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6-Perfluoroalkylated Phenanthridines via Radical Perfluoroalkylation of Isonitriles

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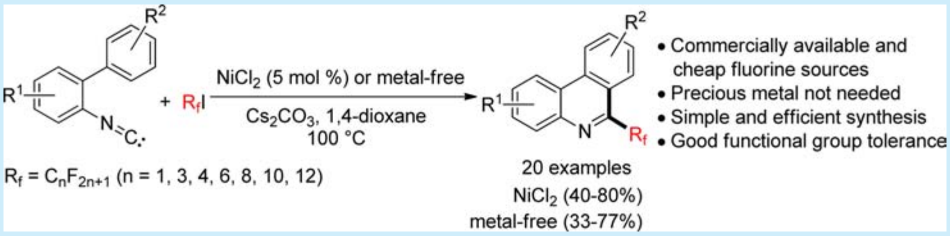
Supporting Information

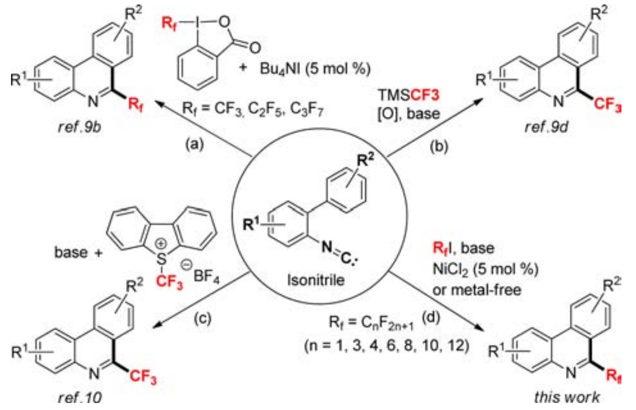


ABSTRACT: A simple and efficient approach to 6-perfluoroalkylated phenanthridines starting with readily prepared isonitriles and commercially available cheap perfluoroalkyl iodides as perfluoroalkyl radical precursors is described. Various 6-perfluoroalkylated phenanthridines are obtained in moderate to excellent yields. The sequence comprises a perfluoroalkylation with concomitant arene formation.

The introduction of fluorine-containing functional groups into organic molecules enhances their solubility, bioavailability, and metabolic stability.[1] Therefore, development of novel synthetic methods for the construction of C−R$_f$ bonds is important.[2] Among fluorine-containing functional groups, the trifluoromethyl and perfluoroalkyl substituents are highly important structural units, which can be found in many compounds used in medicinal chemistry, agrochemistry, and also in materials science.[3] Over the past decades, significant progress has been made on aromatic trifluoromethylation.[2,4] In contrast, aromatic perfluoroalkylation has been less intensively investigated.[5] Hence, the development of novel and efficient methods for perfluoroalkylation of aromatic compounds is highly desirable, but challenging.

The structural entity of the phenanthridines can be found in various bioactive natural alkaloids and in medicinally relevant compounds,[6] which show diverse biological activities such as antibacterial, antitumoral, cytotoxic, and antileukemic.[7] Therefore, it is important to develop novel methods for their preparation. Recently, the radical isonitrile insertion reaction has emerged as a powerful strategy for the construction of the phenanthridine scaffold.[8,9] Using this approach, a series of 6-substituted phenanthridines were readily prepared by radical addition to 2-isocyanobiphenyls with subsequent homolytic aromatic substitution (HAS). Due to potential applications of 6-fluoroalkylated phenanthridines in medicinal chemistry, we[9b] and Zhou[9d] independently reported the preparation of 6-trifluoromethylated phenanthridines via radical trifluoromethylation of 2-isocyanobiphenyls (Scheme 1, a and b). Moreover, Yu reported the preparation of the same compound class via a nonradical pathway (Scheme 1, c).[10] However, all of these methods are mostly restricted to the preparation of trifluoromethylated phenanthridines, and it is difficult to construct 6-perfluoroalkylated phenanthridines, since perfluoroalkyl analogues of the applied trifluoromethylation reagents (Togni's reagent, Umemoto's reagent, or Ruppert−Prakash reagent) are expensive and/or not commercially available. Therefore, we decided to develop a simple, efficient, and general method for the construction of 6-perfluoroalkylated phenanthridines using readily available perfluoroalkyl sources.

