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An Efficient and Practical Synthesis of 2,4-Substituted Pyrido[4,3-*d*]pyrimidin-5(6*H*)-ones

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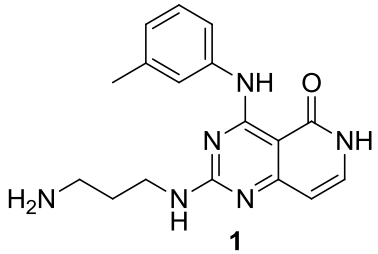
GlaxoSmithKline, Research and Development, 1250 South Collegeville Road, Collegeville, PA 19426

Abstract: We describe an efficient synthesis of 2,4-substituted pyrido[4,3-*d*]pyrimidin-5(6*H*)-ones, which involves the acid-promoted cyclization of cyano enamine **15** to afford 2,4-bis-thiomethyl pyrido[4,3-*d*]pyrimidin-5(6*H*)-one **17** as a key intermediate. Selective displacement of the 4-methylthio group by a wide range of anilines followed by oxidation of the 2-methylthio group and subsquent substitution by amines enabled the synthesis of a variety of 2,4-disubstituted pyrido[4,3-*d*]pyrimidin-5(6*H*)-ones.

Bicyclic pyrido[4,3-*d*]pyrimidin-5(6*H*)-one is an important scaffold that can be found in a number of biologically active compounds. Recently, a series of publications and patent applications have disclosed the synthesis of pyrido[4,3-*d*]pyrimidin-5(6*H*)-ones, developed as GAA activators[1] and kinase inhibitors[2-6]. In addition, pyrido[4,3-*d*]pyrimidin-5(6*H*)-ones serve as pivotal intermediates for the synthesis of 2,4-disubstituted pyrido[4,3-d]pyrimidines as autotaxin inhibitors[7] and Syk kinase inhibitors [8]. While unsubstituted pyrido[4,3-*d*]pyrimidin-5(6*H*)-one could be derived from the reaction of triazine and ethyl acetoacetate in the presence of sodium ethoxide in a low yield[1], substituted pyrido[4,3-*d*]pyrimidin-5(6*H*)-ones have been largely prepared by an approach involving the cyclization of an enamino ester[3-9.]

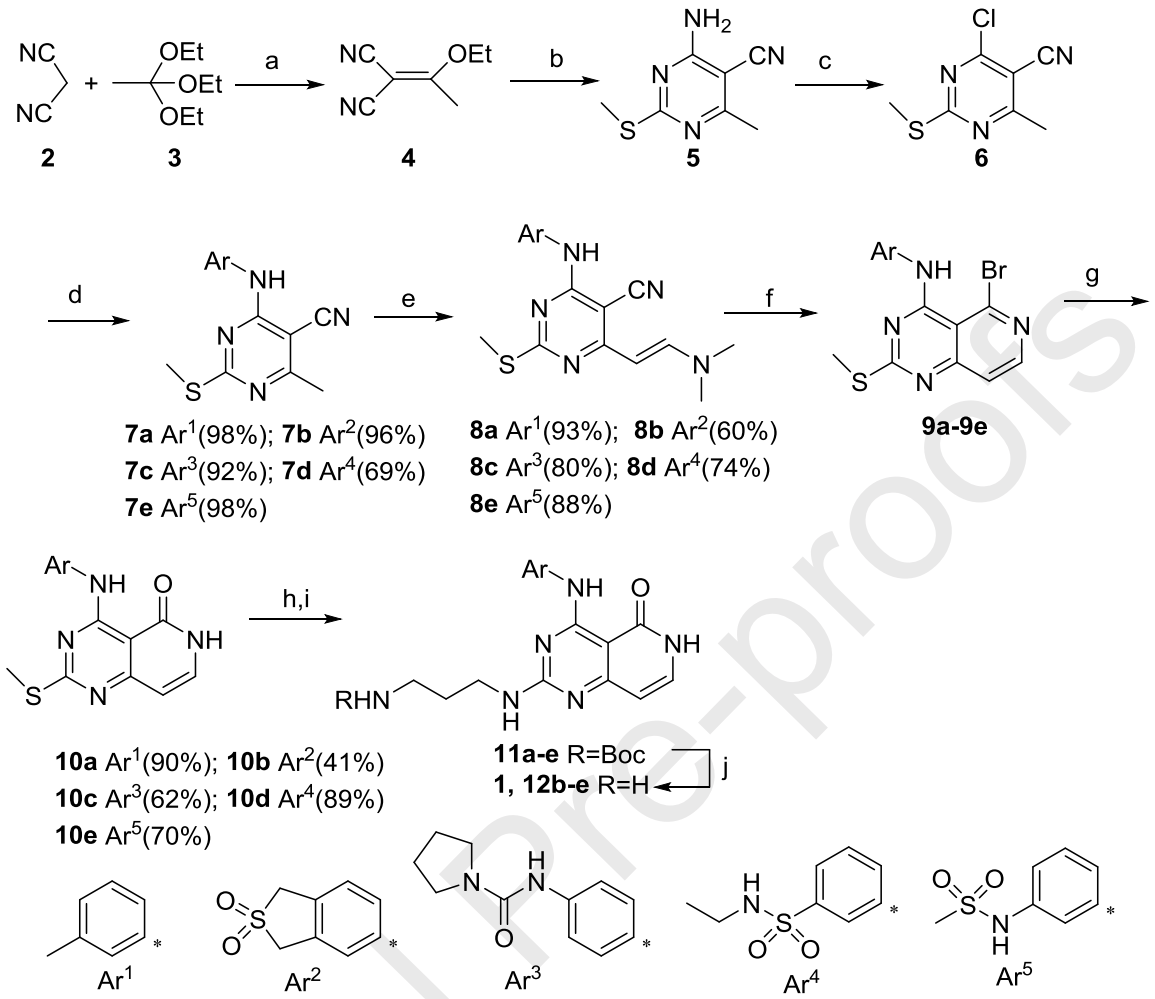
In the course of a drug discovery program optimizing kinase inhibitors, we sought an efficient synthetic route to quickly prepare analogs of biologically active hit molecule **1**. Optimally, we envisioned a synthesis of 2,4-substituted pyrido[4,3-*d*]pyrimidin-5(6*H*)-ones that was amenable to flexible late stage analog derivatizations at the 2- and 4-positions. When we embarked on our own synthetic campaign, the synthesis of

