Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

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Cite this: DOI: 10.1039/c0xx00000x

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ARTICLE TYPE

1-Trifluoromethylated isoquinolines *via* radical trifluoromethylation of isonitriles

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

A simple and efficient approach to biologically important 1-trifluoromethylated isoquinolines starting with readily prepared β-aryl-α-isocyano-acrylates and commercially available Togni reagent as CF_3 radical precursor is described. These transformations occur in the absence of any transition metal and the title compounds are obtained in moderate to excellent yields. This protocol comprises a trifluoromethylation with concomitant isoquinoline framework construction.

In the past decade, the synthesis of CF_3-containing aromatic compounds has caught great attention from the synthetic community because of their wide application not only in materials science and agrochemistry, but also in medicinal chemistry.[1,2] The arene solubility and lipophilicity can be significantly improved upon introducing a trifluoromethyl group as an arene substituent. As compared to their non CF_3-congeners, trifluoromethylated arenes show higher membrane permeability, increased bioavailability[3] and higher metabolic stability. Therefore, the development of novel and efficient methods for incorporation of the CF_3 moiety into aromatic compounds is of importance.

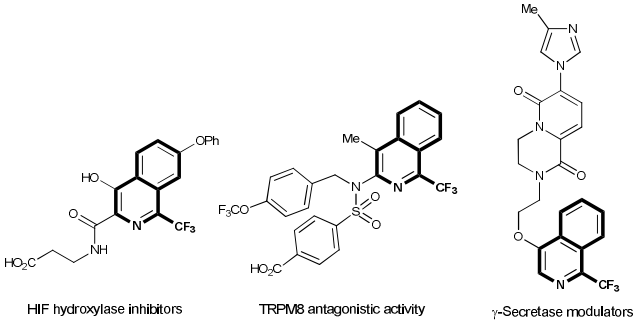
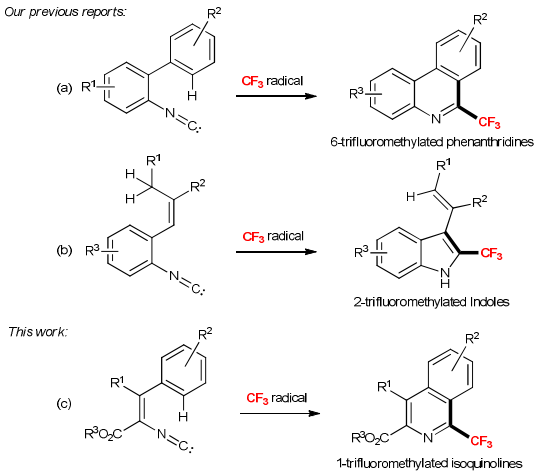


Figure 1 Representative biologically active *N*-heterocycles containing the 1-trifluoromethylated isoquinoline scaffold.

The isoquinoline scaffold is a privileged chemical entity, which can be found in various natural products, drug candidates, and biologically active compounds.[4] There is continuing interest in the development of novel synthetic methods for the preparation of isoquinolines.[5] In particular, novel synthetic approaches to 1-trifluoromethylated isoquinolines are required due to their prominent biological activities (Fig. 1).[6]

Conventional methods for preparation of 1-trifluoromethylated isoquinolines rely on coupling reactions of aryl halides with trifluoromethylation reagents[6d,6e,6f,6g] and on the Bischler-Napieralski reaction[6a]. However, the former approach requires halogenation of the preformed isoquinoline core and the latter approach suffers from multistep reaction sequences and generally harsh reaction conditions. As a complementary approach we present herein radical trifluoromethylation of isonitriles for preparation of 1-trifluoromethylated isoquinolines.

Recently, the radical isonitrile insertion reaction has emerged as a powerful strategy for the construction of various heteroarenes.[7,8] Along the lines, we have disclosed that isonitriles can be used as highly efficient CF_3 radical acceptors for preparation of 6-trifluoromethylated phenanthridines[8b] and 2-trifluoromethylated indoles[8g] (Scheme 1, a and b).



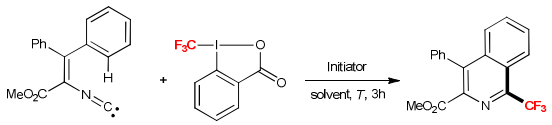
Scheme 1 Construction of important *N*-heterocycles by radical trifluoromethylation of isonitriles.

