Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX-XXX

pubs.acs.org/OrgLett

Scalable Synthesis of Trifluoromethylated Imidazo-Fused N-Heterocycles Using TFAA and Trifluoroacetamide as CF_3-Reagents

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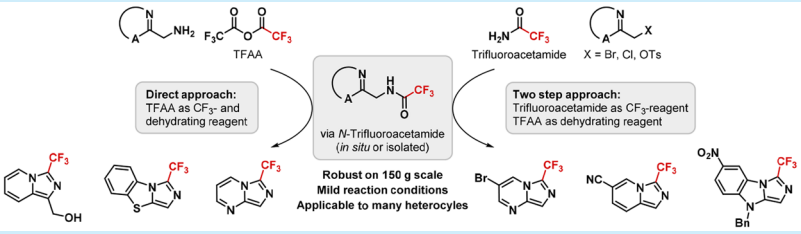
Supporting Information



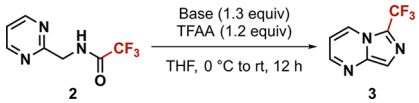
ABSTRACT: A scalable synthesis of trifluoromethylated imidazo-fused N-heterocycles from heterocyclic benzylamines using TFAA as trifluoromethylating reagent is presented. The reaction proceeds via intermediate benzylic *N*-trifluoroacetamides followed by dehydrative cyclization to the products. To further broaden the scope and practicality, a new method for the preparation of benzylic *N*-trifluoroacetamides via alkylation of trifluoroacetamide with benzyl (pseudo)halides was developed. Both methods proceed under mild conditions, and their symbiosis provides access to a wide range of novel CF_3-heterocycles.

The development of new methodologies for the introduction of fluorine into small organic compounds has become a major research interest in academic and industrial chemistry laboratories over the last two decades.[1] This rapid expansion of fluorination reactions can be attributed to the beneficial effects that fluorine and fluorine-containing groups exert in pharmaceuticals and agrochemicals: fluorinated compounds often show increased metabolic stabilities and improved pharmacokinetic properties compared to their nonfluorinated analogs.[2] Among the above-mentioned *fluorine-containing groups*, the trifluoromethyl (CF_3) group is the front-runner and received the most attention by the organic synthetic community.[3] Different approaches for the trifluoromethylation of arenes and heteroarenes have been disclosed, using radical,[4] nucleophilic,[5] or electrophilic[6] trifluoromethylating reagents. From a process chemist's point of view, most of these reagents are impractical to use on scale[7] due to their high price,[8] their poor atom economy, or general safety concerns.[9] Therefore, many CF_3-containing arenes are still prepared by radical chlorination of aryl methyl groups followed by high-pressure or high-temperature treatment with HF or SbF_3/SbF_5.[10] These approaches may work well for simple arenes, but the functional-group tolerance under these harsh conditions is, not surprisingly, very low. Therefore, alternative protocols that proceed under mild conditions using inexpensive CF_3-sources are still an urgent synthetic need.

Inexpensive and atom-efficient CF_3-sources are trifluoroacetic acid (TFA) and its anhydride (TFAA). TFAA is available on metric ton-scale for $35/kg.[11] The use of TFAA in trifluoromethylation reactions has been scarce. Recently, Stephenson et al. described an elegant radical trifluoromethylation of arenes and heteroarenes using TFAA as the trifluoromethylating reagent, underlining the great potential of this reagent in the aspect of CF_3 chemistry.[11] In this paper, we disclose the facile synthesis of trifluoromethylated N-heterocycles from heterocyclic benzylamines using TFAA as an inexpensive CF_3-source and dehydrating agent. The reaction is operationally simple, shows a high functional group tolerance, and is robust on at least a 150 g scale.

For a recent campaign, we needed to rapidly produce 100 g of 6-(trifluoromethyl)imidazo[1,5-*a*]pyrimidine (**3**). We envisioned its synthesis from commercially available pyrimidin-2-ylmethanamine HCl (**1**) and TFAA via in situ formation of the corresponding trifluoroacetamide **2** followed by dehydrative cyclization (Scheme 1). For screening purposes, we prepared *N*-trifluoroacetamide **2** separately and tested different bases for its conversion into the desired product. Several bases (Cs_2CO_3, DBU, or KO*t*Bu) left the starting material unreacted when treated with a slight excess of TFAA. On the other hand, the use of triethylamine or sodium hydride (NaH) resulted in full conversion of trifluoroacetamide (**2**) and clean formation of the product (**3**). For safety and handling reasons,[12] triethylamine (NEt_3) was our base of choice.

