate were added to the yellow mixture. The ethyl acetate layer was separated and washed with water (2 x), brine, dried over magnesium sulfate and evaporated *in vacuo* to give a yellow oily residue to which minimal *n*-butyl chloride was added. The solid which crystallized was filtered to afford 0.55 g (37%) of **10**, mp 119-120° (*n*-butyl chloride): ir (Nujol): 1695, 1680 (C=O), 1600 (C=N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.20 (s, 3H), 2.50-2.95 (m, 3H) 3.18-3.31 (m, 4H), 3.36 (s, 3H), 5.00-5.15 (m, 1H), 5.37 (s, 1H); ms: (EI) 269 (M^+).

Anal. Calcd. for $C_{11}H_{15}N_3O_3S$: C, 49.06; H, 5.61; N, 15.60. Found: C, 49.26; H, 5.53; N, 15.64.

Carrying out the above procedure without the addition of water gave **10** in 28% yield.

Methyl 7-Methylamino-2,3-dihydro-5-oxo-7*H*-thiazolo[3,2-*a*]-pyrimidine-3-acetate (**12**).

A stirred suspension of 2.0 g (9.2 mmoles) of the hemihydrate of **5** in 30 ml of methanol was treated with 4.5 ml of 25 weight percent of sodium methoxide in methanol (Aldrich) and 4.0 ml of methyl iodide at room temperature. A solution formed. After stirring overnight, excess water and 150 ml of methylene chloride were added to the reaction mixture. The organic layer was separated immediately and washed with water, brine and dried over magnesium sulfate. Evaporation of solvent *in vacuo* gave a white solid which was suspended in *n*-butyl chloride and filtered to give 0.7 g (30%) of **12**, mp 184-185° (acetonitrile); ir (Nujol): 3280 (NH), 1720, 1700 (C=O), 1645 (C=N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.77-3.13 (m, 5H), 3.25 (d, J = 12 Hz, 1H), 3.63-3.82 (m, 4H), 4.68-4.96 (m, 1H), 4.98 (s, 1H), 5.23-5.40 (m, 1H).

Anal. Calcd. for $C_{10}H_{13}N_3O_3S$: C, 47.05; H, 5.13; N, 16.46. Found: C, 47.28; H, 5.17; N, 16.32.

Compound **12** was also prepared by the following method. A solution of 1.0 g (3.9 mmoles) of **4** in 20 ml of methanol was charged with 3.5 ml of 25 weight percent sodium methoxide in methanol and 3.0 ml of methyl iodide. The reaction mixture was stirred at room temperature overnight. At this point, only a small amount of product had formed as revealed by tlc comparison (20:1 methylene chloride/methanol) with an authentic sample of **12**. Since the reaction tested neutral to wet litmus paper, the same amounts of sodium methoxide in methanol and methyl iodide were added and the reaction mixture was heated at reflux until the reaction tested neutral again to wet litmus paper again. Addition of the above amounts of sodium methoxide and methyl iodide followed by heating was repeated four more times. Excess

water and 150 ml of methylene chloride was added to the reaction mixture. The organic layer was separated and washed with water, brine, dried over magnesium sulfate and evaporated *in vacuo* to give a yellow oily solid residue to which *n*-butyl/chloride/acetonitrile was added. Filtering gave 0.35 g (35%) of a solid which on recrystallization from acetonitrile had the same melting point, ir and nmr as **12**.

REFERENCES AND NOTES

[1] E. Campaigne, K. Folting, J. C. Huffman and T. P. Selby, *J. Heterocyclic Chem.*, **18**, 575 (1981).

[2] E. Campaigne and T. P. Selby, *J. Heterocyclic Chem.*, **16**, 725 (1979).

[3] T. P. Selby, *J. Org. Chem.*, **53**, 2386 (1988).

[4] Professor Campaigne is currently Professor Emeritus of Chemistry, at Indiana University, Bloomington, Indiana.

[5] Ethyl 4-bromocrotonate was commercially available (Aldrich) as a 75% technical material.

[6] A crude sample of 4-bromocrotononitrile was readily prepared by heating crotononitrile and *N*-bromosuccinimide with a catalytic amount of azobisisobutyronitrile in carbon tetrachloride under a high intensity heatlamp overnight. It was used directly without distillation and in excess in the next reaction.

[7] A. Bruylants and P. Couvreur, *Bull. Soc. Chim. Belg.*, **61**, 253 (1952).