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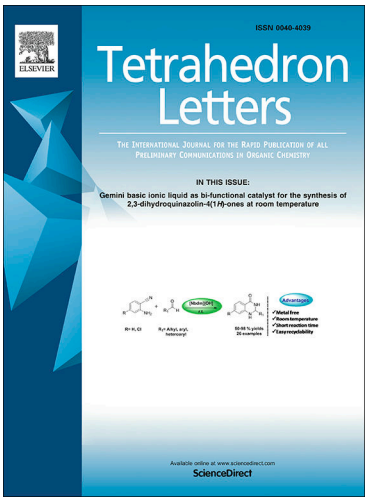

Improved synthesis of sterically encumbered heteroaromatic biaryls from aromatic β-keto esters

Brandon R. Rosen, Ehesan Ul Sharif, Dillon H. Miles, Nicholas S. Chan, Manmohan R. Leleti, Jay P. Powers

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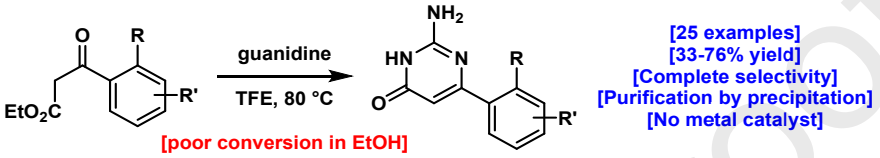

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Improved synthesis of sterically encumbered heteroaromatic biaryls from aromatic β-keto esters

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ABSTRACT

A protocol for the synthesis of hindered 4-aryl 2-aminopyrimidines from β–keto esters is described. The process employs trifluoroethanol as an essential additive to promote the guanidine condensation reaction, enabling the synthesis of 25 aryl- and heteroaryl substituted aminopyrimidines in good yields and high purities with no column chromatography. The conditions described herein are readily scalable and have been employed in the large-scale synthesis of the clinical $A_{2a}/A_{2b}R$ antagonist AB928.

Aryl substituted 2-aminopyrimidines represent a broadly adopted pharmacophore in drug discovery.[1–6] The inclusion of this motif in several FDA-approved and investigational medicines underscores its importance, as exemplified by the chemical structures of Xermelo (**1**, telotristat ethyl), Momelotinib (**2**), Braftovi (**3**, encorafenib), and Gleevec (**4**, imatinib). The central core of each of these molecules contains an aryl substituted 2-aminopyrimidine, the synthesis of which is typically straightforward. A common approach is the Suzuki–Miyaura cross-coupling of an appropriately substituted halopyrimidine and arylboronic acid to forge the Ar–Ar bond.[7–10] Alternatively, these heterocycles can be prepared by condensation of a functionalized guanidine onto a β–keto ester or appropriate surrogate.[11–14]

