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The Synthesis of Pyrimidineisothiazolones. The Effect of Temperature on the Addition of Aryl Amines to Functionalized Pyrimidines.

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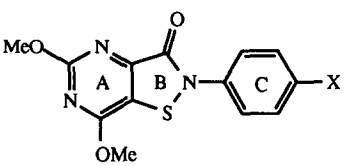
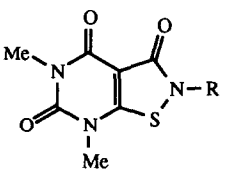
Abstract: A new synthesis for the hither-to-unknown pyrimidine isothiazolones **1** and **2** is detailed. The low temperature selectivity of amine nucleophiles on 6-chloropyrimidine-5-acylbromides (**12**) for the acylbromide over the ring chloride provides a new procedure for the functionalization of 5-carboxypyrimidines.

As part of our drug discovery effort in the area of inflammatory diseases, we identified a novel class of pyrimidine fused isothiazolones, **1** and **2**, as therapeutic targets for the area of cartilage protection. A paper by Schaper[1] on the use of monothiomalonic amides to make 3-oxo-2,3-dihydroisothiazolo[5,4-*d*]pyrimidines, is the only literature report to our knowledge, relating to the synthesis of this class of compounds. We desired an expeditious route to **1** more amenable to the production of C-ring analogs, as well as an accessible synthesis of the hither-to-unknown isomer(s), **2**. Also detailed is an interesting temperature selectivity effect observed on the addition of amine nucleophiles to doubly activated pyrimidines (**12**). This procedure is a new method for selectively adding functional groups to the pyrimidine framework.



1a X=OMe
1b X=CF_3
1c X=H

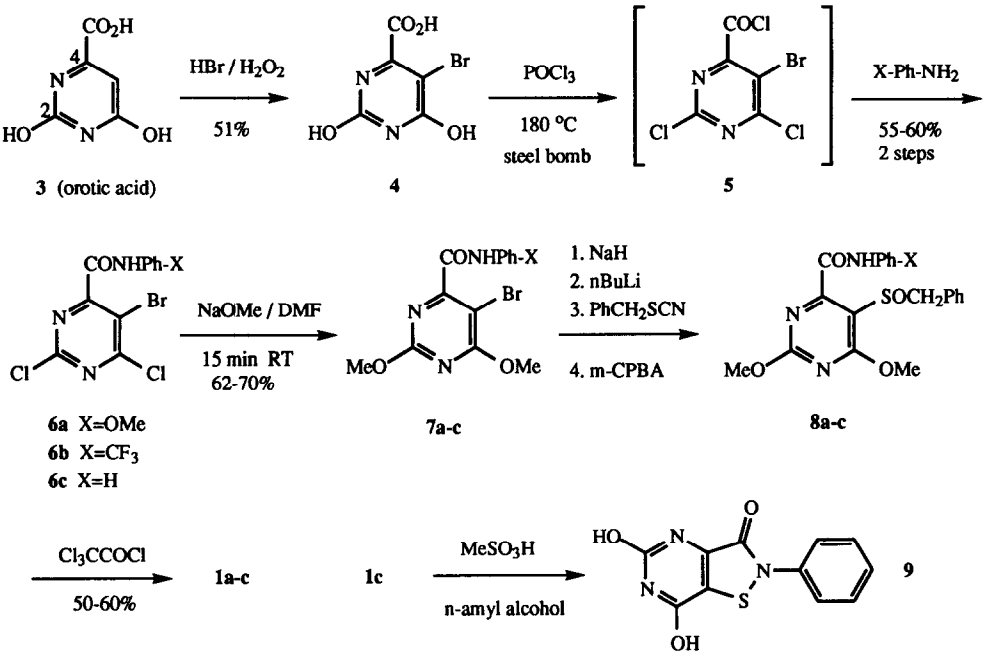


2a R=Ph
2b R=p-BrPh
2c R=Bzl

Our synthetic route to **1** is given in Scheme 1. Complementary to the Schaper synthesis of the pyrimidine isothiazolone **1**, in which the pyrimidine ring was formed from suitably substituted acyclic precursors, we chose to take advantage of the readily available orotic acid **3**, as starting material. This allowed us to examine oxygen substituents in the 2 and 6 positions of the A-ring. 5-Bromoorotic acid **4** was prepared in 51% yield by the action of HBr/H_2O_2 on **3**. Conversion of the 4-carboxy group of **4** to an acid chloride (as an amide precursor) proved to be problematic due to the insolubility of **4** in a variety of solvents appropriate for chlorination. However, by heating **4** in $POCl_3$ (20 ml/g) at 170 °C for 6 h in a steel bomb, followed by azeotropic removal of the excess phosphorous oxychloride with toluene, and reaction with an appropriately substituted aniline, we obtained **6a-c** in 50-60% yield for the two step procedure.

