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A Bifurcated Pathway to Thiazoles and Imidazoles Using a Modular Flow Microreactor

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A scalable method for the preparation of 4,5-disubstituted thiazoles and imidazoles as distinct regioisomeric products using a modular flow microreactor has been devised. The process makes use of microfluidic reaction chips and packed immobilized-reagent columns to effect bifurcation of the reaction pathway.

Introduction

Many strategic opportunities can arise when enabling technologies, such as flow chemical methods,[1] microwave techniques,[2] and solid-supported reagents and scavengers are utilized within integrated synthesis platforms.[3] In the following studies, we set out to further exemplify these concepts by developing reliable protocols and suitable equipment that can effect multistep transformations without or with minimal usage of labor intensive practices, such as aqueous workups, distillations, or chromatographic separations. We have already applied these methods to a wide variety of reactions that include Diels-Alder reactions,[4] Suzuki and Heck coupling processes,[5] Curtius rearrangements,[6] enzymatic transformations,[7] deprotection reactions,[8] hydrogenations,[9] fluorinations,[10] and alkylations[11] to prepare natural products,[7,12] peptides,[7,8a] and heterocyclic compounds.[13] In this communication, we describe a new procedure that creates a scalable automated flow chemistry procedure to divert different reactivity patterns cleanly to alternative product outcomes.

In recent years, there has been considerable interest in substituted and bicyclic derivatives of thiazoles and imidazoles as pharmaceutically interesting compounds.[14] Several recent patents and papers[15] have described related thiazoles motifs (Figure 1, **1**) that inhibit or modulate the activity of cyclin-dependent kinases (CDK) and glycogen synthase kinase-3 for example. These indications clearly signal their potential use in prophylaxis or in treatments of disease states mediated by CDK ranging from cancers to bacterial and fungal infections (including activity against MetAP1).[16,17]

While many synthetic methods have been devised to synthesize simple thiazoles,[18] only a few are reported for the preparation of compounds substituted only at the 4 and 5 positions.[19] Recently, we described the preparation of a small collection of 4,5-disubstituted oxazoles by a base-mediated condensation between an acyl chloride and ethyl isocyanoacetate using a bespoke small-footprint modular flow

reactor.[13a] As an extension of this work, we believed that the corresponding thiazole compounds could be prepared in flow mode via the analogous base-mediated condensation of the isocyanide with an isothiocyanate. This approach was first reported by Suzuki[20] as a batch process and was of special interest because of the considerable flexibility that the route allows in the direct introduction of a substituent on the exocyclic nitrogen atom. Interestingly, in subsequent work by Solomon,[21] the formation of the regioisomeric imidazole was observed as a minor side-product, which could be isolated in low yield but only after extensive column chromatography. We became intrigued by the idea of using a flow microreactor device in combination with an immobilized base to synthesize and separate the two possible regioisomeric products by exploiting the different chemical reactivities of the compounds and thereby bifurcating the reaction pathways.

Results and Discussion

Basic Reactor Description. The microreactor used for this research is a dual channel system driven by two independent variable HPLC pumps capable of delivering flow rate ranges of 0.05−5 mL/min with a 45 bar software monitored pressure shut off limit. Each pump is used to supply an independent solvent driven reagent stream through an interconnecting 1/16 in. o.d. Peek tubing (i.d., 5×10^{-3} in.; 125 μm) linkage. The staring materials are initially automatically dispensed (liquid-handler unit) and stored in reagent loops (0.5−10 mL) until required; when they are switched into line to flow into the main reactor (consisting in this case of a reactor chip and an immobilized reagent prepacked column assembly) via two 6-port 2-position switching valves. The two reagent flow streams exit the reagent loops and are combined within
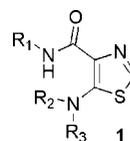
Figure 1. General template for pharmaceutically active thiazole compounds.

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Scheme 1. General Reaction for the Synthesis of Thiazole and Imidazole Products

Table 1. Solvent Investigations

solvent[a]	time (h)	conversion (%)[b]
hexane	24	no reaction
THF	6	100
MeCN	2	100
toluene	12	40
CH_2Cl_2	4	complex mixture
DMF	12	100

[a] All the reactions were conducted using 1 mmol of PS-BEMP, 1 mmol of ethyl isocyanoacetate, and 1 mmol of 4-bromophenyl isothiocyanate in 10 mL of solvent. [b] Consumption of starting material as determined by LC-MS analysis.

