ORGANIC LETTERS

2012
Vol. 14, No. 15
3920–3923

A "Catch–React–Release" Method for the Flow Synthesis of 2-Aminopyrimidines and Preparation of the Imatinib Base

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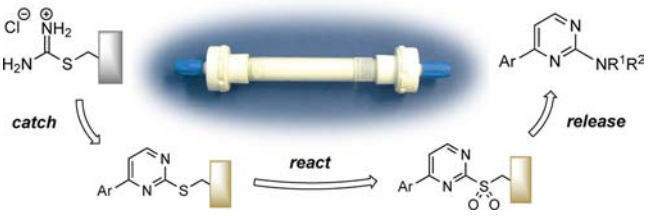
Received June 19, 2012

ABSTRACT



The development of a monolith-supported synthetic procedure is reported, taking advantage of flow processing and the superior flow characteristics of monolithic reagents over gel-phase beads, to allow facile access to an important family of 2-aminopyrimidine derivatives. The process has been successfully applied to a key precursor on route to Imatinib (Ar = 3-pyridyl, R^1 = 2-methyl-5-nitrobenzyl, R^2 = H).

Finding cleaner and more expedient methods to assemble functional molecules is an important driver for organic synthesis. Recently, advances in enabling tools such as flow technologies have had a significant impact on the way in which many of these chemicals are produced;[1] this is especially true in the delivery of heterocyclic building blocks for medicinal and agrochemical discovery. Accordingly, we and others have been exploring the benefits of flow based synthesis to expand the diversity and facilitate the scaleup of several relevant heterocyclic materials;[2,3] most recently we have targeted the preparation of biologically important 2-aminopyrimidines.[4] Herein we wish to report an improved approach to these compounds, which have traditionally been accessed via cross-coupling methods,[5a] by halogen substitution[5a,b] or by displacement of alkylthiols.[5c,d] This thiol displacement, which enables late-stage diversification, is a particularly synthetically powerful sequence owing to the ease of preparation of the starting material.

However, this process is under-represented in the literature due, at least in part, to the release of sulfur-containing byproducts which are often malodorous or toxic. We concluded that loading the initial thioether precursor onto a solid support could circumvent many of these drawbacks. In this way both the release of sulfurous byproducts during substitution and the potential for the final product to become contaminated with toxic thiourea byproduct are minimized. Furthermore, flow based methods can be harnessed to perform reagent loading as well as reaction steps to afford functionalized materials in an automated fashion.

Macroporous monolithic columns have been identified as an effective format for solid-phase chemistry.[6] The use of this type of support for flow based catch–react–release

(1) Mason, B. P.; Price, K. E.; Steinbacher, J. L.; Bogdan, A. R.; McQuade, D. T. *Chem. Rev.* **2007**, *107*, 2300.

(2) (a) Herath, A.; Dahl, R.; Cosford, N. D. P. *Org. Lett.* **2010**, *12*, 412. (b) Opalka, S. M.; Longstreet, A. R.; McQuade, D. T. *Beilstein J. Org. Chem.* **2011**, *7*, 1671. (c) Palde, P. B.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1.

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(5) For recent examples, see: (a) El-Deeb, I. M.; Lee, S. H. *Bioorg. Med. Chem.* **2010**, *18*, 3860. (b) Saczewski, J.; Paluchowska, A.; Klenc, J.; Raux, E.; Barnes, S.; Sullivan, S.; Duzynska, B.; Bojarski, A. J.; Strekowski, L. *J. Heterocycl. Chem.* **2009**, *46*, 1259. (c) Agarwal, A.; Srivastava, K.; Puri, S. K.; Chauhan, P. M. S. *Bioorg. Med. Chem.* **2005**, *13*, 4645. (d) Almario-Garcia, A.; Ando, R.; Aritomo, K.; Frost, J. R.; Li, A.-T.; Shoda, A.; Uehara, F.; Wanatabe, K. WO 01/70727 A1, 2001.

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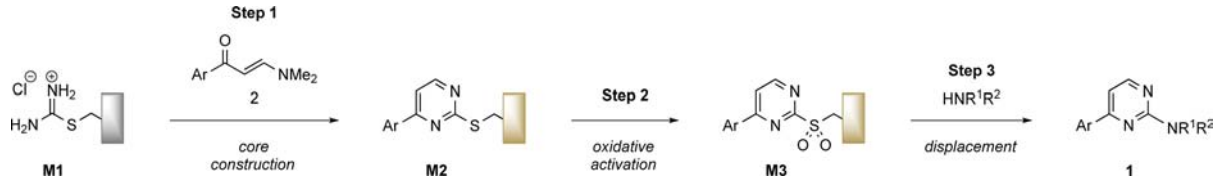
10.1021/ol301673q
Published on Web 07/19/2012

