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Utility of 4,6-dichloro-2-(methylthio)-5-nitropyrimidine. An efficient solid-phase synthesis of olomoucine

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Abstract—4,6-Dichloro-2-(methylthio)-5-nitropyrimidine has been utilized as a building block for an efficient nine-step synthesis of olomoucine. The methodology reported herein is applicable to the regiocontrolled solution and solid-phase synthesis of libraries of highly substituted purines, as well as other related scaffolds.

1. Introduction

Due to interest in multi-substituted purines as mediators of biological process, including their activity as ATP competitive kinase inhibitors, a number of solid-phase methods for their library synthesis have recently been advanced.[1] In general, these protocols fall into two classes. In one class, primarily pioneered by Schultz and co-workers, a pre-formed purine with displaceable functionality is loaded onto resin, and after further manipulation, cleavage is conducted to afford final products.[1a–o] This method has the advantage of allowing the synthesis of highly substituted compounds, but requires a fixed substitution at position 8 and can suffer from poor regiocontrol in N-9 functionalization. Also, certain N-9 substituents could not be efficiently prepared using the reported alkylation or Mitsunobu procedures (e.g. *t*-butyl and phenyl).

The second class utilizes substituted pyrimidines as precursors to the purine scaffold, which is built up on resin prior to cleavage.[1p] An advantage here is higher flexibility with respect to substitution at the 6, 8 and 9 positions, with the possibility for complete regiocontrol with respect to N-9 functionalization. Reports to date using this on-resin de novo purine synthesis have not realized the potential for complete purine substitution.

In this preliminary report, we describe our use of the versatile scaffold 4,6-dichloro-2-(methylthio)-5-nitropyrimidine[2] **1** in a solid-phase synthesis of olomoucine **2**.[3,4] This synthesis serves as a specific example of a general methodology that can deliver highly substituted purine libraries **3** with complete regiocontrol (Fig. 1).

2. Results and discussion

Our synthesis of olomoucine is shown in Scheme 1. Argogel MB-CHO resin[5] (loading: 0.4 mmol/g) was subjected to a standard reductive amination[6] protocol using benzyl amine. Loading of the pyrimidine **1** was next carried out in THF at ambient temperature. After a second displacement using methylamine,[7] the thiomethyl moiety was converted to the sulfone by treatment with oxone®. The final displacement was then carried out using *t*-butyldiphenylsilyl protected

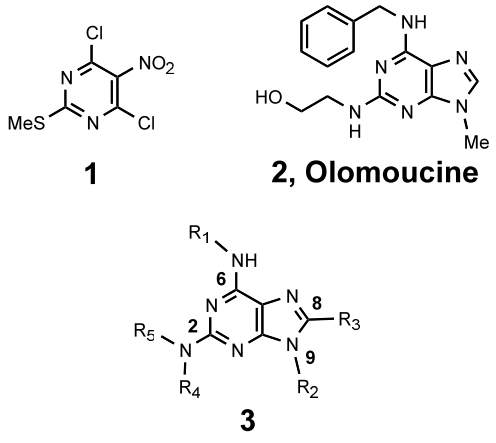

Figure 1.

