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1-Trifluoromethylated isoquinolines via radical trifluoromethylation of isonitriles

Bo Zhang\textsuperscript{a} and Armido Studer*\textsuperscript{a}

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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\textsubscript{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\textsubscript{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.\textsuperscript{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\textsubscript{3}-congeners, trifluoromethylated arenes show higher membrane permeability, increased bioavailability\textsuperscript{3} and higher metabolic stability. Therefore, the development of novel and efficient methods for incorporation of the CF\textsubscript{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.\textsuperscript{4} There is continuing interest in the development of novel synthetic methods for the preparation of isoquinolines.\textsuperscript{5} In particular, novel synthetic approaches to 1-trifluoromethylated isoquinolines are required due to their prominent biological activities (Fig. 1).\textsuperscript{6}

Conventional methods for preparation of 1-trifluoromethylated isoquinolines rely on coupling reactions of aryl halides with trifluoromethylation reagents\textsuperscript{6d,6e,6f,6g} and on the Bischler-Napieralski reaction\textsuperscript{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.\textsuperscript{7,8} Along the lines, we have disclosed that isonitriles can be used as highly efficient CF\textsubscript{3} radical acceptors for preparation of 6-trifluoromethylated phenanthridines\textsuperscript{8b} and 2-trifluoromethylated indoles\textsuperscript{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\textsubscript{3} radical addition to β-aryl-α-isocyano-acrylates with subsequent base-promoted homolytic aromatic substitution (Scheme 1, c).\textsuperscript{9,10}

We have recently shown that the CF\textsubscript{3} radical can be
efficiently generated from the commercially available Togni reagent 2 by using Bu$_3$NBr as a radical initiator.$^{3b,g}$ 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$_3$NBr 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$_3$NBr as an initiator (Table 1, entry 2). The Bu$_3$NBr loading could be further lowered to 5 mol % without affecting the yield, but a further lowering of the Bu$_3$NBr concentration to 1 mol % led to a decreased yield (62%, Table 1, entries 3 and 4). Other solvents, such as CH$_2$CN, 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$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Initiator</th>
<th>mol %</th>
<th>Solvent</th>
<th>T [°C]</th>
<th>Yield (%)</th>
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<tr>
<td>1</td>
<td>Bu$_3$NBr</td>
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<td>1,4-dioxane</td>
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<td>2</td>
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<td>3</td>
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<td>1,4-dioxane</td>
<td>80</td>
<td>76</td>
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<tr>
<td>4</td>
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<td>1</td>
<td>1,4-dioxane</td>
<td>80</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>Bu$_3$NBr</td>
<td>5</td>
<td>CH$_2$CN</td>
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<td>41</td>
</tr>
<tr>
<td>6</td>
<td>Bu$_3$NBr</td>
<td>5</td>
<td>DCE</td>
<td>80</td>
<td>20</td>
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<tr>
<td>7</td>
<td>Bu$_3$NBr</td>
<td>5</td>
<td>EtOAc</td>
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<td>1,4-dioxane</td>
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<td>70</td>
</tr>
<tr>
<td>9</td>
<td>Bu$_3$NBr</td>
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<td>1,4-dioxane</td>
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<td>10$^a$</td>
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<td>1,4-dioxane</td>
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$^a$ All reactions were carried out with 1a (0.2 mmol), 2 (0.3 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-isocyanoacrylates derived from symmetrical and unsymmetrical diaryl ketones proceeded well (for the synthesis of the isonitriles, see Supporting Information), and the corresponding heteroaromatics 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).

**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$^{3b,g}$ and our recent conceptual article$^{12}$, a plausible

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| Table 2 Various 1-trifluoromethylated isoquinolines prepared.$^{3b}$

<table>
<thead>
<tr>
<th>3a</th>
<th>3b</th>
<th>3c</th>
<th>3d</th>
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<td><img src="image3.png" alt="Image of structures" /></td>
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</tbody>
</table>

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-isocyanoacrylates derived from symmetrical and unsymmetrical diaryl ketones proceeded well (for the synthesis of the isonitriles, see Supporting Information), and the corresponding heteroaromatics 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).

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$^1$ All reactions were carried out with 1 (0.2 mmol), 2 (0.3 mmol), and Bu$_3$N (0.01 mmol) in 1,4-dioxane (1.0 mL) at 80 °C under Ar for 3 h.$^b$ Isolated yields. $^c$ Notably, this method can also be applied to the synthesis of perfluoroalkylated isoquinolines. To this end, the 1H reagents 4a$^{11}$ and 4b$^{1b}$ 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.

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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 CF₃-radical and the ortho-iodobenzoic acid anion 3 with Bu₄N⁺ as the counterion (step 2). CF₃-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 (ArylICO₂⁻) 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-acylates. The radical cascade uses the commercially available Togni reagent 2 as CF₃ 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.

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Notes and references

*Westfälische Wilhelms-University, Institute of Organic Chemistry, Corvenstraße 40, 48149, Münster, Germany. E-mail: studer@uni-
muenster.de*

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


Bo Zhang and Armido Studer*

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A simple and efficient approach to biologically important 1-trifluoroalkylated isoquinolines starting with readily prepared β-aryl-α-isocyno-acrylates and Rf-I(III)-reagents (Rf = CF₃, C₂F₆, C₃F₇) is described.