Trifluoromethylation Hot Paper

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6-Trifluoromethyl-Phenanthridines through Radical Trifluoromethylation of Isonitriles**

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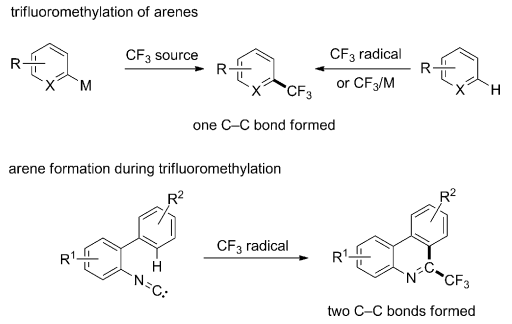
Dedicated to Professor Werner Uhl on the occasion of his 60th birthday

The trifluoromethyl group can be found in many drugs or drug candidates.[1] Chemical and physical properties of biologically active compounds are altered upon incorporation of the CF_3 group. The higher solubility and lipophilicity exerted by the fluorinated methyl group lead to better membrane permeability and increased bioavailability. Importantly, because of the higher resistance toward oxidative degradation, fluorinated compounds generally have higher metabolic stability. Therefore, development of new methods for C–CF_3 bond formation has caught great attention from the synthetic community during the past few years and different methods for the trifluoromethylation of arenes have been developed. Transition-metal-catalyzed[2] and radical[3,4] aromatic trifluoromethylation have been studied intensively (Scheme 1).



Scheme 1. Arene trifluoromethylation and formation of trifluoromethylated phenanthridines. M = metal.

In most of these cases, trifluoromethylation occurs at preformed arenes.[5] We present herein the preparation of trifluoromethylated phenanthridines by a conceptually novel approach in which the arene core is constructed during the trifluoromethylation process. In contrast to the reported methods, which proceed through single C–C bond-forming transformations, our approach comprises two C–C bond formations. Regiochemistry problems that may arise in arene trifluoromethylation are not an issue using this route.

Arylisonitriles are well established radical acceptors in cascade reactions for the construction of heteroarenes.[6] To our knowledge, reactivity of isonitriles toward the electrophilic CF_3 radical was not investigated to date. We therefore embarked on a program to test readily prepared biarylisonitriles as substrates for the formation of trifluoromethylated phenanthridines. The phenanthridine core is an important substructure present in many natural products with different biological activities, such as antibacterial, antitumoral, cytotoxic, and antileukemic.[7a] Fagaronine (protein kinase C and DNA topoisomerase 1 inhibitor)[7b] and trisphaeridine (DNA intercalator)[7c,d] are representative members of such natural products (Figure 1).

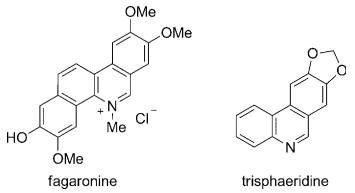


Figure 1. Biologically active phenanthridines.

As source of the CF_3 radical we used the Togni reagent **2**,[8,9] and initial investigations were conducted on isonitrile **1a**. Because CF_3 radicals are generated in the reaction of Cu^I salts with the Togni reagent,[9a,b,j] we first screened various Cu salts as initiators/catalysts (see mechanistic discussion below) in 1,4-dioxane at 70 °C using a slight excess (1.2 equiv) of the trifluoromethylation reagent **2**.

We were pleased to find that the phenanthridine **3a** was formed in moderate to good yield (42–61 %) in the presence of CuI, CuTC, CuOAc, CuBr·SMe_2, and CuCN. Exemplary, the result obtained with CuOAc is depicted in Table 1 (entry 1; for full list of results, see the Supporting Information). The structure of **3a** was determined by X-ray analysis (Figure 2).[10]

These experiments showed that isonitriles are stable toward the oxidative Togni reagent. A further improvement was achieved upon switching to Fe-based initiators/catalysts.[11] The FeX_2 salts with X = Cl, Br, I, and acac provided **3a** in 66–73 % yield (entries 2–5). Other solvents, such as MeOH, $CHCl_3$, $ClCH_2CH_2Cl$, CH_3CN, and EtOAc, resulted in lower yields (entries 6–10). The yield was further increased by using 1.5 equiv of **2** (entries 2, 4, and 5) and a yield of 82 %

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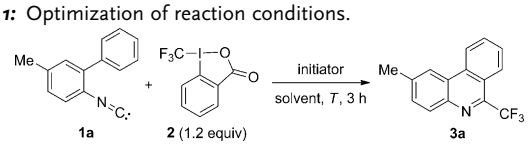
Table 1: Optimization of reaction conditions.



