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1-Trifluoromethylisoquinolines from α-Benzylated Tosylmethyl Isocyanide Derivatives in a Modular Approach

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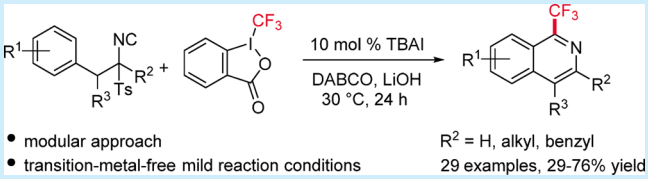
Supporting Information

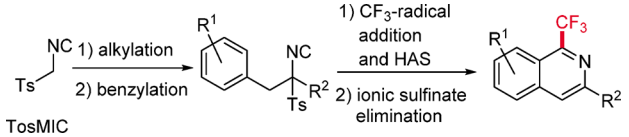
ABSTRACT: The preparation of various 1-trifluoromethylisoquinolines from α-benzylated tosylmethyl isocyanide derivatives and the commercial Togni reagent using a radical cascade is reported. The starting isocyanides are readily prepared in a modular sequence from commercial tosylmethyl isocyanide via sequential double α-alkylation, and the radical reaction proceeds under mild conditions with high efficiency without any transition-metal catalyst via electron catalysis. This valuable protocol has been successfully applied to the total synthesis of CF_3-mansouramycin B.



The isoquinoline scaffold is a prominent chemical core structure that can be found in numerous natural products, pharmaceuticals, agrochemicals, and organic materials.[1,2] Efficient synthetic methods have been developed for its construction in the past,[3] including the classic Pomeranz–Fritsch,[4] Bischler–Napieralski,[5] and Pictet–Spengler reactions.[6] Due to the significance of this substructure in various fields, the development of alternative methods that allow for easy access to isoquinolines and their derivatives is still of importance. Along these lines, the synthesis of trifluoromethylisoquinolines has caught great attention from the synthetic community during the past few years.[7] This has been fostered by the fact that the introduction of a trifluoromethyl group into a lead compound generally improves its lipophilicity, bioactivity, and metabolic stability.[8]

Radical trifluoromethylation has been found to be highly valuable for simple and efficient incorporation of a CF_3 group into various π-systems.[9] Although many methods for radical trifluoromethylation of activated and unactivated arenes have been developed, some problems still remain to be solved.[10] Most of the reported trifluoromethylation reactions occur at preformed arenes that generally bear activating substituents and often expensive transition metal catalysts are necessary. Moreover, regioselectivity is a serious problem in such transformations. For certain heteroarenes, the regioselectivity issue can be solved by constructing the heteroarene core during radical trifluoromethylation and in that regard isocyanides have been used as efficient acceptors to construct heterocyclic ring structures via radical isocyanide insertion reactions.[11] Notably, 1-trifluoromethylated isoquinolines have been successfully prepared with complete regioselectivity by radical trifluoromethylation of vinyl isocyanides.[12] However, the geometry of the double bond in these arylalkenyl isocyanides has to be controlled since only the *cis*-β-aryl vinyl isocyanides are eligible for heteroarene construction. In contrast to aryl and vinyl isocyanides that have been intensively explored, there are few studies on the use of alkyl isocyanides as radical acceptors in cascade reactions. The problem lies in the ready fragmentation of alkyl radicals in the intermediate imidoyl radicals generated after radical addition to the isonitrile moiety resulting in cyanation. In fact, Ito and Stork introduced alkyl isocyanides as efficient radical cyanation reagents.[13] Since imidoyl radicals derived from addition of the CF_3 radical to an isonitrile moiety undergo fast intramolecular homolytic aromatic substitution (HAS),[12b,14] we were optimistic that such an HAS can outcompete the possible β-alkyl radical fragmentation and decided to test α-benzyl tosylmethylisocyanide (TosMIC) derivatives as substrates for radical isonitrile insertion reactions. The product of the HAS should readily eliminate tolylsulfinate in an ionic reaction to eventually give the corresponding trifluoromethylated isoquinolines (Scheme 1).

