Development of a general process for the synthesis of highly substituted imidazoles*

Joseph Sisko‡ and Mark Mellinger

Synthetic Chemistry, GlaxoSmithKline, 709 Swedeland Road, P.O. Box 1539, UW2820, King of Prussia, PA 19406-0939, USA

Abstract: Several highly substituted imidazoles have been under investigation at GlaxoSmithKline as potential therapies for the treatment of rheumatoid arthritis and have spawned the need for a general synthetic method for their preparation on a multikilogram scale. We describe herein the optimization of a general method for the preparation of aryl-substituted TosMIC reagents and the ease with which they undergo [3+2] cycloadditions with a host of imines, prepared in situ, to generate densely functionalized imidazoles with various substitution patterns in a completely regioselective manner.

BACKGROUND

It would be difficult to underestimate the importance of imidazoles in the pharmaceutical and agrichemical industries. Some of the best-selling therapies today contain this versatile heterocycle in their core structures. Thus, it is never surprising when new chemical entities emerge from medicinal chemistry groups that contain substituted imidazoles. Such was the case several years ago when the four compounds below (Fig. 1) surfaced as development candidates for the treatment of rheumatoid arthritis.
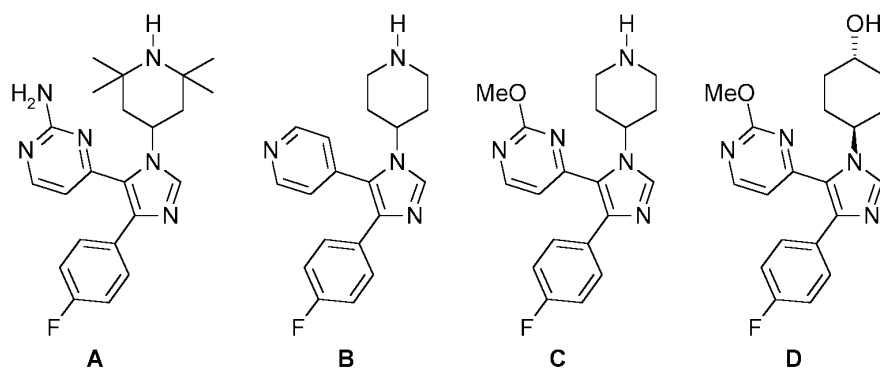
Fig. 1 Four potent and selective p38 kinase inhibitors.

Although the route employed by the discovery groups was intriguing [1] (Fig. 2, where *n* = 0), its use for scale-up to multikilogram quantities was plagued by a number of practical problems. For instance, the aldehydes and imines were difficult to isolate, reactions were run in CH_2Cl_2 and typically

gave yields of less than 50 %, and the ArS- moiety that is ejected during the product-forming step displaced the aryl fluoride in low levels, leading to impurities that were very difficult to remove. Although the literature [2] had suggested that several of these drawbacks could be eliminated by working through the corresponding sulfone (Fig. 2, where *n* = 2), a practical method to prepare this compound remained elusive. We describe in this report efficient and scaleable processes for making the desired sulfonyl isonitriles as well as their utility in preparing multifunctional, polysubstituted imidazoles.
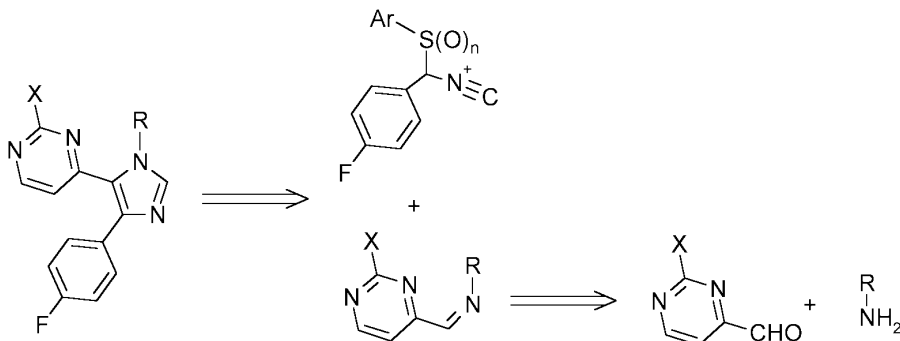

Fig. 2 Retrosynthesis of trisubstituted imidazoles using [3+2] cycloaddition.