Table 2. Comparative Experiments Investigating the Effect of the Base

base[a]	time (h)	conversion (%)[b]
PS-NEt$_2$	24	no reaction
polyvinyl pyridine	24	no reaction
PS-Carbonate	16	100
DBU	5	100 (thiazole only)
BEMP	2.5	100 (thiazole only)
PS-TBD	1	100 (impure)
PS-BEMP	2	100

[a] All the reactions were conducted using 0.5 mmol of base, 0.5 mmol of ethyl isocyanoacetate, and 0.5 mmol of 3-fluorophenyl isothiocyanate in 5 mL of MeCN. [b] Consumption of starting material as determined by LC-MS analysis.

a glass T-configured mixing chip (250 μL−1 mL) where precise blending can be achieved and suitable reaction residence time can be created.[13a] A thermostatically regulated heating unit enables defined chip reaction temperatures to be rapidly established and cycled allowing rapid optimization of reaction temperatures. The effluent flow stream is subsequently directed into a commercially available Omnifit glass column (6.6 mm bore by 150 mm length)[22] containing an immobilized phosphazene base (PS-BEMP, ∼2.4 g, 2.3 mmol/g).[23] A Vapourtec R4[24] unit is used to ensure a consistent heating profile for the reaction column. Finally, the resulting flow stream is collected by an UV-detector triggered fraction collector (254 nm detection frequency).

General Chemical Synthesis. Our initial experiments focused on using ethyl isocyanoacetate as the isocyanide component, while chemical changes were introduced by variation of the isothiocyanate coupling partner (Scheme 1). In a typical procedure: two equimolar solutions of ethyl isocyanoacetate and 4-bromophenyl isothiocyanate (4.5 mL, 0.75 M in MeCN) were combined at a flow rate of 0.1 mL/ min using a drive stream of dry MeCN on a microfluidic reactor chip (1 mL) heated at an optimized 55 °C. The reaction chip was directly connected to a glass column containing prewashed/swelled PS-BEMP, also maintained at 55 °C, which facilitated the base-promoted condensation furnishing the 4,5-disubstituted thiazole **2** as the sole product after 45 min. Evaporation of the solvent yielded the thiazole product **2** in >95% purity but in only 58% isolated yield. We surmised that part of the product was being trapped by the PS-BEMP. Indeed when a solution of an electrophile (2,4′-dibromoacetophenone **3**; 0.75 M in MeCN, 2.5 mL) was subsequently passed through the PS-BEMP containing column, a new product was eluted that was identified as the regioisomeric imidazole adduct **4** in 38% isolated yield (based on the ethyl isocyanoacetate). This result suggests that the second product arises by a different reaction pathway, whereby the initially formed thiolate component (see later for the mechanism discussion) is selectively bound to the PS-BEMP reagent. Interestingly, any excess electrophile used in the reaction was also conveniently trapped by the PS-BEMP (probably as the enolate), permitting the isolation of the imidazole derivative in >95% purity as determined by both LC-MS and ^{1}H NMR.

Investigation of the Reaction Mechanism. An investigation was performed using a premixed sample of the electrophile **3** and ethyl isocyanoacetate in an effort to bias the formation towards the imidazole adduct **4**. However, under these conditions, we obtained a 1:1 mixture of the thiazole **2** and unreacted ethyl isocyanoacetate (corresponding to 60% of the original ethyl isocyanoacetate). No isothiocyanate or 2,4′-dibromoacetophenone **3** was detected, indicating these compounds were scavenged by the PS-BEMP. When an additional solution of the electrophile **3** was passed through the reactor, the corresponding imidazole **4** could be isolated albeit in low yield (14%) and purity (∼65%). The poor conversion of the ethyl isocyanoacetate in this reaction was probably caused by the competitive deprotonation of the electrophilic component **3**. Therefore, for additional comparative purposes, we also repeated the reaction premixing the ethyl isocyanoacetate with iodomethane as a nonenolizable electrophile alternative to **3**. In this case, the iodomethane was not trapped by the immobilized base, and we collected a 3:2 mixture of the thiazole and the corresponding methylated imidazole, although the solution was contaminated with the excess iodomethane. We also wished to establish the stability of the trapped intermediate under flow conditions. Therefore, a PS-BEMP containing column was again charged with ethyl isocyanoacetate and 4-bromophenyl isothiocyanate solutions, and the initial thiazole product was eluted. The column was maintained under pressure (5 bar) at the constant 55 °C reaction temperature for a period of 12 h before elution with a solution of the electrophile **3**. Again, only the heterocyclic imidazole **4** was isolated in an almost identical yield (36%) to that of the direct sequential transformation.