pyrido[4,3-*d*]pyrimidin-5(6*H*)-ones bearing 2,4-diamino substituents had been scarcely reported in the literature.



1

In 1979, Baldwin and co-workers[10] reported the synthesis of naphthyridinone *via* an enamine cyclization, where the treatment of the enamine of 4-methylnicotinonitrile with 30% HBr-HOAc afforded naphthyridinone in 41% yield. Inspired by their work, we explored extension of their synthetic approach to a more complex pyrimidine ring system, such as 4-methyl-2-(methylthio)-6-(m-tolylamino)pyrimidine-5-carbonitrile (**8a**). Herein we describe the development of our initial approach to the synthesis of 2,4-substituted pyrido[4,3-*d*]pyrimidin-5(6*H*)-ones, as outlined in Scheme 1.

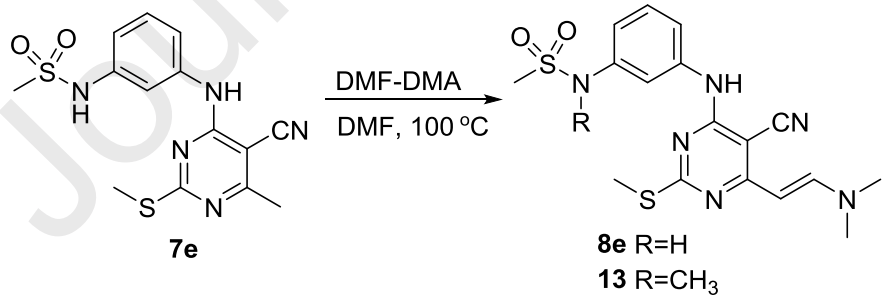


Scheme 1. Reagents and Conditions: a) acetic acid, 90 °C, 66%; b) *S*-methyl-isothiouronium sulfate, NaOMe, CH_3OH, 74%; c) $CuCl_2$, *tert*-butylnitrite, $MgSO_4$, acetonitrile, 80 °C, 68%; d) $ArNH_2$, DIEA, DMF, 75 °C; e) dimethylformamide dimethylacetal, DMF, 100-110 °C, for **7a-d**; or 2.5 eq. *tert*-butoxy bis(dimethylamino)methane (BBDM), DMF, 110 °C, for **7e**; f) 33% HBr/HOAc; g) 6N HCl (aq.)/HOAc, 80 °C; h) mCPBA, DMF; i) *tert*-butyl (3-aminopropyl)carbamate; j) TFA, CH_2Cl_2.