DEVELOPING A PROCESS FOR MAKING ARYL-SUBSTITUTED TosMIC REAGENTS

We have previously described a new procedure for preparing aryl-substituted **T**o**s**yl**M**ethyl **I**so**C**yanides (TosMIC) precursors [3] and the use of the corresponding TosMIC reagents for the preparation of target imidazole A in a one-pot procedure (Scheme 1) [4]. However, an interesting thing happened during the scale-up of the process for making formamide **2**. Although we achieved the expected yield, a 1–2 % impurity was found by HPLC that was later identified as the reduced version of the target molecule (**4a**). To our surprise, we quickly determined that there was none of the corresponding "defluorinated" con-
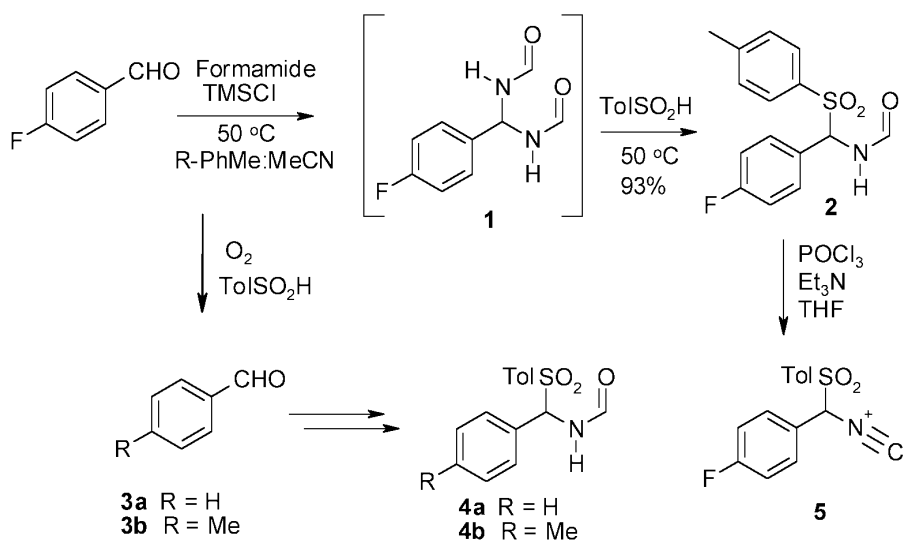
Scheme 1 Multikilogram route to TosMIC reagent **5**.

taminant in the 4-fluorobenzaldehyde or in the bis-formamide (**1**). After considerable detective work, we've learned that the presence of **4a** arises from oxidation of our solvent (toluene) in the presence of O_2 and toluenesulfinic acid. This was confirmed by conducting the same reaction in a *p*-xylene/acetonitrile solvent mixture and finding 1–2 % of the *p*-methylated derivative (**4b**) in the product mixture.

Scaling up the dehydration of formamide **2** to the TosMIC reagent **5** posed a different set of problems. Experimentally, the reaction is quite simple, involving the addition of excess Et_3N to a suspension of formamide in THF containing two equivalents of $POCl_3$. However, evaluation of the process safety data, in particular the accelerating rate calorimetry (ARC) data (Fig. 3), showed that the product decomposes violently as temperatures approach 80 °C. Although this was initially disconcerting, we have safely produced in excess of 500 kg of isonitrile **5** by keeping the reaction temperature near 0 °C during the Et_3N addition and during the water quench. Once isolated, the isonitrile **5** is a stable, crystalline solid that is very easily handled.