Scheme 1. Dehydrative Cyclization of Trifluoroacetamide (2) into Imidazo-Fused Pyrimidine (3)



Received: October 23, 2017

DOI: 10.1021/acs.orglett.7b03291
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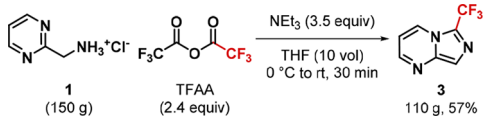
Increasing the amounts of triethylamine and TFAA allowed for the direct preparation of the desired product (**3**) from pyrimidin-2-ylmethanamine HCl (**1**) in 76% yield on 500 mg scale (purification by FC). With regard to scale-up, the high solubility of product **3** in a wide range of classical *anti-solvents* (e.g., methyl *tert*-butyl ether, isopropyl alcohol, ambient H_2O) made its isolation via crystallization very challenging.[13] In addition, we observed oiling out of the low-melting product (mp 99 °C) from nonpolar solvents such as heptane. Thanks to intensive process optimization efforts, we found that after aqueous basic quench of the reaction mixture and removal of THF by distillation the trifluoromethylated product would nicely crystallize at 5−10 °C as yellow, glimmery solid from the aqueous solution. Washing of the cake with cold H_2O followed by drying at 65 °C under reduced pressure provided the desired product in decent yield (110 g, 57%) and excellent purity (>99% a/a, 99% w/w)[14] on 150 g scale (Scheme 2). We anticipate that further process

Scheme 2. Synthesis of 3 from 1 on a 150 g Scale



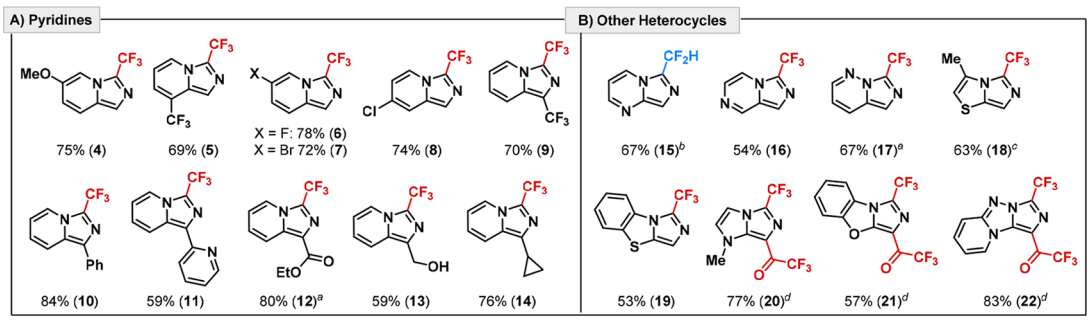
optimizations of the crystallization procedure (volumes,[15] cake washings, etc.) will increase the yield of isolated product and minimize product loss into the mother liquor.