The synthesis started with condensation of malononitrile and triethyl orthoacetate to give (1-ethoxylethylidene)malononitrile **4**. Reaction of **4** with *s*-methylisothiourea and sodium methoxide in methanol afforded 4-amino-6-methyl-2-(methylthio)-5-pyrimidinecarbonitrile **5**. Diazotization of **5** with *tert*-butyl nitrite in the presence of cuprous chloride generated the 2-chloro intermediate **6**, which was then reacted with *m*-

toluidine in the presence of *N*,*N*-diisopropylethylamine (DIEA) in DMF at 65 °C to yield **7a**. With **7a** in hand, we set out to explore pyrido[4,3-*d*]pyrimidin-5(6*H*)-one formation using the synthetic protocols reported by Baldwin and co-workers[10]. To this end, treatment of **7a** with dimethylformamide dimethylacetal (DMF-DMA) in DMF at 75 °C afforded enamine **8a**. Interestingly, when **8a** was reacted with a solution of 33% HBr in acetic acid, we obtained exclusively the bromopyrido[4,3-d]pyrimidine **9a** and did not observe the expected pyrido[4,3-*d*]pyrimidin-5(6*H*)-one **10a**. However, **9a** could be readily hydrolyzed using 6N HCl in acetic acid at 80 °C to afford the pyrido[4,3-*d*]pyrimidin-5(6*H*)-one **10a** in 80% yield over two steps. Oxidation of **10a** with *m*CPBA, displacement of the resulting sulfone with amines, followed by Boc-deprotection afforded desired pyrido[4,3-*d*]pyrimidin-5(6*H*)-one analog **1**. We further expanded the scope and demonstrated the utility of the four step transformation of chloropyrimidine **6** to disubstituted pyrido[4,3-*d*]pyrimidin-5(6*H*)-ones **10b-e** using a variety of substituted anilines.

While the use of DMF-DMA to generate the enamines was generally functional-group tolerant, in certain cases we did encounter undesired alkylation of functional groups as a significant byproduct. For example, treatment of **7e** with DMF-DMA in DMF at 100 °C produced a 1:6 mixture of **8e** and the N-methylated product **13** (Scheme 2). We thereafter discovered that the use of *tert*-butoxy bis(dimethylamino) methane (BBDM)[11] to replace DMF-DMA overcame this issue, affording exclusively the desired enamine **8e**.