1a **2** (1.2 equiv) **3a**

Entry	Initiator	mol%	Solvent	*T* [°C]	Yield [%]
1	CuOAc	10	1,4-dioxane	70	61
2	$FeCl_2$	10	1,4-dioxane	70	69 (76)[a]
3	$FeBr_2$	10	1,4-dioxane	70	66
4	FeI_2	10	1,4-dioxane	70	73 (76)[a]
5	$Fe(acac)_2$	10	1,4-dioxane	70	71 (74)[a]
6	FeI_2	10	MeOH	70	38
7	FeI_2	10	$CHCl_3$	70	49
8	FeI_2	10	$ClCH_2CH_2Cl$	70	46
9	FeI_2	10	CH_3CN	70	32
10	FeI_2	10	EtOAc	70	62
11	$FeCl_2$	10	1,4-dioxane	20	trace[a]
12	$FeCl_2$	10	1,4-dioxane	50	20[a]
13	$FeCl_2$	10	1,4-dioxane	80	82[a]
14	$NiCl_2$	10	1,4-dioxane	70	66
15	$CoCl_2$	10	1,4-dioxane	70	56
16	Bu_4NI	10	1,4-dioxane	80	86[a]
17	Bu_4NBr	10	1,4-dioxane	80	76[a]
18	**Bu_4NI**	**5**	**1,4-dioxane**	**80**	**84[a]**
19	Bu_4NI	1	1,4-dioxane	80	78[a]

[a] With 1.5 equiv of **2**. Entry in bold marks optimized reaction conditions.

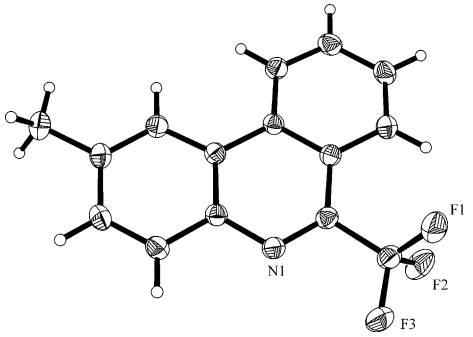
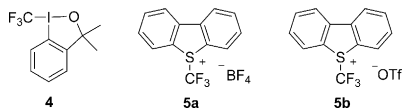


Figure 2. X-ray structure of **3a**.

was achieved upon increasing the reaction temperature to 80°C (entry 13). Alternative CF_3 reagents, such as **4**[8] and **5**,[12] provided poorer results (**4**: traces, **5a**: 10%, **5b**: 7%).



4 **5a** **5b**

As the reaction also worked using other transition metals, such as $NiCl_2$ and $CoCl_2$ (entries 14 and 15), we assumed that the metal might not be involved in the cascade, but only acts as an initiator in a radical chain reaction. Therefore, we also studied the formation of **3a** in the absence of a transition metal and tested Bu_4NI[13] as initiator. Pleasingly, a high yield (86%) was achieved using this transition-metal-free protocol (entry 16). The Bu_4NI loading was further lowered to 5 mol% without affecting the yield to a large extent, but a poorer result was achieved with 1 mol% (entries 18 and 19). Bu_4NBr turned out to be a slightly less efficient initiator (entry 17).

To study the scope and limitations of this approach, various biarylisonitriles **1b–x** were prepared and reacted under optimized transition-metal-free conditions (5 mol% Bu_4NI) to the corresponding phenanthridines **3b–x** (Figure 3). In the biphenyl, the *para* substituent in the