We were curious if our optimized conditions were also viable to access other trifluoromethylated imidazo-fused N-heterocycles.[16] To our delight, a wide range of trifluoromethylated imidazo[1,5-*a*]pyridines could be synthesized (Scheme 3, A). Our conditions allowed for the conversion of electron-rich and electron-poor substrates into the corresponding imidazopyridines (**4**, **5** and **9**). Products (**6**−**8**) bearing halogen substituents in different ring positions were prepared with ease and in good yields. Bromo derivative **7** is a key intermediate to a series of ion-channel modulaters by Gilead.[17] In their patent, the preparation of **7** required isolation of the intermediate trifluoroacetamide, followed by dehydrative cyclization with excess $POCl_3$ (10 equiv) at 180 °C. In strong contrast, our procedure allowed for the one-pot preparation of **7** starting from (5-bromopyridin-2-yl)methanamine at room temperature using only a slight excess of TFAA. The mildness of our reaction conditions is further highlighted by the introduction of several sensitive functional groups, such as heterocycles (**11**), esters (**12**), and even unprotected alcohols (**13**). Many interesting trifluoromethylated heterocycles derived from pyrazine (**16**), pyridazine (**17**), thiazole (**18**), and benzothiazole (**19**) were synthesized and isolated in moderate to good yield (Scheme 3, B). In certain cases, overacylated heterocyclic products were obtained (**20**−**22**). For these highly activated substrates, the use of lower amounts of TFAA did not lead to clean formation of the nonacylated imidazo-fused heterocycles.[18] By switching from TFFA to commercially available difluoroacetic anhydride ($1200/kg),[19] the corresponding difluoromethylated pyrimidine **15** was synthesized on 10 g scale, and isolated in good yield and excellent purity. Such difluoromethylated imidazo-fused pyrimidines (and pyridines) are completely unknown, and could serve as exciting new building blocks in medicinal chemistry and agrochemical laboratories.[20]

The benzylamine starting materials used so far were commercially available, and the majority of them prepared via reduction of the parent aryl nitrile. Even though this sequence is routinely used, it precludes certain functional groups to be present in the benzylamines (e.g., CN, NO_2), and often multistep sequences are necessary to prepare such compounds. In order to circumvent the short-comings of aryl nitrile reduction and to increase the scope and practicality of our novel method, we were eager to find an alternative way to access *N*-trifluoroacetamides such as **24a** from commercially available trifluoroacetamide and heterocyclic benzyl tosylates or halides (**23**). These starting materials are conveniently accessed via halogenation or tosylation of benzyl alcohols, or, in the latter case, also via radical halogenation of 2-picoline derivatives. To our surprise, a Reaxys search delivered only a handful of examples that described the direct benzylation of trifluoroacetamide with benzyl bromides, most of them using sodium hydride as a base. No examples with benzyl tosylates could be found.

Using 6-(bromomethyl)nicotinonitrile (**23a**) as model substrate, we explored its trifluoroacetamidation testing different bases and solvents. After extensive screening, we found that cesium carbonate in THF performed best (Scheme 4, step 1). An excess of trifluoroacetamide (1.7 equiv) had to be used in order to minimize competing overalkylation of product **24a** (see the Supporting Information for further information). These novel conditions allowed for the synthesis of heterocyclic benzylic *N*-trifluoroacetamides bearing a nitrile (**24a**), ester (**24b**), iodo (**24c**), nitro (**24i**), or unprotected benzyl alcohol (**24j**) moiety (Scheme 4, step 1). The majority of these products would be hard or impossible to obtain via a nitrile reduction/acylation strategy, as the attached functional groups are very prone to hydrolytic reduction/cleavage. The reaction also worked when secondary

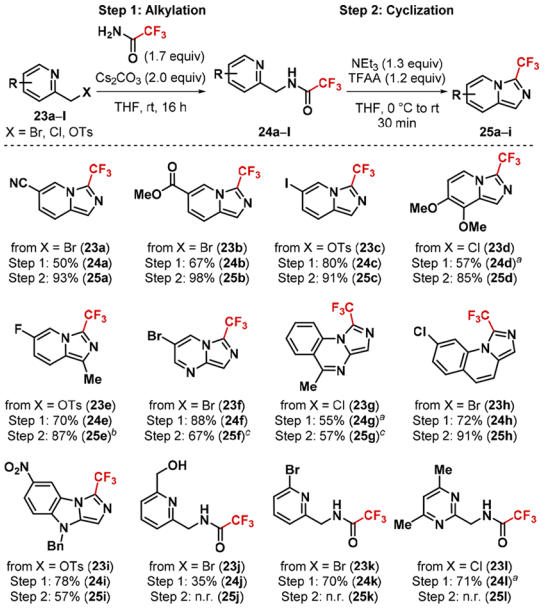
Scheme 3. Synthesis of Trifluoromethylated Imidazo-Fused N-Heterocycles from Heterocyclic Benzylamines*



*Reaction conditions: heterocyclic benzylamine (1.0 equiv), NEt_3 (2.5 equiv), TFAA (2.3 equiv), THF (10 vol), 0 °C to rt, 30 min. [a]0 °C to rt, 16 h. [b]Difluoroacetic anhydride (2.4 equiv) was used. [c]1 h at 0 °C. [d]NEt_3 (3.5 equiv), TFAA (3.3 equiv), 0 °C to rt, 30 min.