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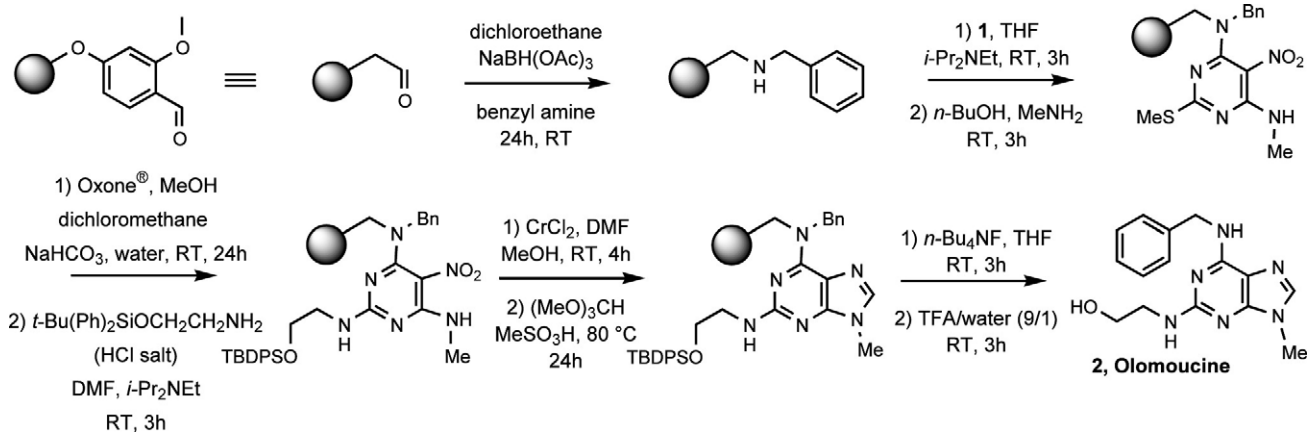
ethanolamine. Reduction of the nitro functionality was required next. In exploring this nitro reduction, we were initially frustrated in applying various literature[8] conditions, however, the method of Miller proved superior in carrying out this transformation without concomitant cleavage.[9] Purine formation was then smoothly effected by treatment of the system with trimethylorthoformate in the presence of catalytic methanesulfonic acid. After fluoride treatment, cleavage under standard conditions using aqueous TFA then provided the final product **2**. Olomoucine formed directly in this manner showed good purity (89%, LC/MS), and the product was purified for comparison of physical characteristics with literature data.[3,10] The overall isolated yield for the nine-step sequence leading to olomoucine, after purification, was 76% (182 mg isolated from 2 g of resin). This corresponds to an average yield per step of approximately 97%.

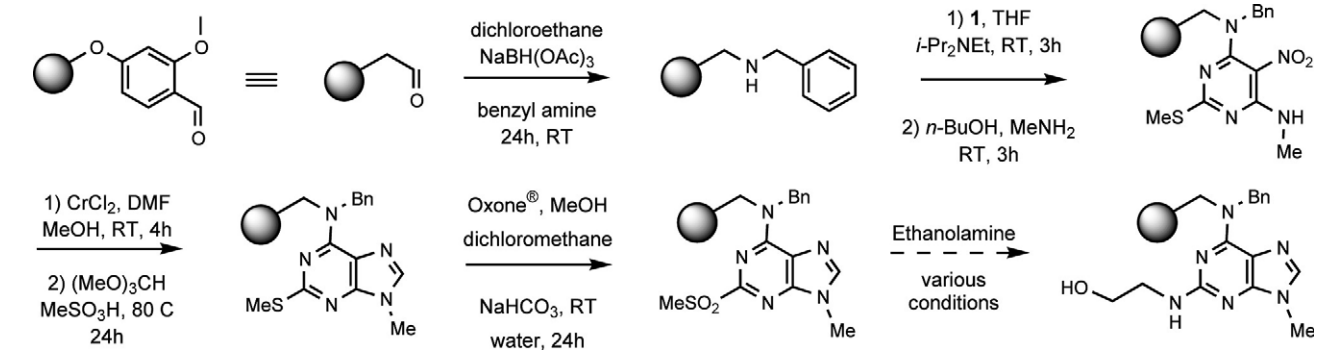
In working out the proper order of events for the successful approach shown in Scheme 1, we initially attempted the sequence shown in Scheme 2. In this variation, the nitro reduction and purine cyclization were carried out prior to sulfone oxidation and attempted displacement. Unfortunately, although the 2-methanesulfonyl purine itself could be cleaved from the resin in good yield and with high purity (>90%, LC/MS), no conditions could be found that would allow an efficient displacement of the sulfone with amines from this fully formed purine scaffold. This observation is similar to that reported by Schultz in a related system.[1c] At best, olomoucine of about 25% purity could be produced using this protocol under highly forcing conditions.