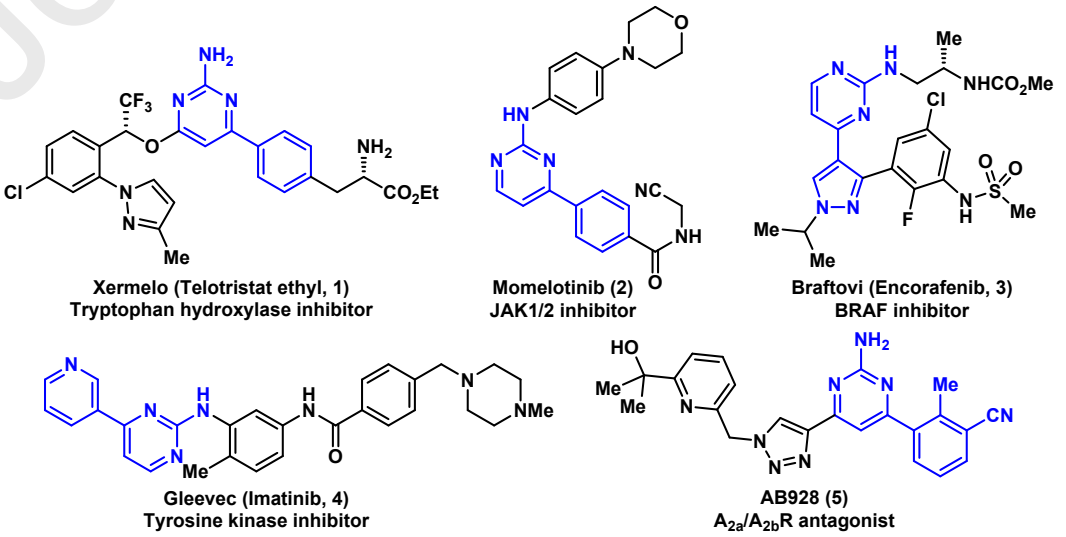
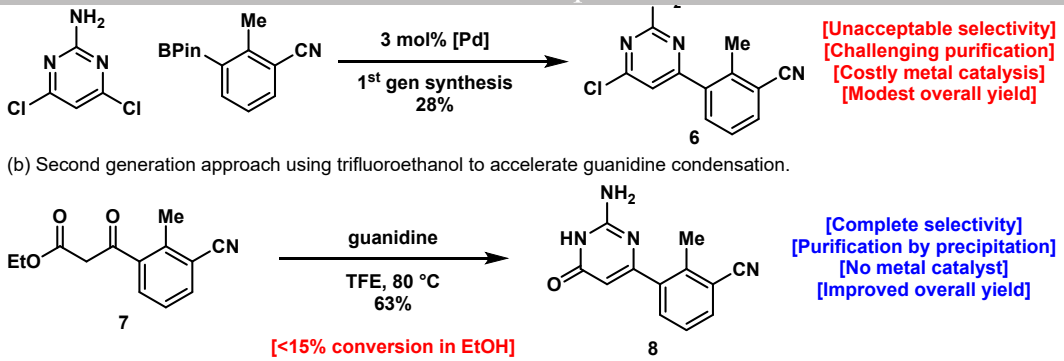


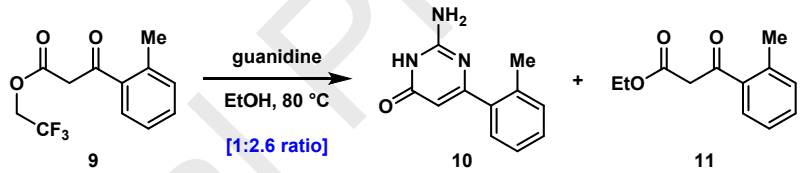
Figure 1. Biologically-active 4-aryl 2-aminopyrimidines.



Scheme 1. Approaches to AB928 intermediate using metal-catalyzed cross-coupling or guanidine condensation.

AB928 (**5**) is a potent and selective dual $A_{2a}/A_{2b}R$ antagonist discovered at Arcus Biosciences currently undergoing clinical trials in multiple cancer settings.[15] As part of ongoing studies focused on the large-scale synthesis of **5**, we found that the synthesis of key intermediate **6** under typical Suzuki cross-coupling conditions was not suitable for the large scale synthesis of AB928 (**Scheme 1a**). Scale-up was hampered by poor selectivity for mono- over difunctionalization of the dichloropyrimidine and the resulting challenging purification. After column chromatography and recrystallization, intermediate **6** was still contaminated with the diaryl substituted product and 4,6-dichloro-2-aminopyrimidine starting material. Additionally, efforts to employ less than 3 mol% of the palladium catalyst resulted in inferior conversions, and the costs associated with these higher catalyst loadings on larger scale were deemed unacceptable.