Temperature and Pressure as a Function of Time

explosion at 80 °C

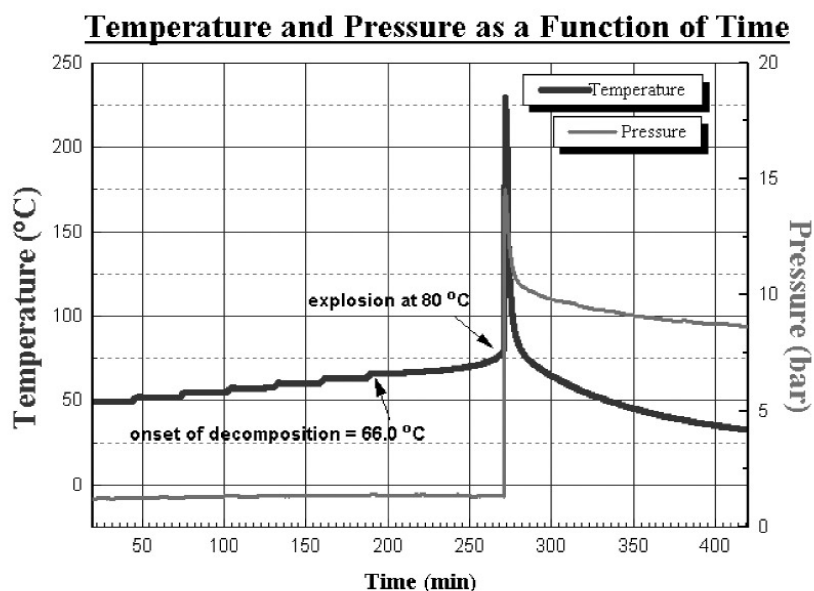onset of decomposition = 66.0 °C

Fig. 3 Accelerating rate calorimetry for isonitrile **5**.

DEVELOPMENT ROUTES TO IMIDAZOLES C AND D

We have previously described the synthesis of target molecule **A** [4], and imidazole **B** can be easily prepared from readily accessible starting materials. For these reasons, the discussion below is focused on the last two targets, **C** and **D**, which provided some of the more significant challenges for scale-up. Although the two retrosynthetic pathways below may look similar (Fig. 4), the changes we introduced made the difference between grams and kilograms.

By the time these compounds were discovered, our medicinal chemistry colleagues were using our TosMIC reagent for their discovery efforts with good success (Fig. 4) [5]. Following procedures developed in our labs [4], the aldehyde and amine were combined in DMF prior to adding the TosMIC reagent and K_2CO_3 to give product in 60–70 % yield. While the TosMIC reagent was obtained from our previous work on imidazole **A**, the second component, aminopiperidine **6**, was readily accessible from
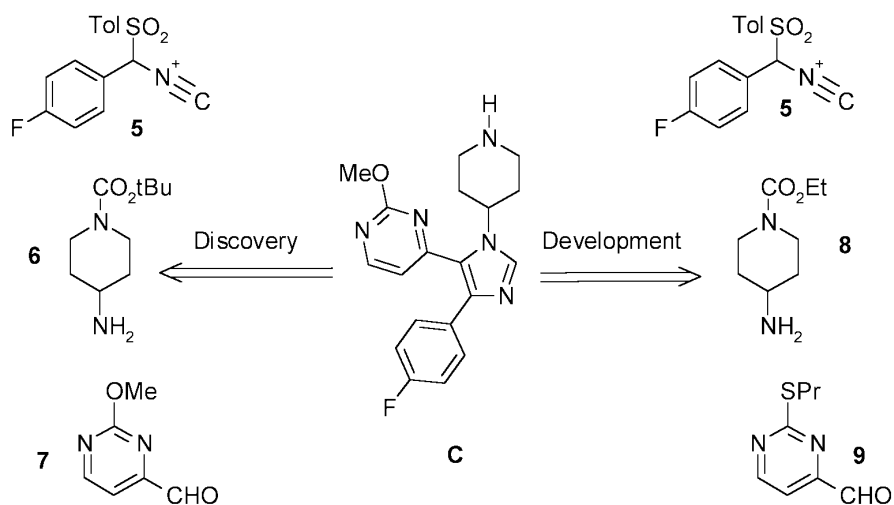
Fig. 4 Discovery and development retrosyntheses to target **C**.

4-piperidone, albeit in three synthetic stages. Unfortunately, a quick evaluation of the final component, aldehyde **7**, revealed that it had several features that made it unattractive for scale-up.