Scheme 1. Proposed Synthetic Route

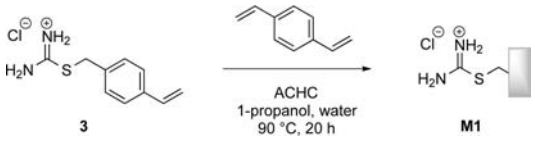


protocols retains all of the benefits of bead-based chemistry but offers a number of practical advantages. For example, the internal structure of a monolith is found to have improved flow characteristics when compared to traditional polymer beads, allowing more efficient and higher-yielding syntheses to be conducted.[7] When the polymer is contained within a column, the flow stream is forced to pass through the monolith, whereas polymer beads are commonly observed to suffer from solution channelling which reduces their effectiveness. In addition, the rigid cross-linked morphology of the monolith prevents significant volume changes due to swelling or shrinking, allowing the use of a wider range of solvents. Of particular importance from a synthetic point of view is the possibility to rapidly generate customized functionalized monoliths without recourse to the specialist equipment that is required for the manufacture of bead-type reagents, and thus they can be prepared at a much lower cost. Indeed, monolithic reactors have already been prepared and used to conduct a wide range of chemistries, having demonstated particular value as reagent sources for flow chemistry platforms.[7−9]

Aminopyrimidines related to **1** have been used previously as targets for solid-supported synthesis[10] due to their significant value as building blocks. Here we propose a simple sequence to prepare structures related to **1** (Scheme 1) which we anticipated could be readily applied using solid-phase monolithic reagents and flow chemistry techniques.[11]

Therefore, an investigation was first conducted to identify a polymerization mixture that could be used to reproducibly generate suitable monoliths of form **M1**, possessing high porosity to reduce back-pressure and high stability to withstand prolonged processing under the flow conditions. The optimized blend required a significant deviation from previous recipes,[7,9] incorporating water and a low molecular weight alcohol to accommodate the different solubility characteristics of the hydrochloride monomer salt **3** and the divinyl benzene cross-linker (Scheme 2). It should also be noted that polymerization of this material to form gel-phase beads would be difficult, since compound **3** is mainly water-soluble and thus the usual biphasic solvent system would be inappropriate.

Scheme 2. Preparation of the Functionalized Monolith **M1**[12]



For the monolith preparation, the monomer, cross-linker, and porogen mixture were homogenized under gentle heating (< 50 °C).[12] The initiator was then added, and the resulting mixture was transferred into glass columns.[13] The columns were sealed at both ends and heated at 90 °C for 20 h in a multichannel convection heater (Figure 1a). After cooling, the monoliths were washed with ethanol at 60 °C to remove the porogen and residual monomer, resulting in rigid white monoliths (**M1**) that completely filled the glass columns (Figure 1b).

The monoliths could be prepared in a range of sizes, allowing for small-scale monolithic reactors (3 mm column diameter) for use with precious materials, or parallel use of multiple columns with 15 mm diameter, currently the largest diameter at which the temperature gradient across the column allows effective polymerization.[7] The monoliths used in this work had an average dry weight of 1.6 g (column size 7 cm ×10 mm diameter), and elemental analysis indicated a loading of 2.4 mmol/g isothiouronium chloride which was

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(10) Masquelin, T.; Sprenger, D.; Baer, R.; Gerber, F.; Mercadal, Y. *Helv. Chim. Acta* **1998**, *81*, 646.

(11) All flow reactions and monolith preparations described below were carried out using Vapourtec R2+ and R4 units, available from Vapourtec Ltd. Website: http://www.vapourtec.co.uk. Multiple steps can be telescoped by sending a programmed sequence of commands to the serial interface of the flow apparatus. For the first use of the Vapourtec system within our group, see: Baumann, M.; Baxendale, I. R.; Ley, S. V.; Smith, C. D.; Tranmer, G. K. *Org. Lett.* **2006**, *8*, 5231.

(12) The optimized polymerization mixture developed for this work consisted of the following: 4-(vinylbenzyl)isothiuronium chloride (**3**; 18.8% w/w); divinyl benzene (DVB cross-linker; 12.5% w/w); 1-propanol (porogen; 57.5% w/w); water (porogen; 10.9% w/w); 1,1′-azobis-(cyclohexane carbonitrile) (ACHC initiator; 1% w/w relative to **3** + DVB).

(13) Commercially available Omnifit glass chromatography columns with fixed end pieces, with 10 mm bore and 100 mm length. Website: http://www.omnifit.com.