These experiments suggested one of two possible scenarios: (1) either the base-prompted cyclization was proceeding via competing pathways to yield the two regioisomeric products with the thiol moiety of the imidazole species being

Scheme 2. Proposed Intermediate Structures
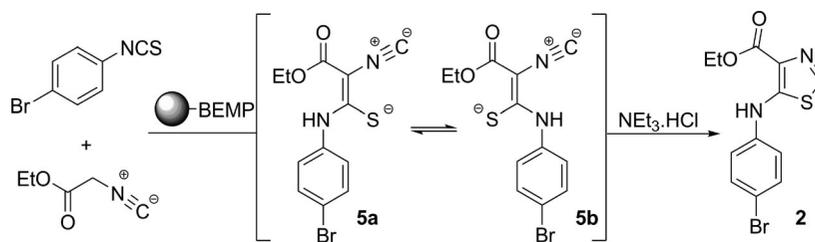
Table 3. Thiazole and Imidazole Homologues
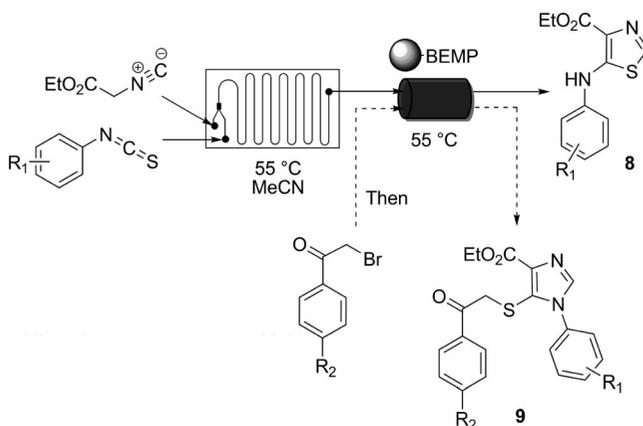
entry	R₁	R₂	isolated yield 8	isolated yield 9	combined yield (%)
1	4-Cl	OMe	47.5	47.5	95
2	4-Br	Br	53	30	83
3	4-OMe	H	96	4	100
4	3-F	Br	68	28	96
5	3-OMe	Br	84	5	89
6	2-OMe	H	90	7	97
7	3,5-CF₃	OMe	83.5	10.5	94
8	3,4-Cl	CN	53	26	79
9	4- NO₂	N/A	97	-	97

trapped as its corresponding salt, only to be released in the presence of an alkylating agent, or (2) that an open-chain intermediate was being formed, which remained immobilized on the resin but could subsequently undergo alkylation, cyclization, and release to yield the alternative substituted imidazole product.

To test these hypotheses, we repeated our initial reaction protocol, first, mixing a solution of ethyl isocyanoacetate and 4-bromophenyl isothiocyanate. This gave a reproducible 58% isolated yield of the expected thiazole **2** (Scheme 2). Next a solution of triethylamine hydrochloride was passed through the PS-BEMP column. In this case, only the thiazole adduct **2** was isolated, although in a lower 23% yield when the solvent was removed. Importantly, it was observed that immediately following elution, a second compound with an identical mass to that of the thiazole product **2**, but
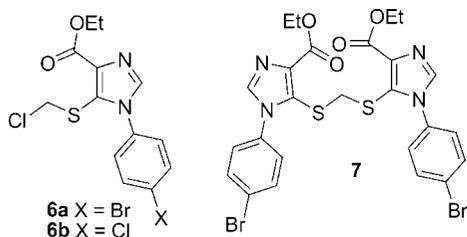
Figure 2. Dichloromethane adducts.

with a different retention time could be detected by LC-MS. This compound was rapidly converted on standing to yield the thiazole product **2**. Despite repeated attempts, we have been unable to further characterize this species; nevertheless the accumulated evidence implies that its identity is probably that of the noncyclized material. This being the case, it is interesting to speculate on the reason for the formation of this intermediate and its stability. It must be assumed that its formation occurs through attack of the ethyl isocyanoacetate upon the isothiocyanate, followed immediately by a second deprotonation via the PS-BEMP leading to the formation of two possible configurations of the thiolate intermediate (**5a** and **5b**, Scheme 2). Considering the electronics of the two species it is plausible that the intermediate **5a** with the adjacent thiolate and isocyanide would rapidly cyclize to yield the thiazole product **2**. Alternatively, the aniline remains uncyclized when it is *cis* to the isocyanide (**5b**); this may be due to the nitrogen being less nucleophilic or that **5b** is a more stable salt.