Reaction of NaOMe in DMF for 15 min at RT, gave selective displacement by methoxide of the chlorides , affording **7a-c** in 60-70% yields. To form the B-ring (isothiazolone), we next required installation of sulfur, in the 6-position of the pyrimidine ring of **7**. Difficulty in displacing the 5-bromo group with a variety of sulfur nucleophiles encouraged us to employ an electrophilic sulfur reagent to effect this transformation. Normal amide deprotonation with NaH followed by Li - halogen exchange with nBuLi and trapping with dibenzyldisulfide produced, after workup, the 5-protio material only. Use of the more electrophilic benzylthiocyanate[2] gave the required 5-benzyl sulfides in 30-40% yields, which were readily oxidized with mCPBA to their corresponding sulfoxides **8a-c**. Ring closure to give the desired isothiazolones **1a-c** was accomplished by dropwise addition of **8a-c** in CH_2Cl_2 to a solution of trichloroacetyl chloride in

Scheme 1



methylene chloride. In the case of **1a**, conversion to the corresponding 2,4-*bis*-oxo derivative **9** was also accomplished by treating the former with methanesulfonic acid in n-amyl alcohol.

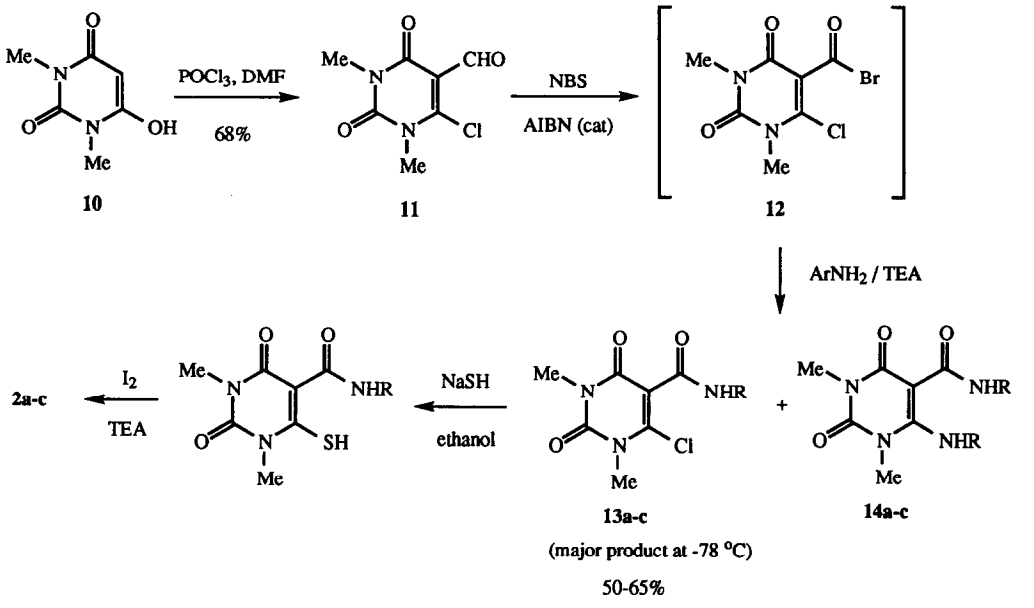
The N,N-dimethyl substituted positional isomers, **2a-c**, were prepared via a similar route, starting with N,N-dimethylbarbituric acid **10** (Scheme 2). As mentioned, these compounds were previously unreported in the literature. Vilsmeier reaction on **10** gave the corresponding 6-chloro-5-aldehyde **11** in 68% yield following

recrystallization from water.[3] Analogous to our procedure in Scheme 1, conversion of the aldehyde to the corresponding amide was first attempted via the more circuitous route of oxidation to the carboxylic acid, conversion to the acid chloride and subsequent reaction with an appropriate aniline. We discovered that direct conversion of the aldehyde to the acid bromide[4], was possible by heating **11** with NBS in CCl_4 and a catalytic amount of AIBN. Dilution[5] with CH_2Cl_2, cooling to -78 °C and slow[6] addition of the amine and external base triethylamine, gave good yields of the corresponding chloroamides **13a-c**.