Scheme 1. α-Benzyl TosMIC Derivatives as CF_3-Radical Acceptors for the Construction of 1-Trifluoromethylisoquinolines



Importantly, TosMIC is a cheap and commercially available reagent that can easily be doubly alkylated, thus allowing for ready variation of the benzyl and R^2 substituents in these CF_3-radical acceptors (modular approach).[15] The double alkylation of TosMIC was achieved using slightly modified literature protocols (see the Supporting Information)[15] and as a CF_3-radical precursor we applied the commercial Togni reagent **2a**.[16] We have previously shown that radical-chain reactions with **2a** are efficiently initiated using tetrabutylammonium iodide

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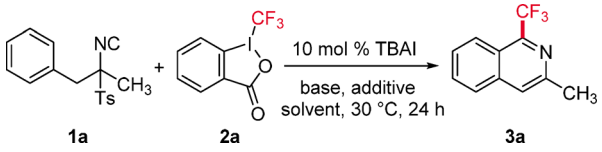
Org. Lett. XXXX, XXX, XXX–XXX

(TBAI).[17] Isocyanide **1a** was selected as test substrate, various organic and inorganic bases were screened, and initial experiments were conducted in 1,4-dioxane at 30 °C using 2.0 equiv of **2a** (Table 1).

Table 1. Reaction Optimization[a]



1a **2a** **3a**

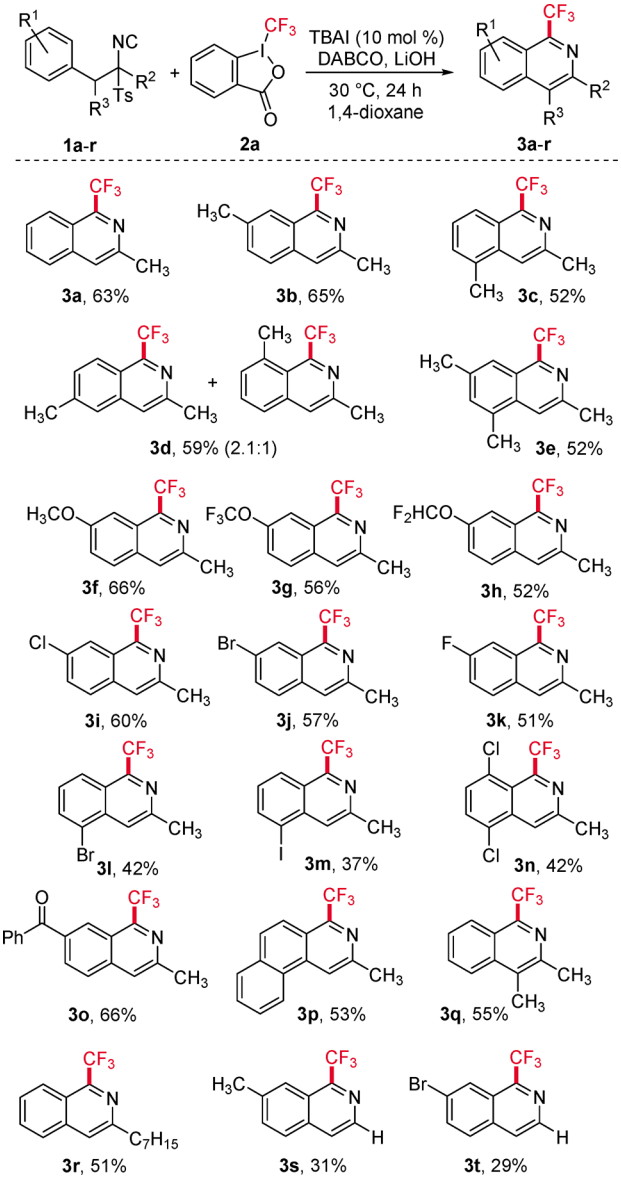
entry	base	additive	solvent	yield[b] (%)
1	K_2CO_3		1,4-dioxane	11
2	Cs_2CO_3		1,4-dioxane	14
3	CsF		1,4-dioxane	10
4	NMM		1,4-dioxane	31
5	DABCO		1,4-dioxane	33
6	**DABCO**	**LiOH**	**1,4-dioxane**	**67 (63)**[i]
7	DABCO	NaOH	1,4-dioxane	62
8	DABCO	KOH	1,4-dioxane	48
9	DABCO	LiOH	CH_3CN	64
10	DABCO	LiOH	THF	47
11	DABCO	LiOH	EtOAc	60
12	DABCO	LiOH	CH_2Cl_2	43
13[c]	DABCO	LiOH	1,4-dioxane	66
14[d]	DABCO	LiOH	1,4-dioxane	53
15[e]	DABCO	LiOH	1,4-dioxane	40
16[f]	DABCO	LiOH	1,4-dioxane	35
17[g]	DABCO	LiOH	1,4-dioxane	59
18[h]	DABCO	LiOH	1,4-dioxane	42