Investigation into the Batch Reaction. In order to determine if any specific variations to the reaction composition or mechanism occurred because of working in the flow domain, for example, through changes in reagent or product concentrations, reaction times, or reactor design, we also conducted a number of batch experiments.

The batch reaction between 4-bromophenyl isothiocyanate and ethyl isocyanoacetate performed at ambient temperature was screened in a selection of solvents (Table 1) and with different bases, both polymer-supported and solution-phase (Table 2).

The reaction in hexane showed low solubility of the starting materials and consequently gave no significant reaction. Performing the same reaction in toluene resulted in only 40% conversion after 12 h, but the solution also contained a number of unidentified minor byproducts. The more polar solvents (THF, MeCN, and DMF) gave quantitative conversions, although MeCN as a solvent showed a significant rate enhancement. It is worth noting that it has been previously reported that BEMP is a more effective base when used in MeCN.[25] Somewhat unexpectedly, we observed that when using CH_2Cl_2 as solvent we obtained a mixture of the thiazole **2**, the 5-chloromethylsulfanyl imidazole **6a,** and some of the dimeric compound **7** in 10:3:1 ratio (Figure 2). A similar result was also found when CH_2Cl_2 was used as the solvent/electrophile to elute a PS-BEMP column following a flow reaction. In addition, the ratio between the monosubstituted **6a** and disubstituted product **7** could be altered by changing the flow rate, and at high flow rates (1.25 mL/min), the dimer **7** could be eliminated entirely. These results were also consistent with our previous
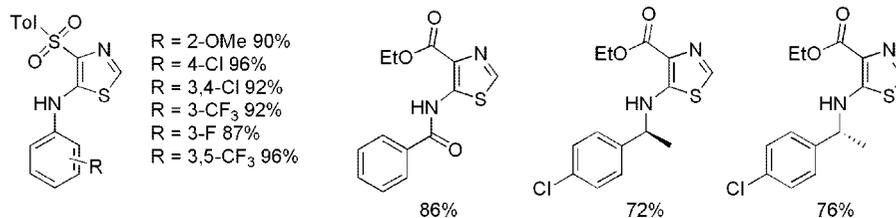
Figure 3. Selective thiazole formation.
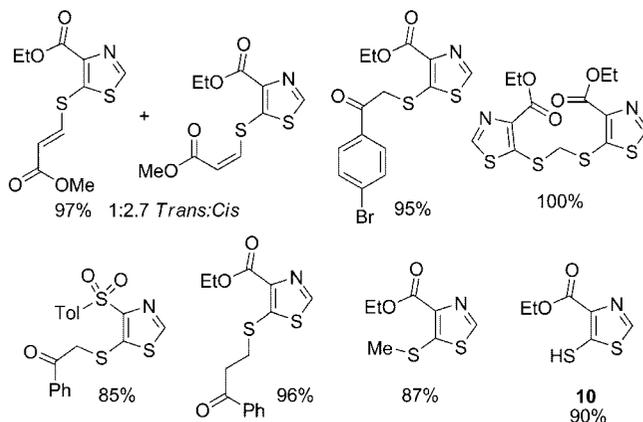
Figure 4. Carbon disulfide derivatives. All compounds were >95% purity as determined by ^{1}H NMR and LC-MS analysis.

experiments using iodomethane as an electrophile in terms of product ratio and intermediate reactivity.