The most direct route to this pyrimidine aldehyde was through the general procedure first described by Bredereck [6]. Heating neat pyruvaldehyde dimethyl acetal and *N,N*-dimethylformamide dimethyl acetal generates the vinylogous amide **10** (Scheme 2). Without isolation, **10** was treated with urea and base, but none of the desired pyrimidone was isolated.
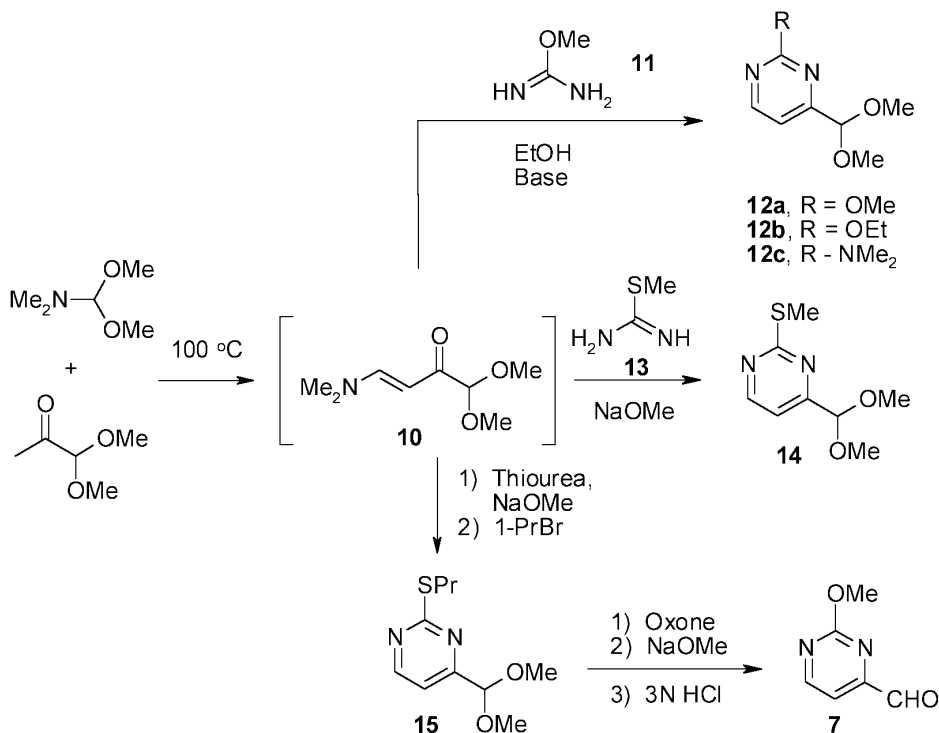
Scheme 2 Alternative approaches to 2-methoxypyrimidine-4-carboxaldehyde.

Replacing urea with *O*-methyl isourea (**11**) and heating with K_2CO_3 in EtOH generated the desired product, **12a**. However, the product was contaminated with equal amounts of the ethoxy derivative **12b** and the *N,N*-dimethyl derivative **12c**, each presumably arising from displacement of the methoxy group of **12a** by the other nucleophiles present in the reaction mixture. Since neither of these options looked feasible, we looked to prepare the desired compound by way of the more stable thioalkyl pyrimidines. Thus, heating vinylogous amide **10** with *S*-methyl pseudothiourea (**13**) in MeOH with NaOMe generated thiomethyl pyrimidine **14**. However, the stench associated with this reaction was so noxious that it was obviously unsuitable for scale-up. We circumvented this problem by going in a step-wise fashion, first treating **10** with thiourea in base to generate the thiopyrimidine compound which could be smoothly alkylated with 1-PrBr to generate **15** in 70–75 % yield in a one-pot process. Oxidation of the sulfide using Oxone® [7], followed by displacement of the sulfone moiety, cleanly gave the 2-methoxypyrimidine acetal **12a**. Unfortunately, hydrolysis of the acetal moiety of **12a** produced the desired aldehyde **7** that was difficult to isolate owing to its appreciable water solubility, and that was also prone to displacement at the 2-position. Although aldehyde **7** was, in fact, a reliable partner for making target molecule **C**, its drawbacks for large-scale production greatly outweighed its advantages.