An interesting temperature effect was noted for this step. Addition of the amine at 0 °C or greater to the chloroacid bromide **12**, resulted in production of the *bis*-addition product **14** only. This selectivity constitutes a useful sequence for the 5,6-functionalization of barbiturates and uracils, an otherwise difficult task.[7]

Displacement of the Cl with NaSH in ethanol was accomplished at RT with short reaction times. Cyclization to the corresponding pyrimidine isothiazolones **2a-c** was efficiently carried out using 1.1 equivalents of I_2 and TEA in CH_2Cl_2. This one-step method of ring closure to form the isothiazolone **2** was

Scheme 2



attempted on the sulfide precursor of **1** but was found to be unsuccessful. This necessitated the two step oxidation, cyclization procedure described in Scheme 1.

In conclusion, we have provided two general synthetic routes to the pyrimidineisothiazolones **1** and **2**,

starting from readily available materials. The low temperature addition of amine nucleophiles to **12** provides a useful entry into 5-carboxy-6-substituted uracils. Our biological data pertaining to the evaluation of these compounds as cartilage protectants will be included in a subsequent publication.

References and Notes

1. Schaper, W. *Synthesis* **1985**, 861-867.

2. For the use of the related reagent MeSCN as an electrophile, see: Brandsma, L.; Verkruijsse, H.D. *Preparative Polar Organometallic Chemistry* , Springer-Verlag, New York, 1987, v. 1, p 169.

3. Takeshi, A.; Yanada, R.; Bessho, K.; Yoneda, F.; Armarego, W.L.F. *J. Heterocyclic Chem.* **1991**, *28*, 1537; Yoneda, F. *Methods in Enzymology, Vol 66*, Academic Press Inc., **1980**, pp 267-277.

4. Marko, I.E.; Mekhalfia, A. *Tetrahedron Lett.* **1990**, *31*, 7237-7240.

5. It was found that filtration of the succinimide by-product, removal of the CCl_4 followed by dilution with dry CH_2Cl_2 did not offer any advantage in selectivity or yield over simply diluting the acid bromide intermediate with CH_2Cl_2 directly, followed by addition of the amine. The succinimide by-product from the bromination step appears inert to the amide forming conditions. Example procedure (**13a**); Aldehyde **11** (2.0 g, 9.9 mmol), N-bromosuccinimide (1.94 g, 11.0 mmol) and 25 mg of AIBN were combined in 40 ml of dry CCl_4 and heated to reflux under nitrogen. After 30 min, the red colored solution was cooled to ambient temperature and 45 ml of dry CH_2Cl_2 was added followed by cooling of the homogeneous solution to -78 ^oC. Aniline (0.9 ml, 9.9 mmol) and TEA (1.2 equivs.) in 5 ml CH_2Cl_2 were added via syringe pump over 90 min (see reference 5). The reaction is then quenched at -78 with 5% HCl/MeOH then allowed to reach ambient temperature. The solution is washed with 10% HCl (aqueous), saturated sodium thiosulfate, brine then dried over $MgSO_4$. Solvent removal gave a crude yellow solid that was purified on SiO_2 (75% ethyl acetate - hexane). Product **13a** 1.8 g (58%); tlc Rf 0.4 (75% ethyl acetate / hexane), ^{1}HNMR (300 MHz, $CDCl_3$) 10.48 (1H, br s), 7.62 (2H, d, 7.5), 7.35 (2H, t, 7.5), 7.13 (1H, t, 7.5); EIMS 294 (M+H, base peak Cl pattern), 260 (20); IR KBr, 3036, 1732, 1690, 1654; Elemental Analysis - calculated %C 46.17, %H 3.58, %N 12.43; Found %C 46.01, %H 3.62, %N 12.33. (Trace of **14a** also obtained).

6. Slow addition of the amine and TEA in CH_2Cl_2 was accomplished using a syringe pump over a time course of 90 min. The reaction was in fact determined to be instantaneous and the slow addition is necessary to prevent an increase in internal temperature. Faster addition times resulted in production of more of **14**.

7. Introduction of functionality into the 6-position of uracils and 5 acyl uracils have met with limited success. For example see Tanaka, H.; Hayakawa, H.; Miyasaka, T. *Tetrahedron* **1982**, *38*, 2635.

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