Encouraged by these results, we envisioned that 1-trifluoromethylated isoquinolines can be obtained by CF_3 radical addition to β-aryl-α-isocyano-acrylates with subsequent base-promoted homolytic aromatic substitution (Scheme 1, c).[9,10]

We have recently shown that the CF_3 radical can be

efficiently generated from the commercially available Togni reagent **2** by using Bu_4NI as a radical initiator.[8b,g] We therefore initiated our studies by investigating radical trifluoromethylation of readily prepared α-isocyano cinnamic acid ester **1a** with **2** (1.2 equiv) in the presence of Bu_4NI as an initiator in 1,4-dioxane at 80 °C for 3 h. Gratifyingly, the desired isoquinoline **3a** was obtained in 75% yield (Table 1, entry 1). A worse result was achieved by using Bu_4NBr as an initiator (Table 1, entry 2). The Bu_4NI loading could be further lowered to 5 mol % without affecting the yield, but a further lowering of the Bu_4NI concentration to 1 mol % led to a decreased yield (62%, Table 1, entries 3 and 4). Other solvents, such as CH_3CN, DCE, and EtOAc provided lower yields (Table 1, entries 5-7). Decreasing temperature to 60 °C also afforded a slightly lower yield (Table 1, entry 8) and increasing temperature to 100 °C did not affect the yield to a large extent (Table 1, entry 9). However, yield was further increased upon using 1.5 equiv of **2** (80%, Table 1, entry 10).

Table 1 Optimization of reaction conditions[a]



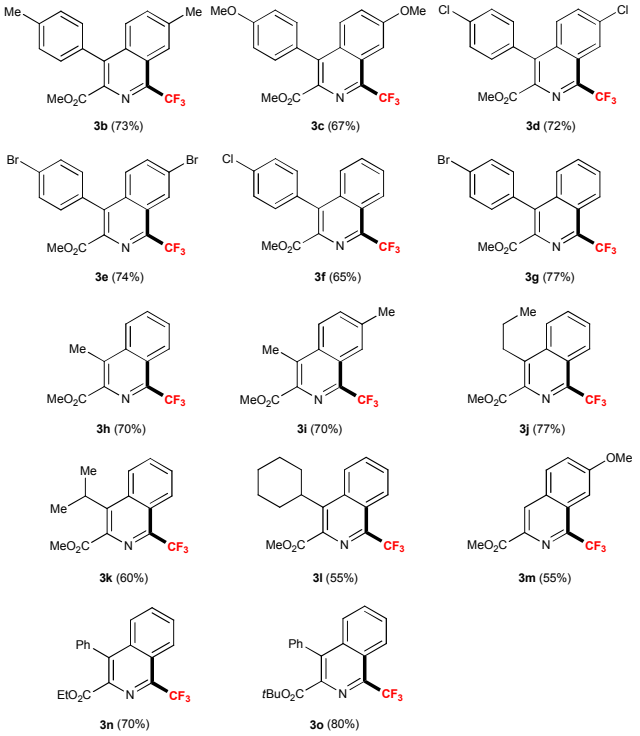
1a **2** **3a**

Entry	Initiator	mol %	Solvent	*T* [°C]	Yield[b] (%)
1	Bu_4NI	10	1,4-dioxane	80	75
2	Bu_4NBr	10	1,4-dioxane	80	43
3	Bu_4NI	5	1,4-dioxane	80	76
4	Bu_4NI	1	1,4-dioxane	80	62
5	Bu_4NI	5	CH_3CN	80	41
6	Bu_4NI	5	DCE	80	20
7	Bu_4NI	5	EtOAc	80	70
8	Bu_4NI	5	1,4-dioxane	60	70
9	Bu_4NI	5	1,4-dioxane	100	76
10[c]	**Bu_4NI**	**5**	**1,4-dioxane**	**80**	**80**

[a] All reactions were carried out with **1a** (0.2 mmol), **2** (0.24 mmol), and initiator (0.02 mmol) in 1,4-dioxane (1.0 mL) at 80 °C under Ar for 3 h. [b] Isolated yields. [c] Using 1.5 equiv of **2**.

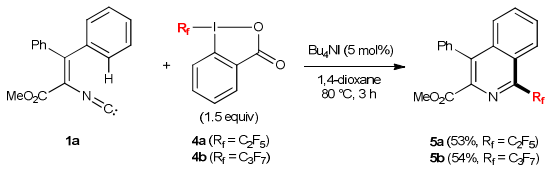
With optimized reaction conditions in hand, the scope and limitations of the isoquinoline synthesis were investigated (Table 2). Reactions with various β,β-diaryl-α-isocyano-acrylates derived from symmetrical and unsymmetrical diaryl ketones proceeded well (for the synthesis of the isonitriles, see Supporting Information), and the corresponding heteroarenes **3b-3g** were isolated in good yields (65-77%, Table 2). Electronic effects of the substituents at the arene rings did not affect the reaction outcome to a large extent. Importantly, olefin isomerization did not occur under the applied conditions and homolytic aromatic substitution occurred regioselectively at the arene ring *cis* to the isonitrile functionality (see **3f** and **3g**). β-Alkyl-α-isocyano cinnamic acid esters, where the aryl and isonitrile groups are *cis*-oriented, undergo the radical cascade reaction smoothly to provide the corresponding isoquinolines **3h-3l** in moderate to good yields (55-77%). A slightly lower but still good yield was obtained for an α-isocyano cinnamic acid ester derivative lacking the additional β-substituent (**3m**: 55%, Table 2). The ester group in the β-phenyl-α-isocyano cinnamic acid esters (ethyl and *tert*-butyl) could also be varied to give the corresponding isoquinolines **3n** and **3o** in good yields (**3n**: 70%; **3o**: 80%). To document the practicability of the method, we repeated the final experiment at larger scale (2 mmol) and isolated isoquinoline **3o** in 71% yield (0.53 g, see Supporting Information).