While considering our options for developing a scaleable process for the synthesis of **C**, we found that the carboxyethyl piperidine **8** was commercially available at a reasonable price, saving three synthetic steps. However, given the challenges mentioned above for the synthesis of aldehyde **7** and its known instability at the 2-position under conditions that would be required to remove the ethyl carbamate function, we soon recognized the need for a different approach for introducing the methoxypyrimidine group. The successful approach is highlighted in Scheme 3.
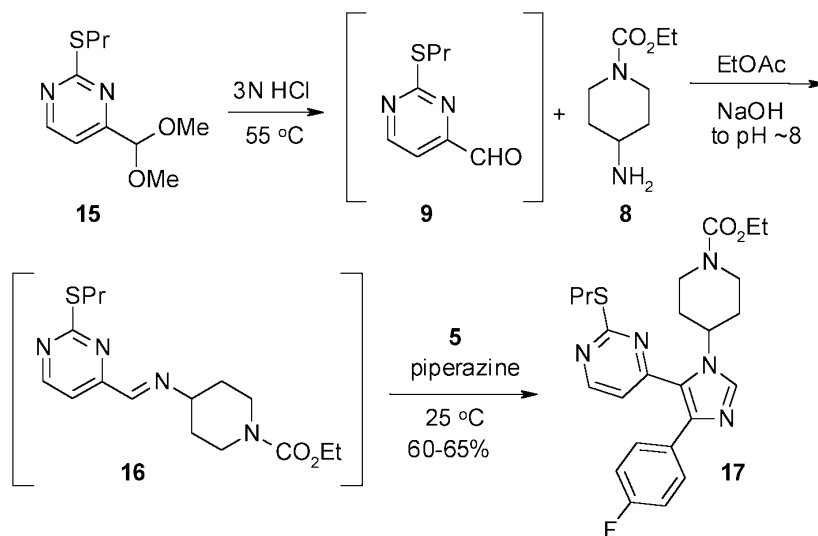
**Scheme 3** Scaleable synthesis of a valuable precursor to target **C**.

2-Thioalkyl pyrimidines are known to be considerably more stable than their alkoxy derivatives and we had already demonstrated a one-pot synthesis of **15**, making it an attractive starting point. Hydrolysis of the acetal function of **15** with 3N HCl gave the aldehyde **9**. Without isolation of the aldehyde, we added aminopiperidine **8** and EtOAc to the reaction mixture. Adjusting the pH to 8 with NaOH induced rapid formation of imine **16**, which separated into the organic layer. After separation of the aqueous layer, TosMIC reagent **5** and piperazine were added, which led to clean formation of the imidazole product **17** in 60–65 % isolated yield, even at a 200-gallon scale.

The final conversion of carbamate **17** to target **C** was ultimately accomplished in a single operation, as shown in Scheme 4. Cleavage of the carbamate group was accomplished using 9 N H_2SO_4 at 100 °C. After neutralization with NH_4OH and extraction of the product into MeOAc, the piperidine product was separated and purified by extraction into dilute aqueous HCl. Addition of MeOH and Oxone produced **19a,b** (*n* = 1 and 2, respectively) as a 3:1 mixture, each of which underwent smooth and rapid conversion to **C** upon addition of NaOH to pH 8–8.5. Addition of water to the reaction mixture induced the precipitation of **C** which was isolated as a white solid in 75–80 % from **17** in >98 % purity by HPLC.
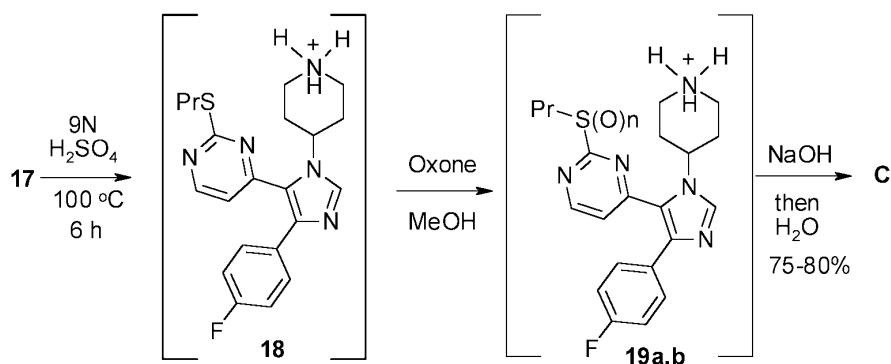
Scheme 4 High-yielding conversion of imidazole **17** to target **C**.

