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Development of Methylthiomethyl (MTM) Protection for N^1 of Pyrrolo[2,3-d]pyrimidin-2,4-diones.

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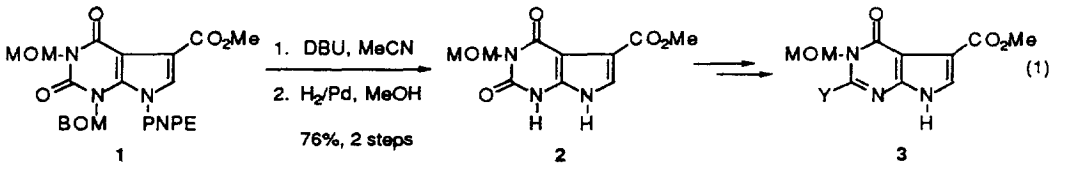
Abstract: This paper describes the application of the methylthiomethyl (MTM) protecting group for the N^1 position in differentially protected pyrrolo[2,3-*d*]pyrimidin-2,4-diones. By reaction of selected systems with SO_2Cl_2 at low temperature resulted in selective formation of N^1-chloromethyl derivatives. Subsequent heating in aqueous THF with silica gel afforded the deprotected compounds in good yield. Selectivity in the presence of N^3 methoxymethyl (MOM) and benzyloxymethyl (BOM), and N^7 p-nitrophenethyl protection was achieved.

The implementation of practical nitrogen protecting groups is a particularly critical area of consideration when designing routes to complex nitrogen containing molecules.[1] Due to the variable nature between various forms for nitrogen functional groups, i.e., amines, amides, and heterocyclic N-H's, it is difficult to apply protection strategies from one group to the other. There remains a need for the development of new and selective protecting groups, especially for less basic heterocyclic N-H groups. In the past we have shown the viability of using *p*-nitrophenethyl (PNPE) and 2,4-dimethoxybenzyl[2] protection for pyrrole N-H's as part of a program focused on the development of general strategies for the synthesis of pyrrolo[2,3-*d*]pyrimidine nucleosides.[3] In this report we disclose the use of methylthiomethyl (MTM) as a selective protecting group for the N^1 position in differentially protected pyrrolo[2,3-*d*]pyrimidin-2,4-diones.

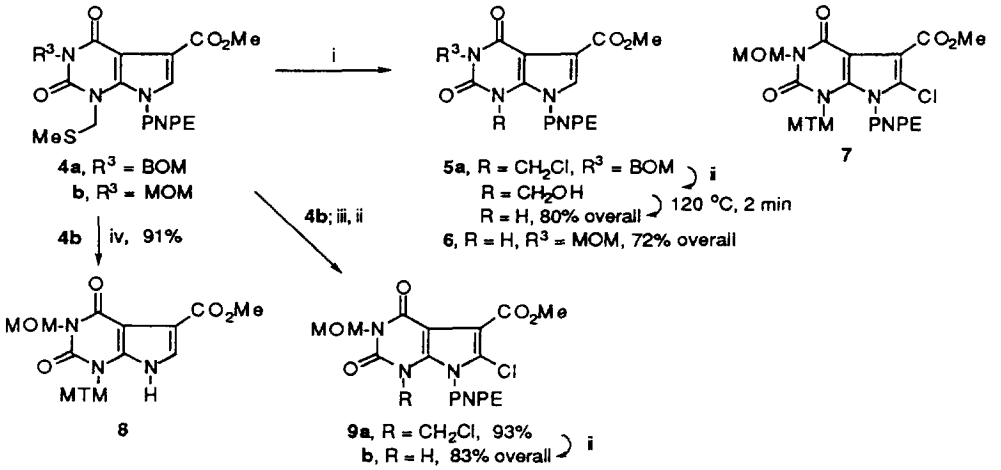
Previously our attempts to attach a protected ribose unit onto N^1 protected pyrrolo[2,3-*d*]pyrimidin-2,4-diones met with failure due to the steric bias imposed by this group.[4] To overcome this limitation it was reasoned that conversion of N^1 to its sp^2 hybridization state would be required.[5] To ascertain this possibility, the previously described compound **1** was treated with DBU and resulted in facile elimination of the PNPE group. Further exposure of this material to Pearlman's catalyst under a hydrogen atmosphere cleaved the benzyloxymethyl