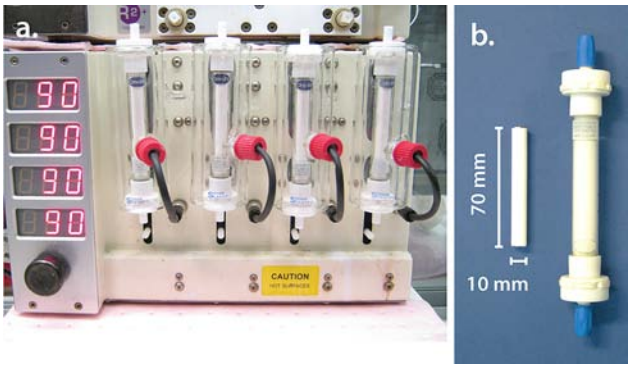
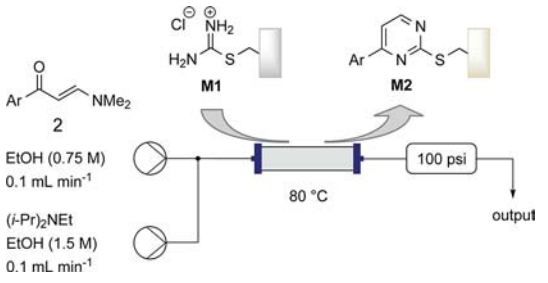


Figure 1. (a) A batch of monoliths undergoing the curing process in a convection heater. (b) Prepared monolithic reagents, removed from and within the glass column reactor.

highly reproducible over multiple monoliths. The monoliths were typically prepared in batches of four or more and could be stored as sealed columns for periods of several weeks at room temperature without any noticeable degradation.

The monoliths were then reacted with solutions of a substituted enaminone **2**[14] in the presence of Hünig's base to construct the pyrimidine core (**M2**, Scheme 3). Taking advantage of the solid-supported regime, more than one stoichiometric equivalent of the enaminone could be used in order to drive the reaction to completion, without sacrificing the purity of the immobilized intermediate. The surplus enaminone could be readily recovered from the output stream and recycled.

Scheme 3. Cyclization with Enaminones **2** (the "Catch" Step)[a]

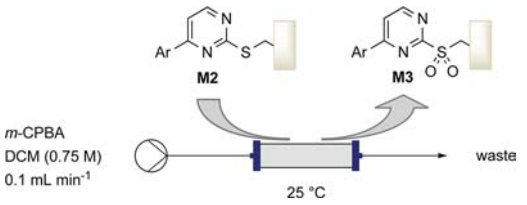


[a] The two reagents were pumped continuously in separate streams from stock solutions, mixing in a T-piece immediately before entering the monolith to minimize undesired reactions. The combined flow rate gave a residence time of approximately 15 min.

Following a washing regime of the monolith to remove any unbound reactants, elemental analysis of the polymer postreaction indicated a loading of 2.0 mmol/g, based on N analysis. Further evidence for the formation of the required pyrimidine **M2** was provided by the disappearance of the ^{13}C resonance of the thiouronium center at 171 ppm detected using Magic Angle Spinning NMR spectroscopy, as well as characteristic changes in the IR spectra, notably new absorptions in the regions of 1250 and 1400 cm^{-1}.

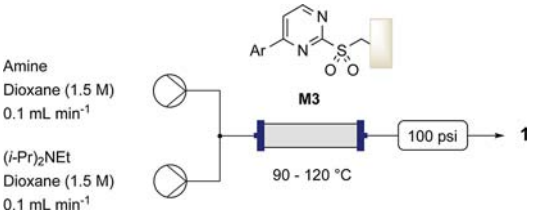
The thioether unit of **M2** was subsequently activated by oxidation prior to its displacement with an amine nucleophile (Scheme 4). *m*-CPBA was chosen as the oxidant, due to its high solubility and existing precedent for use in this type of process.[10]

Scheme 4. Oxidative Activation of Monolith **M2**



An excess of *m*-CPBA was used for this transformation, to encourage complete oxidation of all of the sulfur atoms on the monolith. Despite this, elemental analysis suggested that statistically there was a mixture of sulfone and some sulfoxide present; however, both were expected to undergo the desired displacement reaction. Consequently, release of the heterocycles was achieved by substitution of **M3** using various amine nucleophiles (Scheme 5).

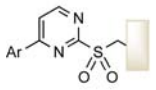
Scheme 5. Amine Displacement of 2-Aminopyrimidine **1**



As the S_NAr reaction was found to be slow for certain reagent combinations, the yield was generally improved by increasing the quantity of amine used, and employing a *stop–flow* reaction technique. Under computer control, the reagents were added over several injections. The two main input streams were pumped at 0.1 mL min^{-1} for 50 min, which was sufficient time to fill the monolith (pore volume ~50% of the column volume). The pumps were then stopped, and the reagent mixture was held within the monolith for 1 – 2 h at an elevated temperature to facilitate the reaction (90 °C, or at higher temperature with aniline nucleophiles). The pyrimidines **1** were then eluted as a mixture with the excess amine and could be isolated by aqueous extraction and flash column chromatography. As with any catch and release procedure, this results in a segmented flow process. Nevertheless, it has many of the advantages of a continuous flow procedure, such as easy automation and simplified purification of products.