Table 2 Various 1-trifluoromethylated isoquinolines prepared.[a,b]



[a] All reactions were carried out with **1** (0.2 mmol), **2** (0.3 mmol), and Bu_4NI (0.01 mmol) in 1,4-dioxane (1.0 mL) at 80 °C under Ar for 3 h. [b] Isolated yields.

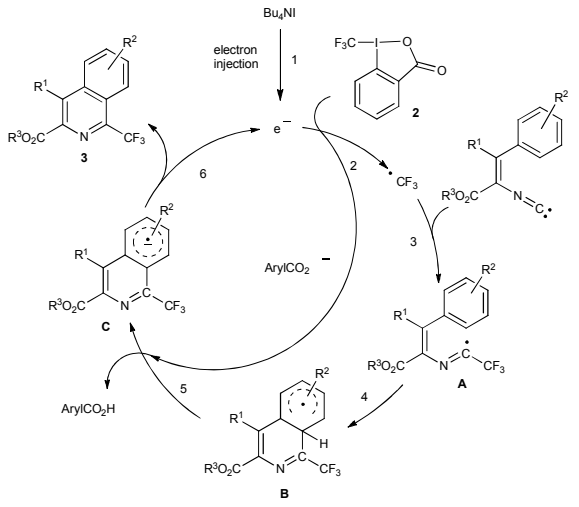
Notably, this method can also be applied to the synthesis of perfluoroalkylated isoquinolines. To this end, the I^{III} reagents **4a**[11] and **4b**[8b] were applied to the radical cascade reaction using **1a** as a substrate to give **5a** and **5b**, documenting the potential of the new method for the preparation of 1-perfluoroalkylated isoquinolines.



Scheme 2 Preparation of 1-perfluoroalkylated isoquinolines.

Preliminary mechanistic studies revealed that CF_3-radicals are likely involved in these reactions. Under standard conditions, formation of **3a** from **1a** was fully suppressed in the presence of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) as a radical scavenger, and the TEMPO-CF_3 adduct was detected by ^{19}F NMR spectroscopy (see Supporting Information). Based on this experiment, our previous reports,[8b,8g] and our recent conceptual article,[12] a plausible

mechanism considering the electron as a catalyst is proposed in Scheme 3. The catalytic cycle is started by electron injection (step 1) from the iodide anion to the Togni reagent **2** generating a CF_3-radical and the *ortho*-iodobenzoic acid anion with Bu_4N^+ as the countercation (step 2). CF_3-radical addition to the isonitrile generates an imidoyl radical **A** (step 3),[7] which cyclizes to the arene to give cyclohexadienyl radical **B** (step 4). We assume that **B** gets deprotonated by *ortho*-iodobenzoate ($ArylCO_2^-$) to radical anion **C** (step 5).[9] This radical anion then further reacts to the product isoquinoline **3** thereby formally liberating the catalytic electron closing the catalytic cycle (step 6).



Scheme 3 Proposed reaction mechanism documenting the role of the electron as a catalyst.

In summary, we have demonstrated a simple and efficient method for the synthesis of 1-trifluoromethylated isoquinolines starting with readily prepared β-aryl-α-isocyano-acrylates. The radical cascade uses the commercially available Togni reagent **2** as CF_3 radical precursor. Various 1-trifluoromethylated isoquinolines were successfully prepared in moderate to excellent yields. Importantly, the method is also applicable to the synthesis of 1-perfluoroalkylated isoquinolines. This transformation occurs without the help of any transition metals and products obtained are of biological importance.

We thank the Deutsche Forschungsgemeinschaft (DFG) for supporting our work.

Notes and references

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† Electronic Supplementary Information (ESI) available: See DOI: 10.1039/b000000x/

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Cite this: DOI: 10.1039/c0xx00000x

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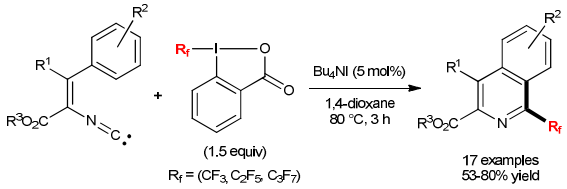

1-Trifluoromethylated isoquinolines *via* radical trifluoromethylation of isonitriles

A simple and efficient aproach to biologically important 1-trifluoroalkylated isoquinolines starting with readily prepared β-aryl-α-isocyano-acrylates and R_f-I(III)-reagents (R_f = CF_3, C_2F_5, C_3F_7) is described.