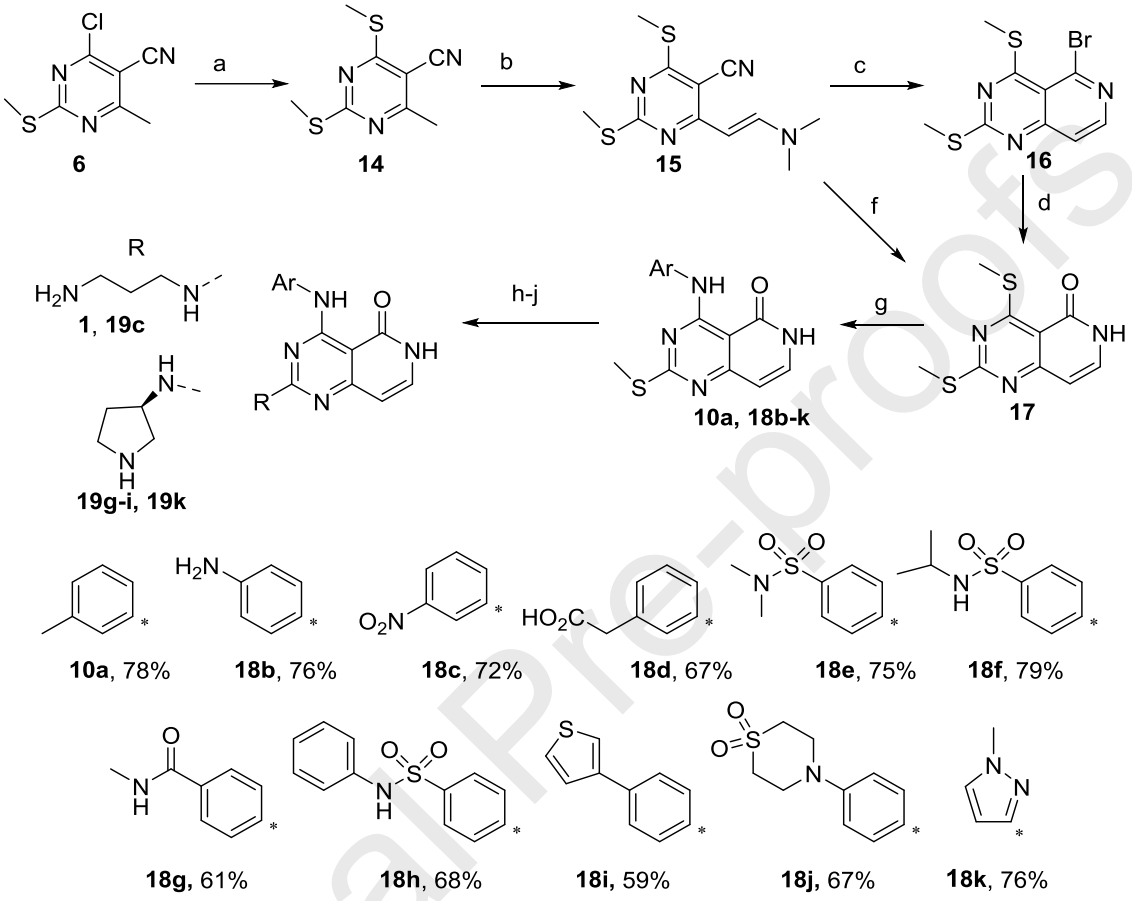


Scheme 2. Enamine formation using DMF-DMA.

The newly developed synthetic route described above allowed us to readily prepare analogs for exploring structure-activity relationship (SAR) at the 2 and 4-positions of the initial hit **1**. However, the major drawback of this approach lies in the fact that the anilines had to be introduced early in the synthesis prior to the ring closure to form pyrido[4,3-*d*]pyrimidin-5(6*H*)-one core, which increased the likelihood of side reactions associated with the functional group incompatibility.

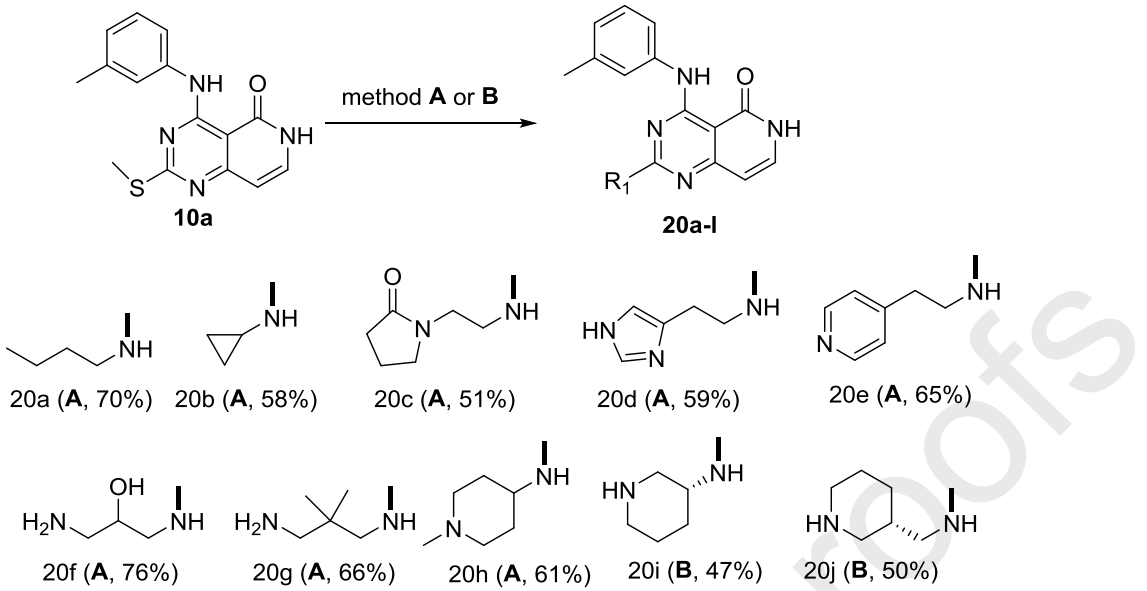
To develop a more efficient synthetic approach to analog preparation, our subsequent efforts focused on constructing an advanced pyrido[4,3-*d*]pyrimidin-5(6*H*)-one intermediate which would allow for late stage independent functionalization of the 2- and 4-positions. Considering leaving groups at these positions needed to be reactive to aniline displacement as well as inert to the conditions for enamine formation and subsequent cyclization, we reasoned that the methylthio group could satisfy these requirements. The methylthio functionality is not only relatively stable toward acids but also could be oxidized if necessary to a more reactive sulfone or sulfoxide leaving group. Thus, the reaction of chloropyrimidine **6** with sodium thiomethoxide efficiently produced 4-methyl-2,6-bis(methylthio)pyrimidine-5-carbonitrile **14**, which was converted to the enamine **15** by heating with DMF-DMA in DMF. The enamino nitrile **15** then underwent cyclization upon treatment with 33% HBr in acetic acid to yield 5-bromo pyrido-pyrimidine **16**, which was subsequently hydrolyzed to pyrido[4,3-*d*]pyrimidin-5(6*H*)-one **17** in 72% yield over two steps. To further simplify the synthesis, we attempted the direct cyclization of **15** of **17** under acidic conditions and eventually found that heating enamine **15** in acetic acid with 10% aqueous HBr or 6N HCl effected cyclization to give the desired pyrido[4,3-*d*]pyrimidin-5(6*H*)-one **17** in good yield.[12] With **17** in hand, we then explored conversion of methylthioether to the methylsulfoxide or methylsulfone. However, oxidation with *m*CPBA initially led to the formation of sulfoxide and sulfone as indicated by LC-MS, but the products decomposed as reaction progressed, making it impossible to separate and isolate the pure sulfoxide and sulfone products. This result prompted us to explore direct displacement of the 2- or 4-methylthio group. After some experimentation, we were pleased to find that the selective replacement of 4-methylthio group could be achieved by heating **17** with anilines in the presence of HCl in