3. Conclusion

In summary, we have presented an efficient solid-phase synthesis of the kinase inhibitor olomoucine. By variation of the individual amines used in each displacement and the orthoester used in the purine cyclization, the methodology outlined in this paper can be utilized to prepare libraries of such purines **3**.[11] To our knowledge, this is the first example of a general methodology for preparing purine libraries with complete regiocontrol and full flexibility for substitution at every position. In consideration of the general and mild conditions used and the acceptable purity and yield of the final cleaved products, we expect to show further utility through the synthesis of highly diverse arrays of purine and purine related libraries. Using the highly substituted pyrimidine scaffold 4,6-dichloro-2-(methylthio)-5-nitropyrimidine **1**, we have also investigated solution-based strategies for library synthesis.[11]



Scheme 1.



Scheme 2.

References

1. (a) Austin, R. E.; Okonya, J. F.; Bond, D. R. F.; Al-Obeidi, F. *Tetrahedron Lett*. **2002**, *43*, 6169; (b) Ding, S.; Gray, N. S.; Wu, X.; Ding, Q.; Schultz, P. G. *J. Am. Chem. Soc*. **2002**, *124*, 1594; (c) Ding, S.; Gray, N. S.; Wu, X.; Ding, Q.; Schultz, P. G. *J. Comb. Chem*. **2002**, *4*, 183; (d) Ding, S.; Gray, N. S.; Ding, Q.; Schultz, P. G. *Tetrahedron Lett*. **2001**, *42*, 8750; (e) Ding, S.; Gray, N. S.; Ding, Q.; Schultz, P. G. *J. Org. Chem*. **2001**, *66*, 8273; (f) Brill, W. K.-D.; Riva-Toniolo, C.; Müller, S. *Synlett* **2001**, *7*, 1097; (g) Brun, V.; Legraverend, M.; Grierson, D. S. *Tetrahedron Lett*. **2001**, *42*, 8161; (h) Brill, W. K. D.; Riva-Toniolo, C. *Tetrahedron Lett*. **2001**, *42*, 6515; (i) Dorff, P. H.; Garigipati, R. S. *Tetrahedron Lett*. **2001**, *42*, 2771; (j) Brill, W. K.-D.; Riva-Toniolo, C.; Müller, S. *Synlett* **2001**, *7*, 1097; (k) Chang, Y.-T.; Gray, N. S.; Rosania, G. R.; Sutherlin, D. P.; Norman, T. C.; Sarohia, R.; Leost, M.; Meijer, L.; Schultz, P. G. *Chem. Biol*. **1999**, *6*, 361; (l) Gray, N. S.; Wodicka, L.; Thunnissen, A.-M. W. H.; Norman, T. C.; Kwon, S.; Espinoza, F. H.; Morgan, D. O.; Barnes, G.; LeClerc, S.; Meijer, L.; Kim, S.-H.; Lockhart, D. J.; Schultz, P. G. *Science* **1998**, *281*, 533; (m) Gray, N. S.; Kwon, S.; Schultz, P. G. *Tetrahedron Lett*. **1997**, *38*, 1161; (n) Nugiel, D. A.; Cornelius, L. A. M.; Corbett, J. W. *J.Org. Chem*. **1997**, *62*, 201; (o) Norman, T. C.; Gray, N. S.; Koh, J. T.; Schultz, P. G. *J. Am. Chem. Soc*. **1996**, *118*, 7430; (p) Di Lucrezia, R.; Gilbert, I. H.; Floyd, C. D. *J. Comb. Chem*. **2000**, *2*, 249. Solution-phase methodologies have also been reported. For two recent examples, see: (purines from polyhalo purines); (q) Bakkestuen, A. K.; Gundersen, L.-L.; Langli, G.; Lui, F.; Nolsoe, J. M. J. *Biorg. Med. Chem. Lett*. **2000**, *10*, 1207 and (purines from pyrimidines); (r) Dang, Q.; Brown, B. S.; Erion, M. D. *Tetrahedron Lett*. **2001**, *41*, 6559.