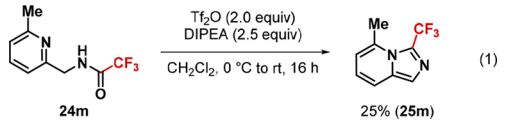
DOI: 10.1021/acs.orglett.7b03291
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 4. Benzylation of Trifluoroacetamide with Benzyl Halides or Tosylates and Subsequent Cyclization*



*Reaction conditions: Step 1: benzyl substrate **23a–l** (1.0 equiv), trifluoroacetamide (1.7 equiv), Cs_2CO_3 (2.0 equiv), THF (20 vol), 0 °C to rt, 16 h. Reaction conditions: Step 2: heterocyclic *N*-trifluoroacetamide **24a–l** (1.0 equiv), NEt_3 (1.3 equiv), TFAA (1.2 equiv), THF (10 vol), 0 °C to rt, 30 min. [a]65 °C, 16 h. [b]0 °C to rt, 16 h. [c]60 °C. n.r. = no reaction.

benzyl tosylate **23e** was used, and *N*-trifluoroacetamide **24e** was obtained in good yield. At elevated temperatures, benzyl chlorides proved to be viable starting materials, and normally 80–99% conversion into the corresponding *N*-trifluoroacetamides was achieved (after 16 h). Despite the incomplete conversion, products **24d** and **24g** were isolated in excellent purity (>99% a/a) on 5 and 2 g scale, respectively, via crystallization of the crude material from isopropyl alcohol, highlighting the innate potential of this reaction toward scale up. The transformation of the benzyl *N*-trifluoroacetamides into the imidazo-fused N-heterocycles proceeded smoothly using a slight excess of base and TFAA, and the trifluoromethylated products were isolated in good to excellent yields (Scheme 4, step 2). This means that the CF_3 groups in all heterocyclic products of Scheme 4 are ultimately derived from inexpensive trifluoroacetamide ($30–100/kg)[19]—to the best of our knowledge the first example of using this reagent in the area of (hetero)aryl–CF_3 bond formation. The method is not without limitations, and *N*-trifluoroacetamides **24j–l** that are substituted in the *ortho*-position to the nitrogen did not cyclize, even at elevated temperature. In order to solve this problem, we performed extensive screenings using **24m** as model substrate (eq 1). Our

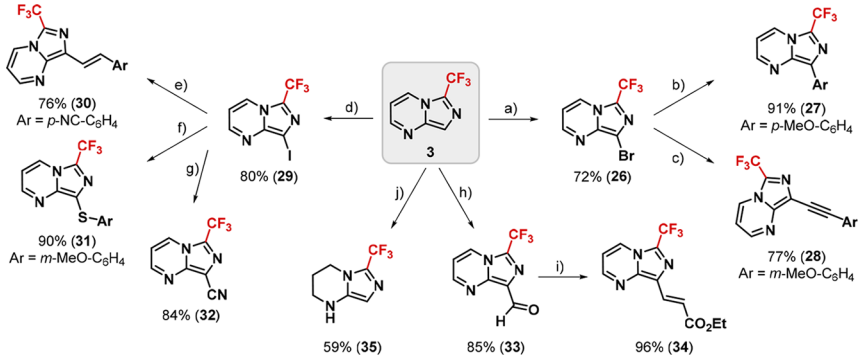


preliminary data suggest that the cyclization of this sterically encumbered substrate is possible by activating the amide functionality with triflic anhydride (Tf_2O) and DIPEA allowing for the formation of **25m**, albeit in low isolated yield (see the SI for further information).[21]