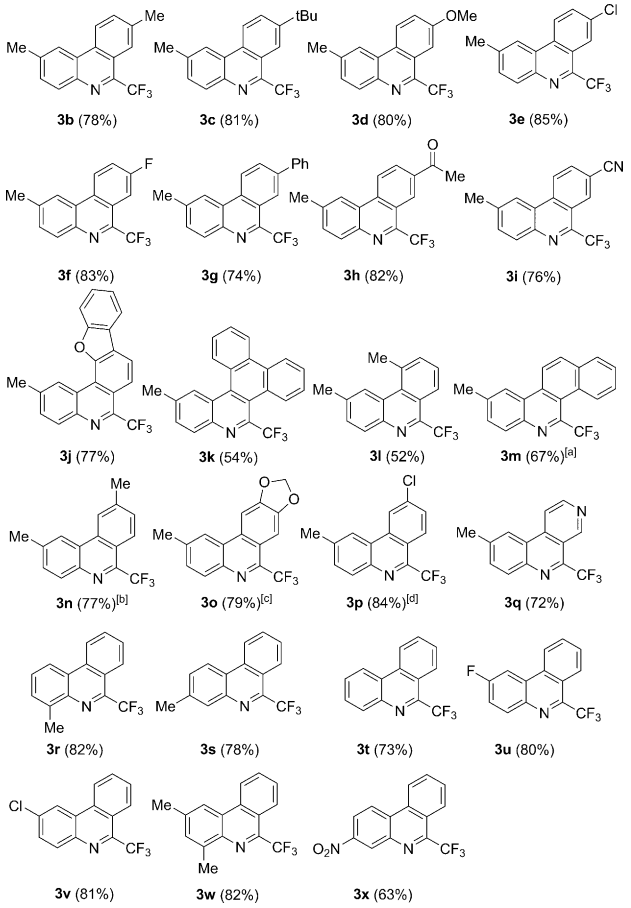


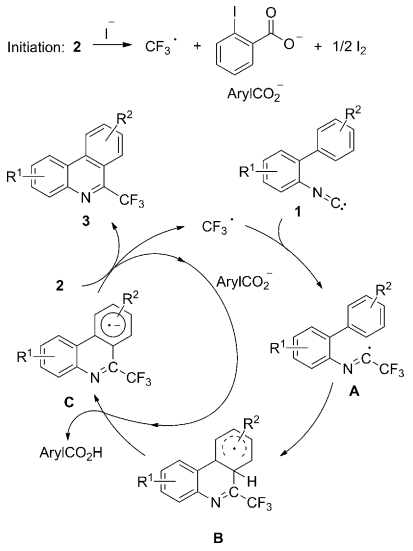
Figure 3. Various synthesized phenanthridines (ratios of regioisomer: [a] 7.4:1; [b] 1.3:1; [c] 2.2:1; [d] 1:1).

arene moiety that does not carry the isonitrile functionality was varied without largely affecting the yield (see **3b–i**). In general, slightly lower but still good yields were achieved for the *ortho*-substituted systems, probably for steric reasons (**3j–l**). To investigate the regioselectivity of the cyclization, we studied *meta*-substituted biphenyls, which were converted in good yields to the corresponding phenanthridines. As expected, regiocontrol was low for such a homolytic aromatic substitution at 80°C (see **3n–p**, selectivities were readily determined by ^{19}F NMR spectroscopy). Cyclization preferably occurred at the position distal to the *meta* substituent (in Figure 3, only the major isomer is depicted). However, the naphthyl derivative reacted with high regioselectivity (7.4:1) to **3m**.[14] A heteroarene such as pyridine is tolerated in the biaryl moiety (**3q**). We also successfully varied substituents at

the arene moiety that bears the isonitrile functionality. For all biaryls tested in this series, the corresponding phenanthridines **3r–x** were obtained in good yields, thus showing the robustness of our method with respect to the substitution pattern of the starting biphenyl. We also successfully ran one reaction at larger scale (2 mmol) and isolated phenanthridine **3e** in 82% yield (0.48 g).

It is important to note that regioselective direct trifluoromethylation of CH of such phenanthridines would be highly challenging, showing a clear benefit of our approach. For example, considering the directing effect of the N atom in pyridines in homolytic aromatic substitutions,[15] regiocontrol in the preparation of **3q** through radical trifluoromethylation of the parent phenanthridine would be a difficult task. In addition, the precursor biphenyls we use in the cascade can be prepared in a modular approach (see the Supporting Information), which allows the fast and efficient formation of different phenanthridine core structures (Figure 3).