Scheme 1. Strategies for Preparation of 6-Fluoroalkylated Phenanthridines via Isonitrile Insertion Reactions



Perfluoroalkyl iodides are commercially available and cheap reagents, which have been utilized as perfluoroalkyl radical sources.[2g] However, in the reported radical aromatic perfluoroalkylation, the generation of perfluoroalkyl radicals from these iodides usually requires harsh reaction conditions or precious iridium and ruthenium photocatalysts.[5,11] More recently, Hu

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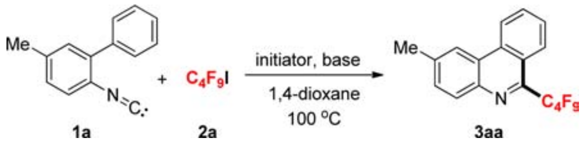
and co-workers have reported iron-catalyzed 1,2-addition of perfluoroalkyl iodides to alkynes and alkenes using perfluoroalkyl iodides as perfluoroalkyl radical sources.[12] Since perfluoroalkylated iodides are rather strong single electron transfer oxidants, we envisioned that the 6-perfluoroalkylated phenanthridines might be readily constructed via radical perfluoroalkylation of isonitriles by the base-promoted homolytic aromatic substitution using simple and cheap perfluoroalkyl iodides as reagents and metal salts as radical chain initiators.[13] Herein, we disclose a simple and efficient method for the construction of 6-perfluoroalkylated phenanthridines using readily available 2-isocyanobiphenyls and perfluoroalkyl iodides as perfluoroalkyl radical sources (Scheme 1, d).

We initiated our studies by investigating radical perfluoroalkylation of readily prepared isonitrile **1a** with a 3-fold excess of perfluorobutyl iodide **2a** in the presence of $FeBr_2$ (5 mol %) as initiator and Cs_2CO_3 (1.5 equiv) as base in 1,4-dioxane at 100 °C in a sealed tube for 20 h. Pleasingly, the targeted product **3aa** was obtained in 70% yield (Table 1, entry 1).

Table 1. Optimization of Reaction Conditions[a,b]



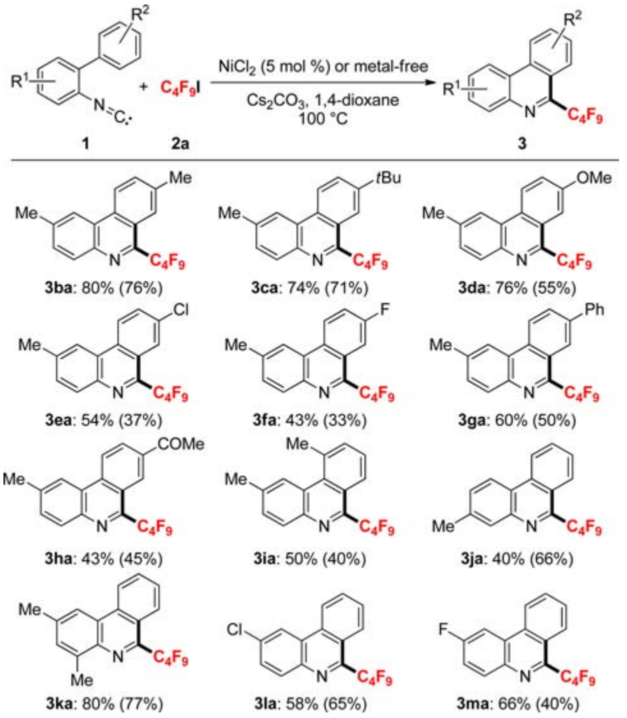
entry	initiator	base	yield[c] (%)
1	$FeBr_2$	Cs_2CO_3	70
2	$FeCl_2$	Cs_2CO_3	65
3	FeI_2	Cs_2CO_3	62
4	$Fe(acac)_2$	Cs_2CO_3	68
5	$Fe(OAc)_2$	Cs_2CO_3	36
6	**$NiCl_2$**	**Cs_2CO_3**	**73[d] (70[e])**
7	$CoCl_2$	Cs_2CO_3	65
8	CuI	Cs_2CO_3	64
9	**none**	**Cs_2CO_3**	**72 (68[f])**
10	none	Na_2CO_3	trace
11	none	K_2CO_3	trace
12[g]	none	Cs_2CO_3	39
13[h]	none	Cs_2CO_3	32
14[i]	none	Cs_2CO_3	48
15[j]	none	Cs_2CO_3	43
16	$NiCl_2$	none	trace
17	none	none	trace

[a] All reactions were carried out with **1a** (0.2 mmol), **2a** (0.6 mmol), catalyst (0.01 mmol), and base (0.3 mmol) in 1,4-dioxane (1 mL) at 100 °C under Ar for 20 h. [b] The reaction was conducted in a sealed tube. [c] Isolated yields. [d] $NiCl_2$ (99.99%) from Aldrich was used. [e] $NiCl_2$ (98%) from Alfa was used. [f] Cs_2CO_3 (99.995%) from Aldrich was used. [g] Using 1.0 equiv of Cs_2CO_3. [h] Using 0.5 equiv of Cs_2CO_3. [i] Using 2.0 equiv of **2a**. [j] Using 1.5 equiv of **2a**.