Owing to the harsh conditions required for the carbamate cleavage and the rather lengthy neutralization and isolation process that follows, we looked for further upgrades to our process. We were pleased to find that unprotected 4-aminopiperidine (**20**) was not only commercially available, but also reacted smoothly with aldehdye **9** to produce the corresponding imine, **21** (Scheme 5). Once again, the ease with which isonitrile **5** reacts with various imines, even in the presence of unprotected functional
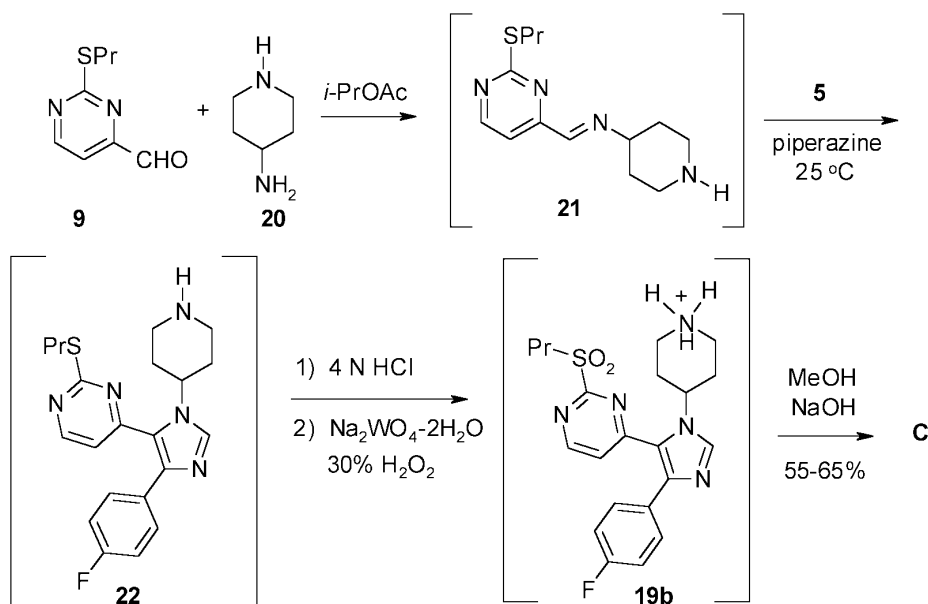
**Scheme 5** Alternative synthesis of target **C**.

groups and water [4], was demonstrated by smooth, one-pot conversion of imine **21** to imidazole **22** promoted by mild bases like piperazine. The product **22** was separated cleanly from the other organic components by adding 4N HCl and collecting the aqueous layer. To this was added $Na_2WO_4 \cdot 2H_2O$ (1 mole %) and excess 30 % H_2O_2 [8], which smoothly and quantitatively oxidized the sulfide to the corresponding sulfone. After quenching any residual peroxide, the solution was diluted with MeOH and made basic with 50 % NaOH to pH 8–9 to induce displacement of the sulfone by –OMe to produce the target molecule. Upon cooling to 0 °C, the product crystallized from solution and was isolated with >96 % purity. Remarkably, this one-pot process delivered the product in 55–65 % isolated yield, based on isonitrile **5**.