Finally, and with a scalable route for **3** in hand, we investigated additional functionalization strategies for this building block (Scheme 5). Bromination and iodination at the activated 8-position proceeded with ease and delivered the halogenated products **26** and **29** in high yields and excellent purity on 5.0 g scale. Both products crystallized directly from the reaction mixture after quench with a basic aqueous solution of $Na_2S_2O_3$. The halogenated derivatives were successfully transformed into the corresponding biaryl **27** (via Suzuki coupling, b), alkyne **28** (via Sonogashira coupling, c), diarylethene **30** (via Heck reaction, e), thioether **31** (via Pd-cat. thiolation, f), and nitrile **32** (via cyanation with CuCN, g). Trifluoromethylated imidazo-fused acrylate **34** was synthesized via Vilsmeier–Haack reaction, followed by treatment of the resulting aldehyde **33** with ethyl (triphenylphosphoranylidene)acetate. Finally, the aromatic part of the pyrimidine ring was selectively reduced via hydrogenation with H_2 over Pd/C, and the tetrahydro derivative **35** isolated in good yield.

The enormous potential of trifluoroacetic anhydride (TFAA) and trifluoroacetamide in the area of trifluoromethylation chemistry is evident: the commercial availability on ton scale,

Scheme 5. Functionalization Strategies of 6-(Trifluoromethyl)imidazo[1,5-*a*]pyrimidine (3)[a]



[a]Conditions: (a) **3**, NBS, MeCN, 0 °C, 30 min; (b) **26**, *p*-$MeC_6H_4B(OH)_2$, Pd(dppf)Cl_2, K_3PO_4, 1,4-dioxane/H_2O 5:1, 85 °C, 16 h; (c) **26**, 3-ethynylanisole, DIPEA, MeCN, 60 °C, 16 h; (d) **3**, NIS, TFA, MeCN, 0 °C, 30 min; (e) **29**, *p*-NC-styrene, Pd$(OAc)_2$, P(*o*-tol)$_3$, NEt_3, DMF, 80 °C, 16 h; (f) **29**, 3-methoxybenzenethiol, Pd_2dba_3, Xantphos, DIPEA, 1,4-dioxane, 110 °C, 16 h; (g) **29**, CuCN, DMSO, 100 °C, 5 h; (h) **3**, $POCl_3$, DMF, 1,2-dichloroethane, 55 °C, 16 h; (i) **33**, ethyl (triphenylphosphoranylidene)acetate, CH_2Cl_2, 0 °C to rt, 2 h; (j) **3**, Pd/C, H_2 (3 bar), EtOH, rt, 2 h. See Supporting Information for reaction details and procedure.

DOI: 10.1021/acs.orglett.7b03291
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low price, and high atom-efficiency make these reagents very attractive for scale up. The use of TFAA as dehydrating and CF_3-reagent allowed us to develop a robust route for 6-(trifluoromethyl)imidazo[1,5-*a*]pyrimidine (**3**) from commercially available pyrimidin-2-ylmethanamine HCl (**1**). Our optimized conditions were also applicable to other heterocyclic benzylamines, and a wide range of novel trifluoromethylated imidazo-fused N-heterocycles were prepared. In addition, we have also developed a method for the synthesis of heteroaromatic benzylic *N*-trifluoroacetamides via the direct alkylation of trifluoroacetamide with benzyl halides or tosylates. The symbiosis of the two methods compliments emerging protocols for the synthesis of trifluoromethylated heterocycles, and we expect that both methods will find widespread applications in academic and industrial organic chemistry laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03291.

Experimental details and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank François Le Goff (Idorsia) for high-resolution mass spectrometry, Kristina Kamin (Idorsia) and Christian Geugelin (Idorsia) for IR measurements, and Dr. Thomas Weller (Idorsia) for support of the project.

■ DEDICATION

Dedicated to our CEO Dr. Jean-Paul Clozel for the successful launch of Idorsia Pharmaceuticals, Ltd.

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(13) Chromatographic purification on scale, should be avoided whenever possible, as it leads to huge solvent and silica gel waste.

(14) % a/a corresponds to area purity by LC/MS. % w/w corresponds to weight purity by ^{1}H NMR against 1,4-dimethoxybenzene as internal standard.

(15) Dilution of reaction mixtures are expressed in volumes (vol) and corresponds to volumes of solvent per gram of limiting starting material (e.g., 10 vol = 10 mL of THF/1 g of heterocyclic benzylamine).

(16) All reactions were carried out on 0.25−1.0 g scale and the products isolated via chromatographic purification.

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DOI: 10.1021/acs.orglett.7b03291
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