We suggest the following mechanism for the phenanthridine formation (Scheme 2). In the initiation step, the iodide reacts with the Togni reagent **2** to give *ortho*-iodobenzoate, the CF_3 radical, and iodine. The addition of the CF_3 radical to the isonitrile functionality in **1** generates the imidoyl radical **A**, which cyclizes to the arene to give cyclohexadienyl radical **B**.[16] The radical nature of the process was supported by the facts that in the presence of the TEMPO radical, phenanthridine synthesis did not occur and TEMPO–CF_3 was detected in the reaction mixture by ^{19}F NMR spectroscopy. We assume that the radical **B** gets deprotonated by *ortho*-iodobenzoate ($ArylCO_2^-$) to the radical anion **C** which then reacts with the Togni reagent **2** through single-electron transfer (SET) to product **3** and the CF_3 radical, thereby sustaining the radical chain reaction.[17,18] **C** can also react with I_2 generated in the initiation step to phenanthridine **3** and iodide. This process allows the regeneration of the initiator. However, because of the low concentration of I_2 compared to reagent **2**, this process is likely to represent only a minor reaction pathway.



Scheme 2. Suggested mechanism.

In order to rank the acidity of the proton in cyclohexadienyl radicals of type **B**, relative pK_a values were obtained from DFT calculations (PW6B95-D3/def2-TZVP).[19] Solvent effects of 1,4-dioxane ($\varepsilon = 2.25$) were accounted for with the COSMO solvation model, and free enthalpies (for $T = 298$ K) were obtained from harmonic vibrational frequencies (for details see the Supporting Information). Calculations were conducted on the intermediate cyclohexadienyl radical **B** ($R^1 = R^2 = H$), which was derived from the unsubstituted biarylisonitrile **1t** ($R^1 = R^2 = H$), using *ortho*-iodobenzoate as base to generate the corresponding deprotonated radical anion **C** ($R^1 = R^2 = H$). The calculated pK_a value of *ortho*-iodobenzoic acid was set to 0 as relative reference (Figure 4). To evaluate the effect of the N atom and the CF_3 substituent on the acidity of **B**, two congeners lacking these moieties were included into the studies.

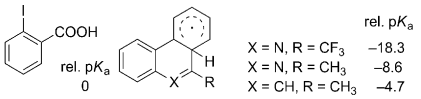
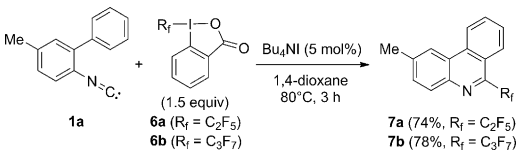


Figure 4. Relative pK_a values of the cyclohexadienyl radical **B**, its derivatives, and 2-iodobenzoic acid, obtained by DFT calculations using a continuum solvent model (298 K, $\varepsilon = 2.25$).

The calculated relative pK_a value of **B** versus *ortho*-iodobenzoic acid (exp. p$K_a = 2.85$ in aqueous solution)[20] is −18.3, resulting in an extremely low predicted pK_a value of circa −15.5 for **B**. This result shows that the benzoate can readily deprotonate **B** to give **C**, which is in line with our suggested mechanism. Successive replacement of the CF_3 group by CH_3 and N by CH lowers the acidity of **B** by circa 10 and 4 pK_a units, respectively. Thus, even the least activated radical ($X = CH$, $R = CH_3$) is more acidic than 2-iodobenzoic acid and will be deprotonated by the benzoate. Obviously, the incorporation of the 2,5-cyclohexadienyl radical moiety into a larger aromatic system and the CF_3 group account for a large part of the extraordinary acidity of **B**. This aspect will be subject to further studies.

Finally, we showed that the method can also be applied to the synthesis of perfluoroalkylated phenathridines. To this end, the I^{III} reagents **6a** and **6b** were prepared[9f] and applied to the cascade reaction using isonitrile **1a** as substrate (Scheme 3). Reactions were conducted under the above-described optimized conditions, and the targeted products **7a** and **7b** were obtained in good yields, clearly showing the potential of the new method for preparation of 6-perfluoroalkylated phenanthridines.



Scheme 3. Formation of perfluoroalkylated phenanthridines.

In summary, we presented a novel approach for the synthesis of 6-perfluoroalkylated phenanthridines starting with readily prepared isonitriles. The radical process uses the commercially available Togni reagent **2** as precursor of the CF_3 radical or readily prepared derivatives thereof. Importantly, perfluoroalkylation occurs without the help of a transition-metal-based catalyst. In contrast to the currently heavily investigated arene trifluoromethylation, in which C–CF_3 bond formation occurs at an intact arene ring, our process comprises a trifluoromethylation with concomitant arene formation. The reactions are experimentally easy to conduct and the products are of biological importance.

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