One final approach to **C** that was briefly investigated is presented in Scheme 6. Although we had discounted using 2-methoxypyrmidine aldehyde **7** because of, among other things, its appreciable water solubility as discussed above, we continued to explore possible avenues for its use in order to limit the number of post-imidazole transformations. As such, we conceived and briefly explored the chemistry shown in Scheme 6. Hydrolysis of the acetal moiety in **12a** leads to smooth conversion to the aldehyde **7**, as noted above. Although **7** itself is quite water-soluble and difficult to isolate, we found that adjusting the pH to 8–9 and adding *t*-BuNH$_2$ and EtOAc quickly and cleanly leads to the imine **23**, which has virtually no water solubility and is easily extracted into the EtOAc in 80 % over-all yield. Addition of 4-aminopiperidine (**20**) to a toluene solution of **23** at reflux for several hours induced trans-imination, driven by removal of the volatile by-product, *tert*-BuNH$_2$. After cooling to ambient temperature and adding EtOAc, TosMIC **5**, and piperazine, HPLC analysis of the product mixture showed the desired product **C** and *t*-Bu imidazole **24** in a 92:8 ratio. Although this route clearly merited further examination, the project was terminated before we had the chance to do so.
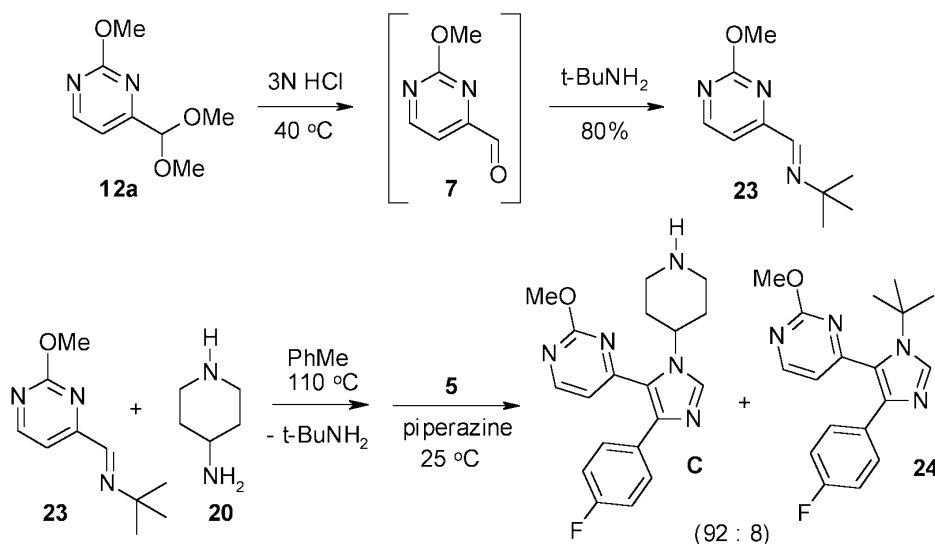

Scheme 6 Trans-imination route to target **C**.

With the successes found in the schemes shown above, devising a practical route to the final target, imidazole **D**, was a fairly simple task (Scheme 7). Hydrolysis of acetal **15** with 3N HCl led to the aldehdye **9**, which, after neutralization, was extracted into EtOAc and treated directly *trans*-4-aminocyclohexanol. To the solution of imine **25** that was produced was added isonitrile **5**, DMF, and K_2CO_3 to give imidazole **26** in 60 % isolated yield in a single pot from acetal **15**. Completing the synthesis involved oxidation of the sulfide with Oxone in MeOH/H$_2$O, then adjusting the pH to 8–9 to induce –OMe displacement of the sulfur group, which was accomplished in a single operation in 90 % yield.
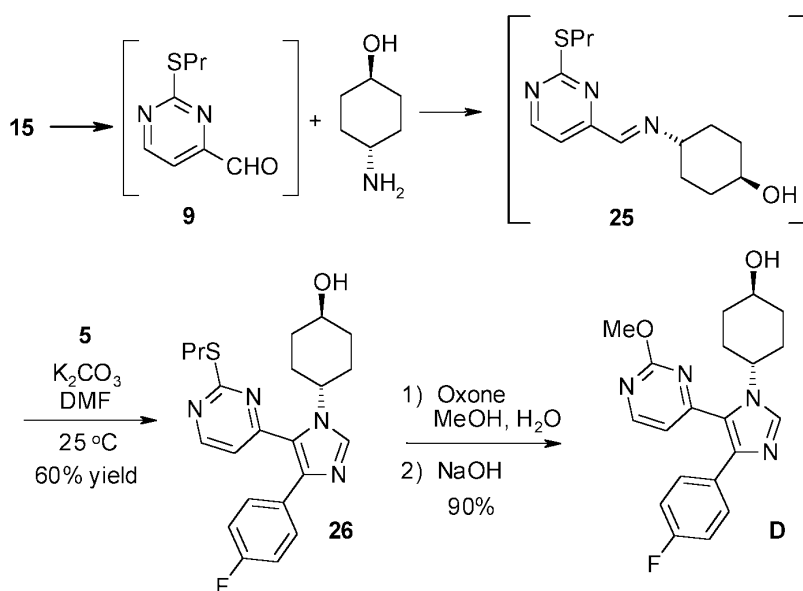
Scheme 7 Concise route to target **D**.