(BOM) group and provided the N^1, N^7 deprotected compound **2**[6] in good overall yield (eq 1). Further efforts to transform **2** into 2-substituted pyrrolo[2,3-*d*]pyrimidin-4-ones **3** were initially troubled by solubility problems.[7] To circumvent this obstacle it seemed obvious to transform the C^2 position prior to removing the PNPE group. To this end we needed to find a new group for N^1 that allowed its selective removal in the presence of N^3 methoxymethyl (MOM) or BOM and N^7 PNPE groups.

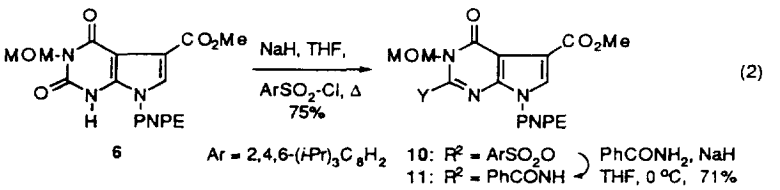


Although there are a number of groups that have been used to protect the N^1 position of uracils (i.e., benzyl,[8a] p-methoxybenzyl,[8b] and BOM[8a]) none of these was deemed appropriate in our system due to the acid sensitivity of the N^3 MOM group and the base sensitivity of the PNPE group. To examine the suitability of the methylthiomethyl (MTM) group[9] in this role, the pyrrolo[2,3-*d*]pyrimidin-2,4-diones **4a,b**[5] were prepared along our previously established route[2] starting with 6-chlorouracil[10] and PNPE protected glycine ethyl ester (Scheme 1). Initial attempts to remove the MTM group from **4a** using metal-assisted hydrolysis conditions ($HgCl_2$ or $AgNO_3$, aq. MeCN)[9] resulted in no reaction. This is likely due to the unavailability of the N^1 nitrogen lone pair to assist in expulsion of the methylthio group during the course of the reaction. It was reasoned that the delocalization of this lone pair onto the adjacent C^2 carbonyl group could be used to assist in the removal this group through a different reaction mechanism. Thus, it was found that exposure of **4a** to 1.0 equivalent of sulfuryl chloride[11] (-78 °C -> rt, aq. $NaHCO_3$ quench) resulted in the rapid formation of a N^1 chloromethyl derivative **5a**,[6] which, upon subsequent warming in aqueous THF in the presence of silica gel, afforded the hydroxymethyl intermediate **5b**. Rapid heating of this material to 120 °C under vacuum expelled formaldehyde and afforded compound **5c**[6] in 80% overall yield. The corresponding N^3-MOM derivative **4b** also underwent ready deprotection using this approach to afford the free amide **6**[6] in 72% overall yield. In this system a minor by-product was isolated from the first step of this sequence which was tentatively assigned a structure to the 6-chloro derivative **7**. This material presumably arose through competitive chlorination at the pyrrole

α-carbon.[12] To confirm this hypothesis, exposure of **4b** to 2.0 equivalents of sulfuryl chloride afforded a new compound **9a**[6] which resulted in replacement of the methylthio group and chlorination at C[6]. Removal of the chloromethyl group from **9a** afforded the deprotected amide **9b**[6] in 83% overall yield from **4b**. To determine to possibility of removing the PNPE group while retaining the N[1]-MTM group, exposure of **4b** to DBU resulted in the free pyrrole **8**[6] in high yield.



In pursuing further transformations in this series of compounds, free amide **6** was converted into 2-benzoylamino derivative **11** via the 2-sulfonyl intermediate **10** using a two-step protocol reported earlier in our route to 2'-deoxyribosyl-7-deazaquanine derivatives.[3] With this derivative in hand, further efforts directed at the synthesis of ribose containing 7-deazaguanosine target molecules is being pursued and will be the topic of future reports from these laboratories.



