Radical perfluoroalkylation – easy access to 2-perfluoroalkylindol-3-imines via electron catalysis†

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Arylisonitriles (2 equivalents) react with alkyl and perfluoroalkyl radicals to form 2-alkylated indole-3-imines via two sequential additions to the isonitrile moiety followed by homolytic aromatic substitution. The three component reaction comprises three C–C bond formations. The endocyclic imine functionality in the products is more reactive in follow up chemistry and hydrolysis of the exocyclic imine leads to 3-oxindoles that show fluorescence properties.

Indoles generally show high biological activity and accordingly they are observed to be prominent substructures in many natural products and drug candidates. Therefore, the development of novel methods allowing easy access to indoles and their derivatives is of importance. The introduction of a CF₃ group into a lead compound has become a general strategy to further improve lipophilicity, bioactivity and metabolic stability of the given lead candidate in agrochemical and medicinal chemistry.

Along these lines, the synthesis of 2-trifluoromethylindoles has gained great attention recently. Radical chemistry has become valuable for simple and efficient incorporation of CF₃ groups into various compounds via direct trifluoromethylation. Recently, we and Yu et al. introduced the radical trifluoromethylation of 2-isocyanobiphenyls as a practical method for the modular synthesis of 6-trifluoromethylated phenanthridines. Isonitriles have also been successfully applied to the preparation of 2-trifluoromethylated indoles via radical trifluoromethylation of 2-isocyanostyrene derivatives with the Togni reagent 2a (Fig. 1a).

The advantages of these radical trifluoromethylation methods over existing processes are that transition metals are not required and the introduction of the CF₃ group occurs regioselectively. Moreover, radical chemistry is ideally suited to run cascades allowing for multiple C–C bond formations. Herein we report the preparation of 2-perfluoroalkylindol-3-imines via a three component cascade comprising two subsequent radical additions to isonitriles using reagents of type 2 (Fig. 1b).

4-Methoxyphenylisonitrile (4a) was used as a test substrate for optimization (Table 1). Pleasingly, the reaction of 4a (4.8 equiv.), 2a (1.0 equiv.) as a CF₃ source and tetrabutylammonium iodide (TBAI, 4.8 mol%) as an initiator at 80 °C in 1,4-dioxane for 22 hours provided 40% of the targeted 2-trifluoromethylindol-3-imine 5a (Table 1, entry 1). Solvent screening revealed that ethyl acetate provided 52% of the targeted 2-trifluoromethylindol-3-imine 5a (Table 1, entry 2 and ESI, †). Among the iodide sources tested (LiI, NaI, KI, CsI, MgI₂, CaI₂), LiI provided the highest yield (60%) (Table 1, entries 8 and 12 and ESI, †). Reactions with 3.8 equiv. the best result is obtained.

Under optimized conditions (Table 1, entry 13) we next investigated the scope and limitations (Fig. 2). Electronic effects strongly influence the reaction outcome and generally better

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† Electronic supplementary information (ESI) available: Experimental procedures, and spectroscopic and crystallographic data as well as computational details are included. See DOI: 10.1039/c6cc02284g
Homologues of Togni reagent 2a bearing longer perfluoroalkyl chains (C$_2$F$_5$ and C$_3$F$_7$) in the reaction with 4a gave the indoles 5j and 5k in 53% and 58% yields, respectively.

The suggested mechanism comprising a base-promoted homolytic aromatic substitution$^{17}$ via electron-catalysis$^{18}$ is depicted in Fig. 3. The initiation of the cascade likely occurs by reduction of the I(III)-reagent 2 with LiI as a formal electron donor$^{8,19}$ to generate a CF$_3$ radical. It is likely that there is an initial substitution of the carboxylate functionality of 2 by the iodide to give an aryl-I(III)ICF$_3$ compound. The I–I bond is weak and upon homolysis the generated iodanyl radical fragments to give a CF$_3$ radical and 2-iodobenzoate. This CF$_3$ radical adds to 4a to give the imidoyl radical A, which further adds to a second isonitrile to generate the imidoyl radical B. Cyclization onto the arene of the first aryl isonitrile leads the cyclohexadienyl radical C, that gets deprotonated by 2-iodobenzoate$^{8}$ to form the radical anion D. 2-Iodobenzoate is generated in the chain by reduction of 2. D is an efficient SET reducing reagent which formally generates an electron giving product 5a thereby closing the catalytic cycle.$^{17}$

Due to the high values of these indole imines (see below) we decided to develop an alternative non-chain process to the target compounds that uses readily accessible azo compounds as radical precursors (Fig. 4).$^{11b}$ After some experimentation we found that heating of isonitrile 4a (3.8 equiv.) in the presence of AIBN (azobis(isobutyronitrile)) 6a in benzene at 100 °C provided the 2-cyanoprop-2-yl indole imine 7a in 81% yield. The yield is calculated on the basis that one equivalent of AIBN is necessary for product formation (AIBN acts as a radical precursor and an oxidant)$^{20}$ and that only about 60% of the AIBN-derived radicals escape the solvent cage.$^{21}$ In analogy, by using 1,1'-azobis(cyclohexanecarbonitrile) 6b the indole 7b was obtained in 78% yield. The yield further improved upon switching to the ester derivative 6c as a radical precursor to give the indole 7c in a high yield (92%).