From the work presented above, it became obvious to us that these aryl-substituted TosMIC reagents were truly versatile for preparing poly-substituted imidazoles under simple and mild conditions, in high yields, and in a completely regioselective fashion. A particularly attractive feature of this methodology was the variety of fruitful reaction conditions employed and the wide assortment of compatible functional groups. We embarked on a systematic study to explore and highlight these qualities, and the results are demonstrated in the examples below [9]. The example in eq. 1 highlights the functional group tolerability without resorting to protecting groups. In addition, it demonstrated that heteroaryl TosMIC reagents can also be readily prepared and employed in a similar manner. Also noteworthy is the fact that chiral amino acids can be employed in the imine formation with complete preservation of the chirality. In the second example (eq. 2), it was found that employing glyoxylic acid as the aldehyde component in this multicomponent reaction leads to 1,4-disubstituted imidazoles in high yield. These compounds presumably arise via decarboxylation of the intermediate tosyl imidazoline. Finally, replacing primary amines in this reaction with NH$_4$OH (eq. 3) leads directly to 4,5-disubstituted imidazoles in good yield.

(1)

(2)

(3)
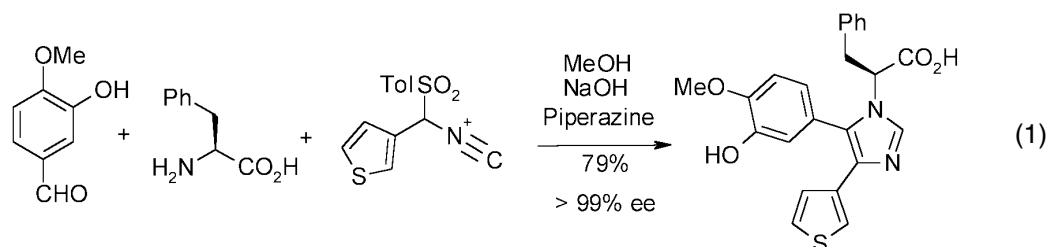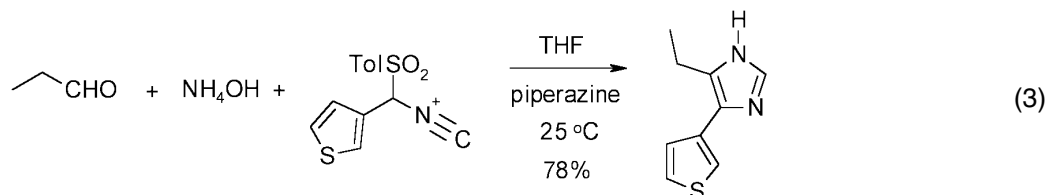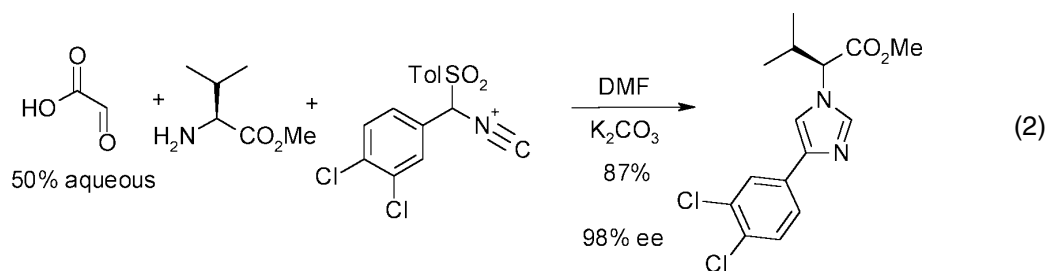
In summary, we have described a highly efficient method for preparing a variety of imidazoles compounds in a one-pot, multicomponent reaction sequence. Yields are uniformly high, reaction conditions are quite mild, and the transformations are experimentally simple. In addition, functional group compatibility is excellent, and introduction of asymmetric centers from chiral amines or aldehydes (not shown) can easily be accomplished.

ACKNOWLEDGMENTS

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