Reaction at higher or lower temperature did not provide a better result (see Supporting Information). Subsequently, a series of other metal salts as initiators was investigated, revealing that $NiCl_2$ is best suited to run this reaction to afford **3aa** in 73% yield (Table 1, entry 6). Other metal salts such as FeX_2 salts (X = Cl, I, acac, and OAc), $CoCl_2$, and CuI, resulted in lower yields (36–68% yield; Table 1, entries 2–5, 7, 8). The fact that various transition metal salts promote the cascade reaction shows that the metal salts do likely not act as catalysts but as initiators. Moreover, as a typical signature for a base-promoted homolytic aromatic substitution, we found that this radical cascade also occurred well with Cs_2CO_3 as the base in the absence of any metal salt initiator (Table 1, entry 9). Other bases such as Na_2CO_3 and K_2CO_3 provided only traces of **3aa** (Table 1, entries 10 and 11). Yield decreased by using 1.0 and 0.5 equiv of Cs_2CO_3, respectively (Table 1, entries 12 and 13). In addition, decreasing the amount of perfluorobutyl iodide **2a** also led to lower yields (Table 1, entries 14 and 15), and reaction did not proceed in the absence of Cs_2CO_3 (Table 1, entries 16 and 17). These results clearly imply that Cs_2CO_3 as a base is essential for this transformation.

With optimized reaction conditions in hand, the scope and limitations of this process were investigated. We first explored the scope with respect to the 2-isocyanobiphenyl component using $NiCl_2$ as the initiator (Scheme 2). Arylisonitriles bearing electron-donating substituents at the *para*-position of the arene ring that does not carry the isonitrile functionality provided the products **3ba** (4-Me), **3ca** (4-*t*-Bu), and **3da** (4-MeO) in good yields (74–80%). Isonitriles bearing electron-withdrawing substituents such as Cl, F, and COMe underwent the radical cascade smoothly to provide the corresponding phenanthridines in moderate yields (**3ea**: 54%, **3fa**: 43%, **3ha**: 43%). A slightly lower but still good yield was obtained for an *ortho*-substituted system, probably for steric reason (see **3ja**: 50%). Arylisonitriles bearing electron-donating or electron-withdrawing substituents at the arene moiety containing the isonitrile functionality were successfully converted to the corresponding phenanthridines **3ja**–**3ma** (40–80%).

Scheme 2. Scope of Arylisonitriles[a,b]

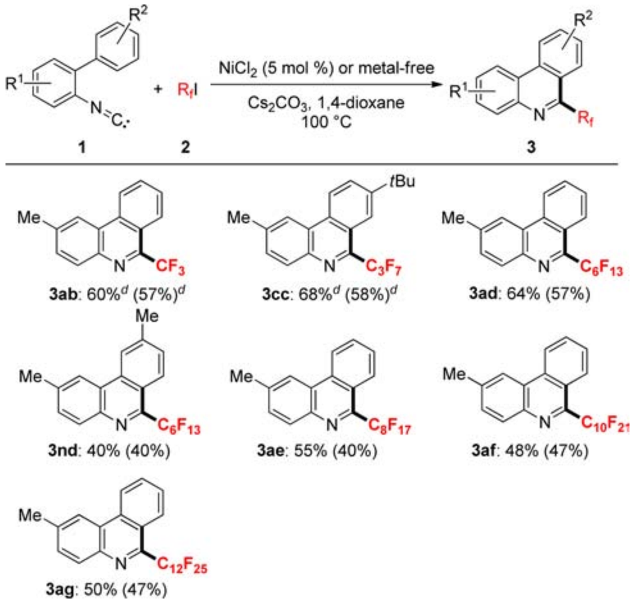


[a] All reactions were carried out with **1** (0.2 mmol), **2a** (0.6 mmol), $NiCl_2$ (0.01 mmol), and Cs_2CO_3 (0.3 mmol) in 1,4-dioxane (1 mL) at 100 °C under Ar for 20 h. [b] Isolated yields. Yields given in parentheses are those obtained for the reactions conducted without added $NiCl_2$ initiator.

All experiments were then repeated by using the metal-free protocol (see yields in parentheses). In most cases, compared to $NiCl_2$-initiated reactions, slightly lower yields were obtained. Along with higher yields, we observed that addition of $NiCl_2$ (5 mol %) generally provided a cleaner reaction. However, for arylisonitriles **1j** and **1l** leading to **3ja** and **3la** yields improved in the absence of Ni-salt.