We also investigated the effect of the base used in the reaction. Weak bases such as the immobilized triethylamine (PS-NEt₂) or pyridine (polyvinyl pyridine) equivalents failed to promote the reaction. A polymer-supported carbonate resin PS-Carbonate gave a good conversion but over a significantly prolonged reaction time. Employing a stronger non-nucleophilic base like DBU did result in good conversion but also influenced the reaction outcome so that only the thiazole product was formed. Likewise, the solution-phase BEMP reagent gave complete conversion but again yielded the corresponding thiazole as the sole product. Interestingly, the polymer-supported DBU equivalent, PS-TBD, gave excellent conversions, but additional unidentified byproducts were observed. The best conditions leading to a high purity product in good yield was obtained using PS-BEMP. In analogy to the flow procedure, filtration of the PS-BEMP (or PS-TBD/PS-Carbonate), followed by washing with MeCN and treatment with a solution of an electrophile, gave the expected secondary imidazole product. The isolated yield and ratio of the two products were identical to those obtained in the previous flow experiments.

It can therefore be concluded that the mechanism and product distribution is only dependent upon the specific nature of the base used rather than the presentation format, loose beads or prepacked columns, or the manner in which the substrates and reagents are brought together. The likely difference observed between the bases in terms of the immobilized and solution-phase species and their influence on the product distribution could be explained in terms of ion pairing and the difference in the associated environments of the ion within a polymer matrix and a solvated media. Such differences have been observed in other reactions such

as the E/Z selectivity in the Wittig reaction[26] or in many transition metal complex catalyzed reactions.[27]

It is our general findings that the same products could be obtained and isolated using either a batch or flow procedure, although it was certainly more convenient and efficient to process the materials within the flow reactor. We therefore sought to establish a generic protocol to create a library of related scaffolds for incorporation into our medicinal chemistry programs using the automated flow reactor platform.

Flow Optimization and Compound Synthesis. Having deduced the mechanistic parameters of the process, we next evaluated the effects of various changes in the concentration and ratio of the reactants, as well as the quantity of the PS-BEMP resin, used. It was determined that only minor changes in product composition and purity were detected within the ranges evaluated (0.1−1.5 M reactants; 1−2 equiv of PS-BEMP); nevertheless, the stoichiometry of the BEMP did effect the final flow rate that could be achieved before breakthrough of unreacted ethyl isocyanoacetate was detected. Consequently, flow rates and reactor temperatures were optimized as a function of reactant concentrations and equivalents of base to match the substrate reactivity to the residence time of the system. A general set of reaction conditions were determined using a 1:1 ratio of the coupling partners (0.75 M solutions in MeCN) combined on a 1 mL glass mixing chip (heated to 55 °C) prior to flowing into a column of PS-BEMP (1.6 equiv, also maintained at 55 °C) using a flow rate of 0.05 mL/min on each substrate input.

Using these conditions, we reacted a selection of aromatic isothiocyanates with ethyl isocyanoacetate to prepare the corresponding heterocyclic systems in good to excellent overall yield (79−100%) and purities (>95%) without the requirement for any additional purification (Table 3). These reactions were repeatedly performed on 3.38 mmol, but the flow process could be readily scaled up (50 mmol); running the flow reactor for an extended period of time and using a larger column of PS-BEMP enabled multigram quantities of material to be generated (>15 g).

From the data (Table 3) and the proposed mechanism, the reason for the difference in product distribution with changing substrate is not completely apparent. However, it can be seen that powerful electronic groups capable of conjugation through the nitrogen on the aryl ring certainly have a distinct and reproducible effect on the selectivity, thereby directing the reaction more towards the thiazole product (entries 3, 5, 7, and 9; Table 3). This can be immediately seen when the methoxy substituted isothiocyanates employed (entries 3, 5 and 6; Table 3) are compared. In these cases, the 2- and 4-substituted methoxy substituents impart greater selectivity