[a]Reaction conditions: **1a** (0.20 mmol), **2a** (0.40 mmol), TBAI (0.02 mmol), DABCO (0.40 mmol), and LiOH (3.0 mmol) in 1,4-dioxane (1.0 mL) were stirred at 30 °C for 24 h under argon atmosphere. [b]Yield determined by ^{19}F NMR analysis using $PhCF_3$ as an internal standard. [c]LiI used as initiator. [d]NaI used as initiator. [e]50 °C. [f]80 °C. [g]rt. [h]Run without TBAI. [i]Isolated yield.

With inorganic bases such as K_2CO_3, Cs_2CO_3, or CsF, the targeted 1-trifluoromethylisoquinoline **3a** was obtained, albeit in a low yield (Table 1, entries 1−3). Switching to organic bases such as NMM and DABCO resulted in slightly improved results (Table 1, entries 4 and 5). We have recently noted the beneficial effect of using DABCO in combination with LiOH as an additive in electron-catalyzed perfluoroalkylation reactions.[18] Gratifyingly, addition of LiOH led to a further improvement of the yield (Table 1, entry 6). NaOH and KOH as additive inorganic bases provided slightly worse results (Table 1, entries 6 and 7). 1,4-Dioxane could be replaced by CH_3CN (Table 1, entry 9), but THF, EtOAc, and CH_2Cl_2 resulted in significantly lower yields (Table 1, entries 10−12). Upon screening other initiators, we found that TBAI can be substituted by LiI (Table 1, entry 13), but NaI is less suited (Table 1, entry 14). Reaction in the absence of TBAI was not efficient (Table 1, entry 18), and 30 °C was identified as the ideal reaction temperature for this cascade (Table 1, entries 15−17).

Having the optimized conditions in hand (see Table 1, entry 6), we first explored the scope and limitations of the radical trifluoromethylation by using various α-benzylated TosMIC derivatives **2b−t**. The aryl group in the benzyl moiety was systematically varied (Scheme 2). *p*- and *o*-tolyl methyl isocyanides reacted well with **2a** and the desired 1-trifluoromethylisoquinolines **3b,c,e** were obtained in good yields

Scheme 2. Cascades Using α-Benzyl α-Alkyl TosMIC Derivatives[a,b]



[a]Reaction conditions: **1** (0.20 mmol), **2a** (0.40 mmol), Bu_4NI (0.02 mmol), DABCO (0.40 mmol), and LiOH (3.0 mmol) in 1,4-dioxane (1 mL) were stirred at 30 °C for 24 h under argon atmosphere. [b]Isolated yield.

(52−65%). In the case of the *meta*-congener, regioselectivity for the HAS was 2.1:1 (see **3d**). Electronic effects exerted by the aryl group do not influence reaction outcome to a large extent, and substrates bearing electron-donating and also -withdrawing groups provided the corresponding products in good yields (**3f−o**). The slightly lower yields obtained for the *o*-halo-substituted systems are likely caused by steric effects. The naphthyl-substituted isocyanide **2p** underwent cyclization to **3p** with complete regiocontrol. As expected, the methyl R^2-substituent can be replaced by a larger *n*-heptyl group (see **3r**). Importantly, also the 4-position of the isoquinoline core can be addressed as documented by the successful preparation of **3q**. 1-Trifluoromethylisoquinolines **3s** and **3t** lacking the R^2-substituent were obtained in lower yields. Likely, the cyclization