(2)

This report discloses the application of the MTM group for protection of the N^1 position of pyrrolo[2,3-*d*]pyrimidin-2,4-diones. Its removal can be effected under mild conditions which retains both acid (MOM or BOM) and base/hydrogenation (PNPE) sensitive protecting groups within the same molecule. Further application of this group for the protection of related amide like heterocyclic NH functions, e.g.., lactams, uracils, and N^1 in guanines and 7-deazaquanines, should be possible.

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References and Notes

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1. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; J. Wiley and Sons: New York, 1991; chapt. 7. Sonveaux, E. in *Protocols for Oligonucleotides Conjugates*; Agrawal, S., Ed.; Humana Press: Totowa, New Jersey, 1994; pp 2-17.
2. Edstrom, E. D.; Wei, Y. *J. Org. Chem.* **1993**, *58*, 403.
3. Edstrom, E. D.; Wei, Y. *J. Org. Chem.* **1995**, *60*, 5069.
4. Edstrom, E. D.; Wei, Y., unpublished results using the sodium-salt glycosidation method and Wilcox's ribose derivative, see: ref 5.
5. For literature precedence involving the glycosidation of 2-amino-4-chloro-5-carbomethoxy-pyrrolo[2,3-*d*]pyrimidine with a protected α-chlororibose derivative, see: Ramasamy, K.; Joshi, R. V.; Robins, R. K.; Revankar, G. R. *J. Chem. Soc., Perkin Trans. I* **1989**, 2375.
6. All new compounds have been characterized by ^1H and ^{13}C NMR, IR, and high resolution mass spectroscopy.
7. For example, treatment of **2** with NaH (1.0 eq) in THF/DMF and triisopropylbenzenesulfonyl chloride (TPBSCl, 1.5 eq) at room temperature resulted in no reaction. However, heating **2** with 2.5 eq of NaH and 3 eq of TPBSCl in THF afforded a new high R_f material tentatively assigned as the 5-carbomethoxy-2,7-di(*p*-toluenesulfonyl)-pyrrolo[2,3-*d*]pyrimidin-4-one. Further use of this compound will be reported elsewhere.
8. a) Kundu, N. G.; Hertzberg, R. P.; Hannon, S. J. *Tetrahedron Lett.* **1980**, *21*, 1109. b) Van Aerschot, A.; Jie, L.; Herdewijn, P. *Tetrahedron Lett.* **1991**, *32*, 1905. c) Kunda, N. G. *Synthetic Comm.* **1981**, *11*, 787. Kunda, N. G.; Khatri, S. G. *Synthesis* **1985**, 323. Defrees, S. A.; Reddy, K. S.; Cassady, J. M. *Synthetic Comm.* **1988**, *18*, 213. d) For a recent report describing the use of methoxycarbonylvinyl protection for the N^3 position of thymidines, see: Faja, M.; Ariza, X.; Galvez, C.; Vilarrasa, J. *Tetrahedron Lett.* **1995**, *36*, 3261.
9. The MTM group has been developed as useful protection for alcohols, see: Corey, E. J.; Bock, M. G. *Tetrahedron Lett.* **1975**, 3269.
10. Thus, 6-chlorouracil was sequentially protected at N^1 and N^3 with methylthiomethyl (MTM) and methoxymethyl (MOM) or BOM groups using previously described reaction conditions, see: ref 3.
11. For the conversion of methylthioethers to alkyl chlorides using this reagent, see: Benneche, T.; Strande, P.; Undheim, K. *Synthesis* **1983**, 762.
12. For related α–chlorination of thiophenes, see: Campaigne, E.; LeSuer, W. M. *J. Am. Chem. Soc.* **1948**, *70*, 415. Godt, H. C. Jr.; Wann, R. E. *J. Org. Chem.* **1962**, *27*, 1459.

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