isopropanol. This reaction proceeded smoothly over a broad range of anilines with high functional group tolerance (**10a**, **18b-k**) including heterocycles such as aminopyrrazole, exemplified by **18k.**



Scheme 3. Reagents and Conditions: a) Sodium thiomethoxide, DMF, 81%; b) DMF-DMA, DMF, 110 ^{o}C, 91%; c) 33% HBr/HOAc; d) 6N HCl (aq.)/HOAc, 80 ^{o}C, 72% over two steps; f) 10% HBr, acetic acid, 83 ^{o}C, 70%; g) $ArNH_2$, conc. HCl, isopropanol, reflux; h) *m*CPBA, DMF; i) *tert*-butyl (3-aminopropyl)carbamate then amine for **10a**, **18c**; (*R*)-tert-butyl 3-aminopyrrolidine-1-carboxylate for **18h-k**; j) TFA, CH_2Cl_2.

In addition to the propylamine moiety contained in **1,** a variety of amines had been readily incorporated to the 2-position of pyrido[4,3-*d*]pyrimidin-5(6*H*)-one core by means of the reaction sequence shown in Scheme 4. The synthesis of target analogs



Scheme 4. Reagents and Conditions: Method A: i) *m*CPBA, DMF; ii) RNH_2; Method B: i) *m*CPBA, DMF; ii) RNH_2,; iii) 4N HCl in dioxane, DCM.

using this novel synthetic route and their biological activity will be reported elsewhere in due course.

In conclusion, we have demonstrated the development of an efficient synthesis of 2,4-disubstituted pyrido[4,3-*d*]pyrimidin-5(6*H*)-ones. The approach features a versatile 2,4-bis(methylthio)pyrido[4,3-d]pyrimidin-5(6H)-one intermediate which was initially prepared from enamino nitrile **15** using a high yielding two-step process. The synthetic efficiency was further improved by achieving the direct acid-promoted cyclization of **15**. Selective displacement of the 4-methylthio group in **17** by a wide range of anilines was successfully accomplished under acidic conditions. Subsequent oxidation of the 2-methylthio ether followed by reaction with amines and deprotection (if necessary), led to the synthesis of a variety of 2,4-disubstituted pyrido[4,3-*d*]pyrimidin-5(6*H*)-ones.

Acknowledgments

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12) In contrast, treatment of enamino nitrile **8a** with 10% aqueous HBr or 6N HCl in acetic acid resulted in a complex mixture.

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- Facile replacement of the 2-methylthio group with diverse amines to biologically significant analogous.
- BBDM is more functional-group tolerant than DMF-DMA for enamine formation

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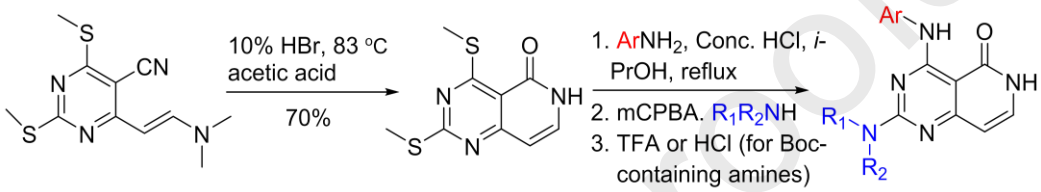

Declaration of interests

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