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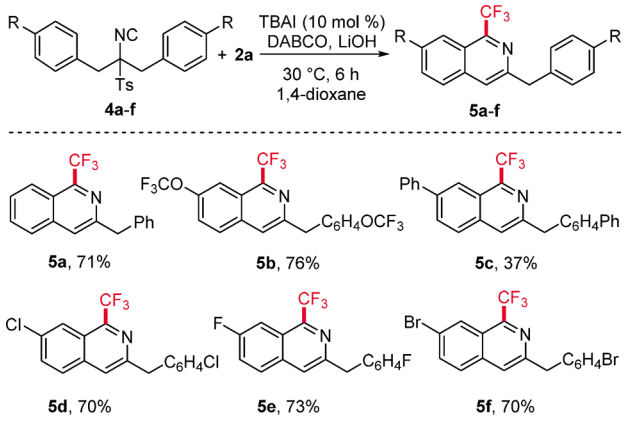
Org. Lett. XXXX, XXX, XXX−XXX

rate constant is smaller in these two cases due to the lacking Thorpe−Ingold effect.

As compared to the unsymmetrical substrates **1**, symmetrical α,α-bisbenzyl TosMIC derivatives **4a−f** are even more easy to access from TosMIC (see the SI). Because of the higher effective molarity of the arene radical acceptor in these systems, yields for the corresponding trifluoromethylated isoquinolines were higher (Scheme 3, see **5a−f**). However, the biphenylmethyl-substituted

Scheme 3. Cascades Using Symmetrical α,α-Bisbenzyl TosMIC Derivatives[a,b]

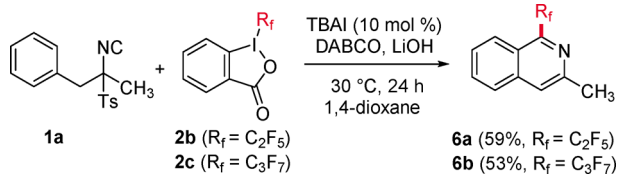


[a]Reaction conditions: **4** (0.20 mmol), **2a** (0.40 mmol), Bu_4NI (0.02 mmol), DABCO (0.40 mmol), and LiOH (3.0 mmol) in 1,4-dioxane (1 mL) were stirred at 30 °C for 6 h under argon atmosphere. [b]Isolated yield.

isocyanide **4c** reacted with significantly lower efficiency. In that case, we noted that the target product **5c** underwent renewed non-regioselective arene trifluoromethylation leading to chain termination under the applied conditions.

We also prepared two homologues of the Togni reagent bearing longer perfluoroalkyl chains (C_2F_5: **2b** and C_3F_7: **2c**). Reaction under optimized conditions with the isocyanide **1a** provided the perfluoroalkylated isoquinolines **6a** and **6b** (Scheme 4).

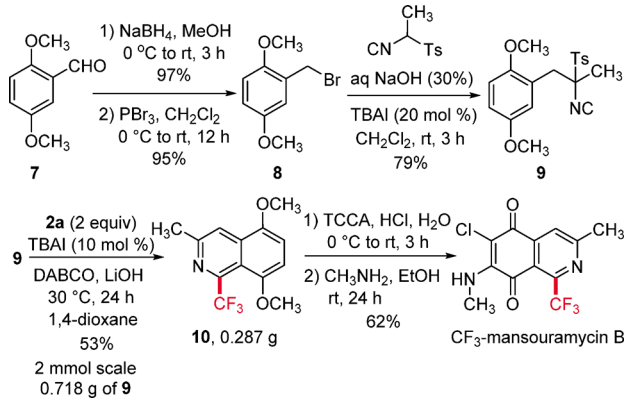
Scheme 4. Preparation of 1-Perfluoroalkylated Isoquinolines



To further illustrate the synthetic potential of this new method, we applied the radical trifluoromethylation to the total synthesis of CF_3-mansouramycin B. Mansouramycin B is an isoquinolinequinone alkaloid occurring in sponges that shows a wide array of biological activities against non-small cell lung cancer, breast cancer, melanoma, and prostate cancer cells. Mansouramycin B also reveals high cytotoxicity against many human cancer cell lines with an IC_{50} value up to 0.089 μmol/L.[19]