Notably, all of the indole imines 5 and 7 show a very intense colour. For example, the indol-3-imine 5a with methoxy-substituents

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**Table 1** Optimization studies

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<tr>
<th>Entry</th>
<th>Equiv. (4a)</th>
<th>Init. (mol%)</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Yield (%)</th>
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</table>

$^{a}$ Isolated yield (reactions run at 0.26 molar). $^{b}$ Addition of Li$_2$CO$_3$ (0.25 mmol). $^{c}$ Addition of LiOH (0.25 mmol).

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**Fig. 2** Various prepared 2-trifluoromethyl or perfluoroalkylindol-3-imines 5a–k (isolated yields).
at the aromatic moiety has a deep red colour (λmax = 478 nm) and the dimethylamino congener 5d shows an intense violet colour (λmax = 564 nm). The UV/vis spectra of these compounds are included in the ESI.† Quantum chemical calculations for these compounds reproduce this difference in absorption very well (λmax (5a) = 479 nm, λmax (5d) = 549 nm with ADC(2)). According to our calculations, these absorption bands are caused by the two lowest-energy singlet–singlet excitations, which are dominated by HOMO → LUMO and (HOMO–1) → LUMO orbital transitions. Their energetic positions are strongly dependent on the electronic nature of the substituents (see the ESI † for details of the calculations).

We next investigated the reactivity of the product indoles using 5a and 7a as substrates. Hydrogenation in ethyl acetate at room temperature (H₂, Pd(C)) provided the corresponding 3-arylamino-2-(trifluoromethyl)-1H-indole 8a and 2-methyl-2-(3-(phenylamino)-1H-indol-2-yl)propanenitrile 8b in 80% and 83% yield, respectively (Fig. 5).

Reaction of 5a with para-toluenesulfonic acid monohydrate (1.0 equiv.) in diethyl ether at an elevated temperature (sealed tube) provided quantitatively half aminal 9a, showing that the endocyclic imine functionality is more reactive (Fig. 6). Hydrolysis of the exocyclic imine can be achieved upon treatment with aqueous HCl (see 10a, 99%). Butyllithium undergoes addition with complete regioselectivity to the endocyclic imine and subsequent hydrolysis of the remaining imine with aq. HCl leads to 3-oxindoles, as documented by the successful preparation of 11a, 11d, and 11e.22  

Whereas the parent indole imines 5 and 7 show intense colour but no fluorescence, all 3-oxindoles prepared are photoluminescent.23 Notably, imine 9a is not fluorescent indicating that the keto functionality in these compounds is important to attain photoluminescence. For hemiaminal 10a we observed strong green emission and a light blue emission was measured for compound 11a. As expected, substituents at the indole moiety influence the emission properties: the amino derivative 11d shows an orange and the methyl derivative 11e a deep blue emission.

The fluorescent species have been further characterized in terms of absorption spectroscopy and photoluminescence quantum yields, as well as fluorescence excitation, emission, and excited state lifetimes in the solid state, in solution at room temperature and in frozen glassy matrices at 77 K (the results can be found in the ESI †). A summary of the photophysical data is listed in Table 2. The broad, unstructured emission bands reveal a significant charge-transfer character for the excited states, as opposed to vibrationally resolved π–π states. Consequently, strong π-donors generate significant red-shifts. Interestingly, no significant blue-shifts can be traced in frozen matrices at 77 K, even though the solvent molecules cannot rearrange their dipole moments to stabilize the excited states. It should be noted that a higher push–pull character has a detrimental effect on the fluorescence quantum yield, which can be related to a stronger solvent coupling both in the excited as well as in the ground state. In the solid state, the quantum yields drop significantly, which can be ascribed to intermolecular interactions (see Table 2).

In summary, we have presented a straightforward access to 2-alkylated indol-3-imines via reaction of (perfluoro)alkyl radicals with two equivalents of an aryl isonitrile. The radical cascade comprises three C–C bond formations. As radical precursors perfluoroalkyl-iodine(III) reagents can be used and


(a) J. Lavelle and J. P. Fouassier, in Encyclopedia of Radicals in Chemistry, Biology and Materials, ed. C. Chagtilabouglu and A. Studer, Wiley, Chichester, UK, 2012, p. 42The Chemistry of Radical Polymerization, ed. G. Moad and D. H. Solomon, Elsevier, New York, 2006, pp. 60–77; (b) In the corrected yields we are taking into account that in the thermal decomposition of the azo compounds the yield of a free radical is just 60% due to the dimerization in the solvent cage.