Thus, we elected to explore an alternative construction of the pyrimidine core employing β-keto ester **7** and guanidine. Following established protocols for pyrimidine synthesis, prolonged exposure of **7** to guanidine carbonate in refluxing ethanol resulted in trace formation of product **8**, likely due to the *ortho*-methyl substituent present on the aryl ring. It quickly became clear that our proposed route to **8** would require the development of novel conditions for this seemingly simple transformation. In this Letter, we report the use of conditions for the synthesis of sterically hindered 6-aryl 2-aminopyrimidinones from β-keto esters using trifluoroethanol (TFE) as an accelerant (**Scheme 1b**).[16–18] This scalable approach to pyrimidine synthesis has enabled the preparation of AB928 for further clinical development with no need to remove hazardous metal contaminants and an improved yield over the previous cross-coupling approach. The optimized procedure is operationally simple and can be employed in the synthesis of a variety of pyrimidine derivatives containing sterically hindered aryl and heteroaryl substituents.



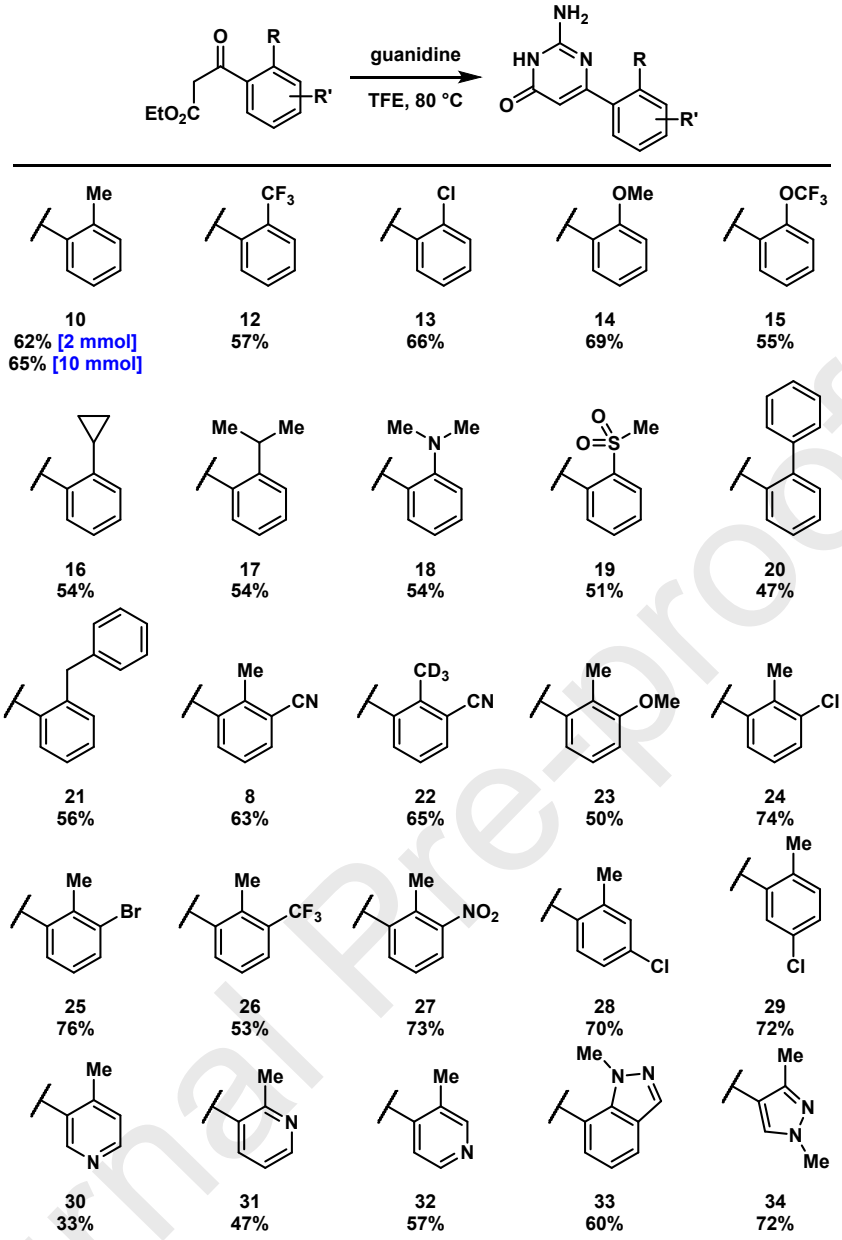
Scheme 2. Initial pyrimidinone synthesis using trifluoroethyl keto-ester.