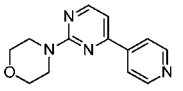
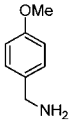
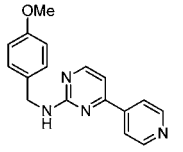
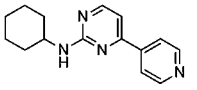
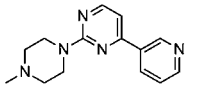
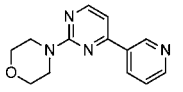
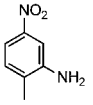
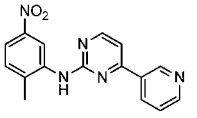
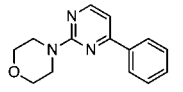
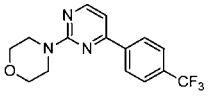
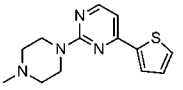
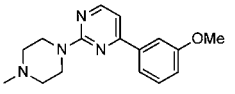
(14) Abdulla, R. F.; Fuhr, K. H. *J. Org. Chem.* **1978**, *43*, 4248–4250.

Table 1. Collection of 2-Aminopyrimidine Derivatives



M3 a-f

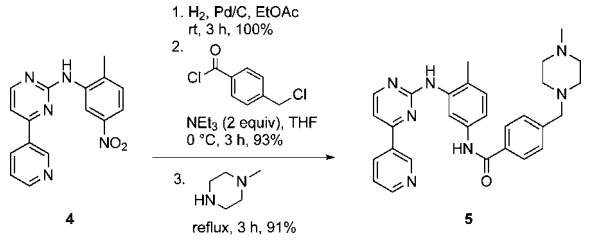
a Ar = 4-*pyridinyl*
b Ar = 3-*pyridinyl*
c Ar = C_6H_5
d Ar = 4-$CF_3C_6H_4$
e Ar = 2-*thiophenyl*
f Ar = 3-$OMeC_6H_5$

entry	monolith	amine	product	yield [a]
1	**M3a**			72%
2	**M3a**			29%
3	**M3a**			50%
4	**M3b**			61%
5	**M3b**			71%
6	**M3b**			48%
7	**M3c**			40%
8	**M3d**			62%
9	**M3e**			56%
10	**M3f**			62%

[a] Isolated yield over all three steps, after purification by flash column chromatography, based on an assumed 4.2 mmol loading of monolith **M1**.

To explore the scope and utility of this process as a general method to access 2-aminopyrimidines, we used a number of aromatic enaminones as starting materials in conjuction with several aromatic and aliphatic nitrogen nucleophiles to effect the final release (Table 1). We were pleased to obtain a collection of products in moderate to good yields over the three contiguous steps. In general, higher recovery of the final product was achieved when more nucleophilic amines were employed in the displacement.

Scheme 6. Access to the Imatinib Base **5**[15,16]



As a further benchmark for proving the applicability of this process, we wished to apply this flow sequence to the preparation of a known pharmaceutical target. We chose to prepare pyrimidine **4**, a known precursor in the synthesis of the tyrosine kinase inhibitor Imatinib **5** (Scheme 6).[15] Following the previously described route, compound **4** was obtained in 48% overall yield (Table 1, entry 6). Advantageously this method circumvents problems encountered with the low solubility of the intermediates, which have hampered previous flow chemistry approaches.[4]

In conclusion, using a new supported thiouronium salt **M1**, we were able to rapidly generate 10 substituted aminopyrimidines **1** from readily accessible enaminones and amines. The supported variant of this reagent offers many benefits over solution-phase synthesis, including simplified isolation of the product, the potential for automation, and containment of toxic and malodorous byproducts. The new monolithic reagent offers benefits over traditional polymer bead reagents, in particular, a more suitable morphology for effective use in a continuous flow regime and a low-cost and accessible preparation procedure. Only one purification operation is required over three steps, and the compounds are retrieved in comparable yields to batch routes to similar targets. The procedure was also attractively deployed in the preparation of the key aminopyrimidine unit **4** found in the Imatinib base (Gleevec).

Acknowledgment. We gratefully acknowledge funding from the EPSRC (R.J.I. and N.N.), Novartis (R.J.I.), the BP 1702 endowment (S.V.L.), and the Royal Society (I.R. B.) and Dr. David Reid (Department of Chemistry, University of Cambridge) for performing MAS NMR experiments.

Supporting Information Available. Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.