2. Syntheses of 4,6-dichloro-2-(methylthio)-5-nitropyrimidine **1**: (a) Harnden, M. R.; Hurst, D. T. *Aust. J. Chem*. **1990**, *43*, 55; (b) Brown, D. J.; Jacobsen, N. W. *J. Chem. Soc*. **1965**, 3770.
3. For the original report of olomoucine, see: Parker, C. W.; Entsch, B.; Letham, D. S. *Phytochemistry* **1986**, *25*, 303. The term olomoucine was coined in 1994 'for convenience', see: Vesely, J. et al. *Eur. J. Biochem*. **1994**, *224*, 771.
4. For recent syntheses, see Refs. 1i and 1n. For bioactivity of olomoucine and related purines, see: Schow, S. R.; Mackman, R. L.; Blum, C. L.; Brooks, E.; Horsma, A. G.; Joly, A.; Kerwar, S. S.; Lee, G.; Shiffman, D.; Nelson, M. G.; Wang, X.; Wick, M. M.; Zhang, X.; Lum, R. T. *Bioorg. Med. Chem. Lett*. **1997**, *7*, 2697.
5. The resin used in this work was purchased from Argonaut technologies, see: http://www.argotech.com.
6. (a) Fivush, A. M.; Willson, T. M. *Tetrahedron Lett*. **1997**, *38*, 7151; (b) Sarantakis, D.; Bicksler, J. J. *Tetrahedron Lett*. **1997**, *38*, 7325.
7. In our optimizations of this step, we found reduced temperatures (<50°C) were necessary to avoid displacement of the unactivated thiomethyl moiety.
8. (a) Lee, C. L.; Chan, K. P.; Lam, Y.; Lee, S. Y. *Tetrahedron Lett*. **2001**, *42*, 1167; (b) Scheuerman, R. A.; Tumelty, D. *Tetrahedron Lett*. **2000**, *41*, 6531; (c) Krchnak, V.; Szabo, L.; Vagner, J. *Tetrahedron Lett*. **2000**, *41*, 2835; (d) Yokum, T. S.; Alsina, J.; Barany, G. *J. Comb. Chem*. **2000**, *2*, 282; (e) Schwarz, M. K.; Tumelty, D.; Gallop, M. A. *Tetrahedron Lett*. **1998**, *39*, 8397; (f) Morales, G. A.; Corbett, J. W.; DeGrado, W. F. *J. Org. Chem*. **1998**, *63*, 1172; (g) See also Ref. 1p.
9. Hari, A.; Miller, B. L. *Tetrahedron Lett*. **1999**, *40*, 245. We found it advantageous to add a protic solvent (MeOH) to achieve efficient reduction with our substrate. We also achieved limited success following: Makara, G. M.; Ewing, W.; Ma, Y.; Wintner, E. *J. Org. Chem*. **2001**, *66*, 5783. In following the latter work, we found THF/water to be more effective than the reported DCM/water with our substrate.
10. Olomoucine was purified using flash column chromatography (80/10/1 ethyl acetate/methanol/triethylamine). Recrystallization (ethyl acetate/methanol/hexanes) then afforded material of 100% purity (LC/MS). This material gave ^{1}H NMR spectra identical to that reported in the literature, and had mp 129.4–130.3°C (lit.[3] 125–126°C). Using commercially available olomoucine (Sigma), we found mp 120.9–125.8°C. A 1:1 mixture of commercial olomoucine and material prepared in this work had mp 123.7–126.4°C and showed a single compound by TLC, LC/MS, and ^{1}H NMR.
11. Further work using pyrimidine **1**, including applications to library synthesis, has been completed and will be reported in detail shortly.