Our initial solution to the sluggish reactivity of **7** was to modify the ester in order to increase its electrophilicity. Thus, as shown in **Scheme 2**, exposing the related trifluoroethyl keto-ester **9** to guanidine carbonate in refluxing ethanol led to a mixture of desired pyrimidinone **10** and keto-ester **11** in approximately 1:2.6 ratio, indicating that **9** was a competent coupling partner in the condensation reaction. Replacing ethanol with TFE solvent to prevent undesired transesterification led to complete conversion of **9** to **10**; the preparation of **9**, however, was inadequate for our needs, and we began to contemplate a synthesis of trifluoroethyl keto-ester **9** directly from **11**. Transesterification of **11** in the presence of TFE was sluggish, and efforts to drive the reaction to completion at elevated temperatures or in the presence of acid additives were unsuccessful. Despite the slow transesterification, we believed we could exploit the dynamic equilibrium and funnel the trifluoroethyl ester to pyrimidinone **8**. Thus, we found that addition of guanidine to a trifluoroethanolic solution of **11** at reflux resulted in complete consumption of **11** and acceptable isolated yields of pyrimidinone **10** after precipitation. This result could be obtained with as little as 10% v/v TFE/ethanol as solvent, though with slightly prolonged reaction time. It is noteworthy that the use of other solvents (e.g. HFIP, DMF, NMP) or additives (e.g. AcOH, TsOH) did not improve conversions, even at temperatures well above the boiling point of TFE. Furthermore, the only detectable byproduct in the reactions was the corresponding acetophenone derived from decarboxylation of **11**; typically, this byproduct was formed in less than 15% yield and could be washed away from the crude mixture prior to precipitation of the product or separated by column chromatography.[19]

With these optimized conditions in hand, we elected to explore the scope of the TFE-mediated cyclization. As shown in **Scheme 3**, a broad range of *ortho*-substituted keto-esters were converted to the corresponding aminopyrimidinones. For example, methyl, trifluoromethyl, chloro, methoxy, and trifluoromethoxy groups were all well-tolerated at the *ortho* position (**10**, **12**–**15**). Larger groups such as cyclopropyl, isopropyl, dimethylamino, methanesulfonyl, benzyl, and even phenyl afforded the corresponding pyrimidinones in synthetically useful yields (**16**–**21**).

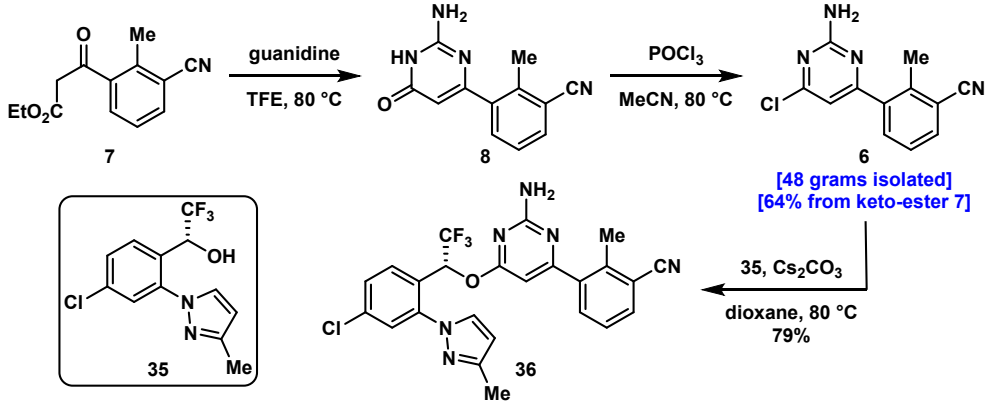
Variation of the electronic nature of the benzene ring was also well-tolerated. Both electron deficient and electron rich aryl keto-esters could be used. Pyrimidinone **8** was prepared in 63% yield, while deuterating the methyl group enabled the synthesis of **22** in a comparable 65% yield. Replacing the cyano group with a methoxy group resulted in a diminished 50% yield of **23**. The electron-deficient chloro, bromo, trifluoromethyl, and nitro arenes **24**–**27** were prepared in good yields. The chlorine atom could be incorporated at other positions of the benzene ring (**28** and **29**); use of the 2-chloro-6-methylbenzoic acid-derived keto-ester, however, led to a complex mixture and less than 20% conversion to product. Furthermore, attempts to employ the 2,6-dimethylbenzoic acid-derived keto-