The key step of our total synthesis of CF_3-mansouramycin B is the formation of isoquinoline **10** via the herein introduced radical cascade cyclization. As illustrated in Scheme 5, the synthesis began with the $NaBH_4$ reduction of commercial **7** to give the corresponding alcohol which upon treatment with PBr_3 provided

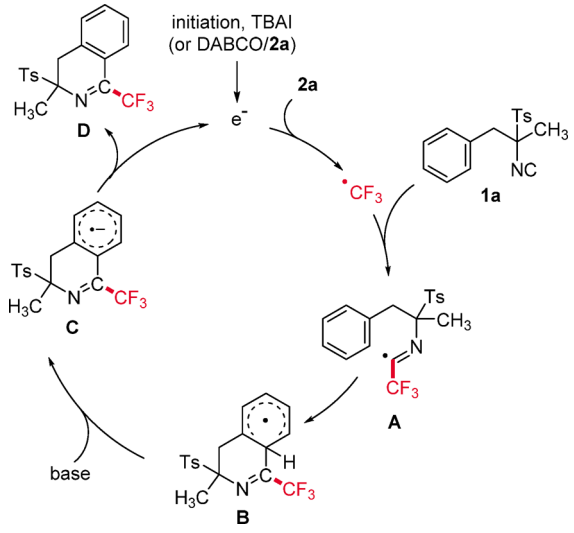
Scheme 5. Total Synthesis of CF_3-mansouramycin B



the benzylic bromide **8** in high yield (92%, over two steps). α-Benzylation of α-methyl TosMIC with **8** afforded isocyanide **9** (79%). Reaction of **9** with Togni reagent **2a** as the key step at larger scale (2 mmol) led to isoquinoline **10** in 53% isolated yield. Following literature protocols, **10** was oxidized with trichloroisocyanuric acid (TCCA) in a H_2O/HCl solution followed by the addition of a solution of methylamine in ethanol to finally afford CF_3-mansouramycin B in 62% yield.[20]

A plausible reaction mechanism for the radical cascade including a base-promoted homolytic aromatic substitution via electron catalysis[21] is proposed in Scheme 6. Initiation occurs

Scheme 6. Plausible Reaction Mechanism



either by reaction of **2a** with TBAI[17] or with DABCO.[22,23] The CF_3 radical generated then adds to the isonitrile functionality of **1a** to give the imidoyl radical **A**, which cyclizes to the arene moiety to afford cyclohexadienyl radical **B**. Radical **B** gets deprotonated either by *o*-iodobenzoate generated in the initial SET reduction of **2a** or by the other bases present in the reaction mixture to afford radical anion **C**. **C** is an efficient SET reducing reagent which is eventually oxidized to generate the intermediate **D** formally releasing an electron to complete the catalytic cycle. Togni reagent **2a** acts as an oxidant in this chain carrying step. Finally, base-promoted elimination of *p*-tolylsulfinate in **D** eventually affords the targeted isoquinoline **3a** (not shown in the Scheme 6).

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In summary, we have demonstrated a novel and practical method for the synthesis of 1-trifluoromethylated isoquinolines starting with readily prepared α-benzylated TosMIC derivatives. The radical process uses the commercially available Togni reagent as the trifluoromethyl radical precursor. Various 1-trifluoromethylated isoquinolines were successfully prepared in moderate to good yields. Reactions proceed via electron catalysis without the help of any transition-metal based catalyst under mild conditions and this cascade shows a broad substrate scope allowing to prepare differently substituted isoquinolines. The successful total synthesis of CF_3-mansouramycin B using the radical cascade as a key step further documents the value of the novel process.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02882.

Experimental procedures, characterization data, and ^{1}H, ^{13}C, and ^{19}F NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(23) Alternatively, TBA(OH) formed from TBAI and LiOH may attack at the carbonyl carbon of the Togni reagent, and this would cause liberation of the CF_3 radical.

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