Scheme 3. Rapid Synthesis of a Pharmaceutically Interesting Bicyclic Compound
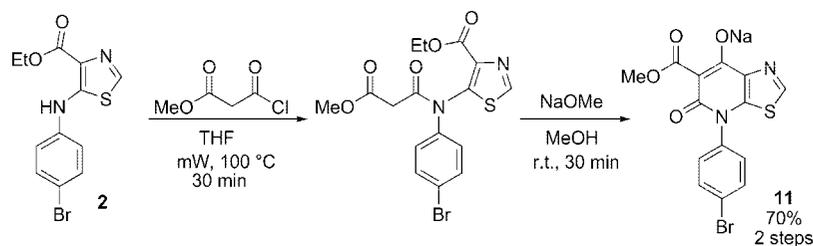
Scheme 4. Synthesis of α-Bromoamide **12** and Structure of HIV-1 RTI Analogue **13**
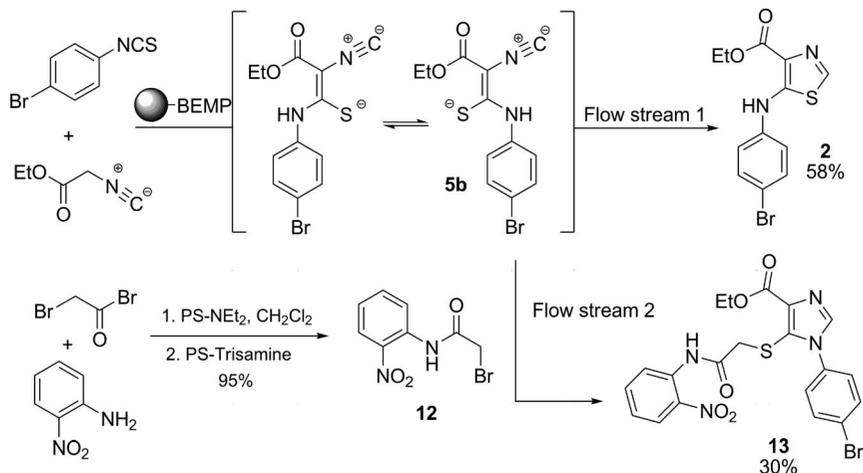
Scheme 5. Quantitative Deprotection of Acetyl Groups Performed in Batch
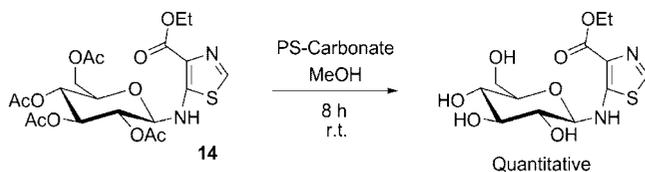
than the corresponding 3-OMe with the better conjugated para group imparting the greatest influence.

In an attempt to extend the versatility of the procedure, we next investigated the generality of the reaction using both ethyl isocyanoacetate and toluenesulfonyl isocyanide in combination with a broader range of isothiocyanates (aliphatic and aromatic). These reaction sets performed equally well but, in all cases, furnished only the corresponding thiazole products (Figure 3) in good isolated yield (72−96%) and excellent purity (>95%).

Similar reactions were also conducted using carbon disulfide as the electrophile (isothiocyanate replacement), furnishing an interesting set of thiazoles with an exocyclic substituted sulfur atom in the 5 position (Figure 4). As might be expected, the products were captured by the PS-BEMP but were easily displaced by the subsequent addition of an electrophile to yield the corresponding alkylated compounds in excellent yield and purity. In addition, unlike in the previous sequence, this material could also be quantitatively displaced from the resin by eluting a dilute solution of acetic acid (0.1 M in MeCN) through the PS-BEMP containing column immediately liberating the free thiol derivative **10**.

Compound Elaboration: An Example of Extended Bifurcation. The basic heterocyclic framework synthesized using the flow chemistry techniques described above create

ideal building blocks for further chemical elaboration. Indeed, the core motifs appear extensively as bioisosteric replacements for many other heteroaromatic units as part of rational drug design strategies aimed at identifying compounds with improved pharmokinetic properties.[17,28] We therefore investigated a series of simple chemical manipulations targeted towards the synthesis of novel pharmaceutical lead series based around existing HIV ligand systems. For example, the readily prepared bicyclic compound **11** exhibits the basic structural architecture present in a series of HIV-integrase strand-transfer inhibititors.[29] Accordingly, by application of the strategy reported by Boros[29] using a modified microwave heating procedure, followed by base-catalyzed cyclization, the thiazole **2** was transformed to the 7-hydroxythiazolopyridone sodium salt **11** in good yield (70% two steps) and purity (>95%) (Scheme 3).