este a limited amount of steric bulk tolerated in the condensation reaction, even under the TFE-accelerated conditions.[20]



Scheme 3. Scope of TFE-mediated guanidine condensation. Reaction conditions: keto-ester substrate (2 mmol), guanidine carbonate (2 mmol), CF_3CH_2OH (2.5 mL), 80 °C. Yields refer to isolated yields as an average of two experiments.

Substituted heterocycles also proved to be efficient partners in the condensation reaction, affording nicotinic acid-derived products **30** and **31** as well as isonicotinic acid-derived product **32**. Substituted indazole **33** was prepared in 60% yield, while pyrazole **34**, which contains the substitution pattern found in encorafenib **3**, was prepared in an efficient 72% yield. It is noteworthy that in all instances, replacing TFE with ethanol as a solvent for the reaction resulted in dramatically diminished or no conversion after 24 hours.



Scheme 4. Synthesis of chloropyrimidine and conversion to aryl ether.

cale by precipitation. As shown in **Scheme 4**, these conditions were readily adopted for the multi-gram scale synthesis of **6**. Following precipitation of **8**, we were able to convert **8** to chloropyrimidine **6** using $POCl_3$ in 64% yield (two steps, 48 grams isolated), intercepting the intermediate previously synthesized by Suzuki-Miyaura cross-coupling. This isolated yield compares favorably and results in a nearly 60% cost reduction for the synthesis of this key intermediate.[21] We elected to further functionalize **6** through an S_nAr reaction employing alcohol **35** to give ether **36** in 79% yield, highlighting the utility of these intermediates in the synthesis of bioactive molecules.

In summary, we have discovered that the synthesis of sterically hindered 2-aminopyrimidines from guanidine and β-keto esters can be expedited using trifluoroethanol as solvent. Exploiting this underutilized solvent results in a dramatic increase in reaction rate, and byproducts can be washed away before the product is precipitated in high purity, thereby avoiding chromatographic separation. This operationally simple route was employed in the large-scale synthesis of a key intermediate for the clinical candidate AB928, replacing a more costly Suzuki-Miyaura coupling route. The conditions described herein can be used in the synthesis of a variety of substituted aminopyrimidines with good functional group tolerance on the keto-ester substrate. We expect that this straightforward procedure will be adopted in other contexts where classical heterocycle synthesis provides a superior alternative to modern cross-coupling.

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20. Related hindered pyrimidine derivatives have been prepared by Suzuki-Miyaura cross-coupling of the corresponding boronic acids. See Ref 5.
21. Cost savings based on quotations provided for the synthesis of 24 kg of compound **6**.

Supporting Information

The Supporting Information is available free of charge and contains experimental procedures, characterization data, and NMR spectra.

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Aut

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Highlights

- Aryl substituted 2-aminopyrimidines are important in drug discovery
- AB928 is a potent A2a/A2bR antagonist undergoing clinical trials in cancer
- Trifluoroethanol promotes reaction between hindered β-keto esters with guanidine