We next investigated the scope of the cascade with respect to the perfluoroalkyl reagent (Scheme 3). To this end, various perfluoroalkyl iodides were surveyed. We found that along with C_4F_9I other commercially available perfluoroalkyl iodides such as C_3F_7I, $C_6F_{13}I$, $C_8F_{17}I$, $C_{10}F_{21}I$, and $C_{12}F_{25}I$ reacted well, and the corresponding products **3cc**−**3ag** were obtained in moderate to good yields (40−68%). In addition, we successfully ran a reaction using CF_3I as CF_3 radical precursor for the preparation of 6-trifluoromethyl phenanthridine and obtained the product **3ab** in 60% isolated yield (Scheme 3).

Scheme 3. Scope of Fluoroalkyl Reagents[a,b,c]



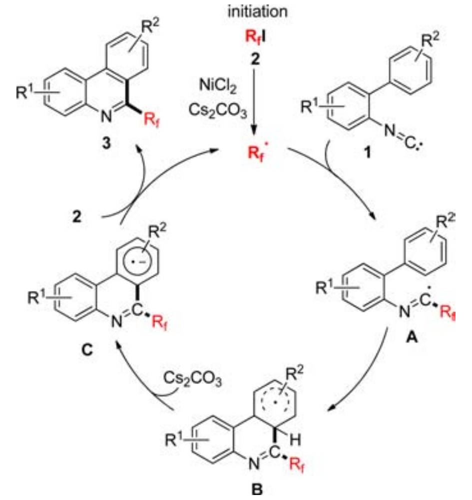
[a] All reactions were carried out with **1** (0.2 mmol), **2a** (0.6 mmol), $NiCl_2$ (0.01 mmol), and Cs_2CO_3 (0.3 mmol) in 1,4-dioxane (1 mL) at 100 °C under Ar for 20 h. [b] Isolated yields. The reactions in the parentheses were conducted without $NiCl_2$. [c] The reaction was conducted in a standard Schlenk tube. [d] The reaction was conducted in a sealed tube.

To address the regioselectivity of this reaction, *meta*-substituted arylisonitrile **1n** was prepared and successfully converted to the corresponding product **3nd** in moderate yield with complete regiocontrol. Cyclization preferably occurred at the position distal to the *meta* substituent (Scheme 3). Also for the series depicted in Scheme 3, reactions were repeated by using the metal-free initiation protocol (see yields in parentheses). In most cases similar or slightly lower yields as compared to the Ni-salt-initiated cascades were obtained.

To support the radical nature of the cascade, reaction of **1a** with **2b** in the presence of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) as a radical scavenger was tested under the standard reaction conditions. Formation of **3ab** was completely suppressed and the TEMPO−CF_3 adduct was identified by ^{19}F NMR spectroscopy.

On the basis of this experiment and previous reports,[9b,12] we propose the following mechanism (Scheme 4). For the Ni-free protocol, perfluoroalkyl radicals are likely generated from perfluoroalkyl iodides thermally upon C−I homolysis. We do currently not think that traces of transition metals derived from the base initiate the reaction, since an experiment conducted with Cs_2CO_3 of very high purity (99.995%) provided a similar result (see Table 1, entry 9). Moreover, we also discard CsI, which might be formed from the starting iodide and the Cs_2CO_3, as an initiator since reaction with CsI and Na_2CO_3 as a base provided only traces of the product. The special role of Cs_2CO_3 on the initiation is not understood.[12] In the presence of $NiCl_2$, the Ni-salt somehow accelerates generation of the perfluoroalkyl radical from the corresponding iodide. Notable, similar results were obtained by using different sources of $NiCl_2$ (see Table 1), and $NiCl_2$ in combination with Na_2CO_3 afforded only traces of the targeted product, again highlighting the special role of the Cs_2CO_3 base for these reactions. Addition of the perfluoroalkyl radical to the isonitrile functionality in **1** provides the imidoyl radical **A**, which undergoes cyclization to generate cyclohexadienyl radical **B**. We assume that **B**, due to the very high acidity of the *α*-proton,[9b] gets deprotonated by Cs_2CO_3 to give radical anion **C**, which then further reacts with perfluoroalkyl iodides in a single electron transfer process to product **3** and the perfluoroalkyl radical, thereby sustaining the radical chain reaction.[13,14]

Scheme 4. Proposed Reaction Mechanism



In summary, we have demonstrated a simple and efficient approach for the construction of 6-perfluoroalkylated phenanthridines starting with readily prepared 2-isocyanobiphenyls and the commercially available and cheap perfluoroalkyl iodides as precursors of the perfluoroalkyl radicals. Various 6-perfluoroalkylated phenanthridines were prepared in moderate to excellent yield. Furthermore, 6-trifluoromethylated phenanthridine was also prepared using this novel method. The reaction shows good functional group tolerance, and importantly, this transformation occurs without precious metal photocatalysts. These issues make this protocol very practical for the synthesis of 6-perfluoroalkylated phenanthridines.

ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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