The corresponding imidazole regioisomer **5b** (flow stream 2) prepared during the same flow reaction (alternative structure to starting material **2**; flow stream 1) but retained by the PS-BEMP was treated with a privileged α-bromoamide **12** to yield, directly from the reactor, the sulfanylimidazole **13** (in 30% yield based on the ethyl isocyanoacetate initially used) as a HIV-1 non-nucleoside reverse transcriptase inhibitor (RTI) analogue (Scheme 4).[30]

Since certain glycosylated thiazoles derivatives have shown specific antimicrobial activity[31] and bear a strong resemblance to nucleosides,[32] these systems have become attractive target molecules for synthesis. A wide range of mono- and disaccharide-bearing isothiocyanates can be readily prepared from the corresponding protected amino sugars[33] or commercially sourced at a reasonable cost presenting a facile method of preparing nucleoside analogues using our flow procedure. Figure 5 shows three examples of
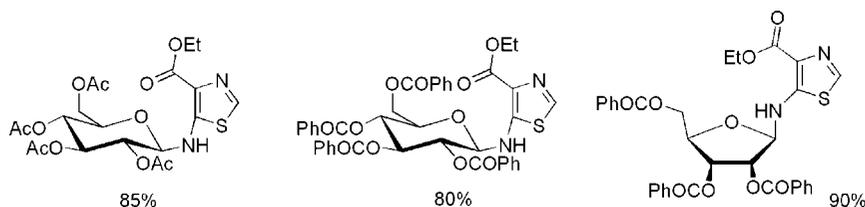
Figure 5. Synthesis of glycosylated thiazoles.
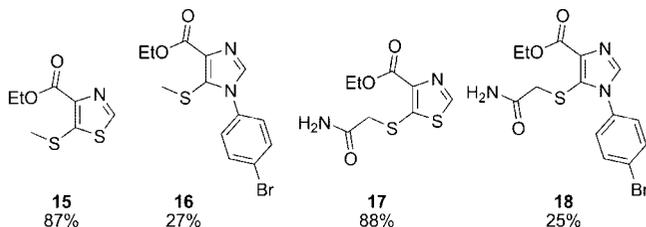
Figure 6. Thioether derivatives prepared for Liebeskind–Srogl coupling.

thiazole-functionalized sugars prepared using the flow reactor. The deprotection of the acetoxy groups of compound **14** can also be readily achieved in quantitative yield (Scheme 5) by using an immobilized carbonate base PS-Carbonate in MeOH.

Finally, because heteroaromatic thioethers have been shown to undergo efficient palladium-catalyzed cross-coupling with boronic acids,[34] we decided to synthesize four representative substrates to examine this chemistry using our flow procedure. Employing either a secondary flow stream of iodomethane or 2-chloroacetamide as the electrophile, we obtained the desired thiomethyl ether **15** (87%) and **16** (27%) or acetamides **17** (88%) and **18** (25%), respectively (Figure 6). However, in each case, the excess electrophile was not effectively trapped by the PS-BEMP column (see above). Therefore, to obtain pure products, an additional nucleophilic scavenger column containing Quadrapure-benzylamine resin (QP-BZA)[13c] was required as an in-line sequestering step, immediately following the PS-BEMP cartridge.

Compounds **16** and **18** were subjected to the standard conditions reported by Liebeskind and Srogl, the reactions were run at 50 °C in air or under oxygen free conditions using 3 equiv of copper(I) thiophene-2-carboxylate (CuTC), 2 equiv of phenylboronic acid, Pd$_2$(dba)$_3$, and tris(2-furyl)phosphine (TFP).[34a] However, these reactions resulted in either no reaction or substantial decomposition; furthermore, the addition of Zn(OAc)$_2$ did not induce the coupling as has been previously described in the original literature.[34a] It has also been reported that the application of microwave irradiation at elevated temperatures can lead to significantly improved reaction profiles. Consequently, we attempted the coupling at 130 °C for 25 min; however this still failed to yield any of the desired product.[34b] As related systems have been shown to couple under similar conditions, we believe it should be possible to effect this type of coupling process. We are therefore currently evaluating alternative procedures to facilitate this chemistry and hope to report these results in the near future.

Conclusion

In conclusion, the work describes the successful continuous flow synthesis of a selection of 4,5-disubstituted thiazoles and imidazoles in good yields and high purities. The flow microreactor configuration and its ready modular capability provide an excellent platform for synthesis intensification and for the future practice of compound assembly. The ability to divert the reaction streams to selectively produce different products based on bifurcation of the reaction pathways is an attractive concept that is well suited to flow-based technologies.

Supporting Information Available. X-Ray crystallographic data, full characterization of novel compounds, and a working description including experimental procedures for use of the flow equipment. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) The reagent polymer-supported 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diaza-phosphorine (PS-BEMP had a loading of 2.3 mmol/g and was purchased from Fluka (catalog no. 20026).

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