Radical C–H Trifluoromethoxylation of (Hetero)arenes with Bis(trifluoromethyl)peroxide

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Abstract: Trifluoromethoxylated (hetero)arenes are of great interest for several disciplines, especially in agro- and medicinal chemistry. Radical C–H trifluoromethoxylation of (hetero)arenes represents an attractive approach to prepare such compounds, but the high cost and low atom economy of existing OCF₃ radical sources make them unsuitable for the large-scale synthesis of trifluoromethoxylated building blocks. Herein, we introduce bis(trifluoromethyl)peroxide (BTMP, CF₃OOCF₃) as a practical and efficient trifluoromethoxylating reagent that is easily accessible from inexpensive bulk chemicals. Using either visible light photoredox or TEMPO catalysis, trifluoromethoxylated arenes could be prepared in good yields under mild conditions directly from unactivated aromatics. Moreover, TEMPO catalysis allowed for the one-step synthesis of valuable pyridine derivatives, which have been previously prepared via multi-step approaches.

Fluorinated agrochemicals and pharmaceuticals are of great importance due to the beneficial effects fluorine and fluorinated groups can have on a molecule’s potency, metabolic stability, selectivity and toxicity.[1] In the last three decades, compounds containing one or more fluorine atoms made up 22% of all globally registered small-molecule drugs[2] while, in the time period 1998–2020, 53% of all new agrochemicals were organofluorine compounds.[3] Trifluoromethoxylated arenes and heteroarenes are attracting increasing attention as up-and-coming fluorine-containing moieties. With a Hansch parameter (Πₗ = 0.88) and a notably lower electron-withdrawing influence than many other groups of Ngai, Togni and Tang disclosed additional Ar-OCF₃ moieties, have been developed.[4] Despite this great potential, the study of OCF₃-substituted (hetero)arenes has been hindered by the lack of practical methods to synthesize them.[5] Direct trifluoromethoxylation reactions, wherein the OCF₃ moiety is installed as an intact functional group onto an arene or heteroarene are especially scarce. With no electrophilic sources of the OCF₃ group available and cross-coupling methodologies hampered by the inherent instability of the OCF₃ anion towards β-fluoride elimination, radical trifluoromethoxylation arguably represents the most attractive approach. In 2018, Ngai and co-workers reported a breakthrough in this area by introducing a bench stable reagent A (Scheme 1a) that provides the OCF₃ radical upon photochemical activation.[6] Subsequent reports by the groups of Ngai, Togni and Tang disclosed additional OCF₃ moieties.[7] The OCF₃ moiety allows for a fine-tuning of a molecule’s biological activity and bioavailability. Furthermore, fluorine-specific stereoelectronic effects result in unconventional conformational preferences not encountered with other substituents.[8] To date, several drugs (e.g. Pretomanid, Delamanid, Sonidegib, Riluzol, Celikalim) and agrochemicals (e.g. Indoxacarb, Thifluamide, Flurprimidol) featuring an Ar-OCF₃ moiety, have been developed.[8]

Scheme 1. Radical C–H trifluoromethoxylation of (hetero)arenes. a) Previously reported reagents. b) This work: BTMP as a practical OCF₃ source.

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sources (B-D), which could be employed in radical C–H trifluoromethoxylation reactions with unactivated arenes.\(^9\)

While these reagents are bench stable and convenient on a laboratory scale, each is prepared from either the Togni I or Togni II electrophilic trifluoromethylating reagents. The high cost of these precursors makes large-scale applications unpractical while stoichiometric amounts of organic by-products are produced, which must be separated from the reaction mixture.

With the aim of developing a practical method suitable for larger scale production of trifluoromethoxylated arene and heteroarene building blocks, our attention was drawn to bis(trifluoromethyl)peroxide (BTMP, 1) as a potential source of \(\text{OCF}_3\). This compound can be prepared on a large scale from the inexpensive bulk chemicals CO and F\(_2\), and is remarkably stable towards both thermal and photochemical decomposition.\(^7\) A small number of studies demonstrate, however, that BTMP can transfer an \(\text{OCF}_3\) group onto organic substrates, although the forcing conditions (high temperature,\(^8\) UVA light\(^9\)) employed to activate the peroxide drastically limited the substrate scope and resulted in only low yields and selectivities. Here we report the successful application of BTMP as a practical trifluoromethoxylating reagent under mild conditions employing either visible light photoredox or TEMPO catalysis (Scheme 1b). Using both activation modes, trifluoromethoxylated arenes could be prepared in a single step from simple aromatic feedstocks. The potential of these methods for the production of valuable \(\text{OCF}_3\)-containing building blocks is further demonstrated by the one-step preparation of (trifluoromethoxy)pyridines, which till now have been prepared via multi-step syntheses.

In an initial experiment, BTMP (1, 1 eq.) was condensed into an acetonitrile solution containing the photocatalyst [Ru(bpy)\(_3\)][PF\(_6\)]\(_2\) (bpy = 2,2'-bipyridine, 1 mol%) and benzene (2a, 10 eq.).\(^{10}\) After 16 h irradiation with visible light from blue LEDs, we were delighted to observe efficient formation of (trifluoromethoxy)benzene 3a in 48% \(^{19}\)F NMR yield (internal standard = PhCF\(_3\)). Working on the hypothesis that single electron transfer from the excited photocatalyst to BTMP followed by mesolysis results in \(\text{OCF}_3\) formation, alternative single electron reductants were tested.\(^{11}\) In addition to light-mediated activation of BTMP by various photocatalysts, the simple metal salt CuCl (1 eq.) also led to the formation 3a in 50% NMR yield without light irradiation. Photocatalysis with [Ru(bpy)\(_3\)][PF\(_6\)]\(_2\), however, remained the most efficient approach and optimization of the other reaction parameters led to a set of standard conditions that provided 3a in 74% NMR yield (1.5 mol% [Ru(bpy)\(_3\)][PF\(_6\)]\(_2\), 5 eq. 2a, 0.1 eq. KF, 0.2 M MeCN, blue LEDs, rt, 16 h).

The scope of the photocatalytic C–H trifluoromethoxylation with a selection of aromatic feedstocks is shown in Scheme 2. A range of diverse substituents on the arene was tolerated, with electron-withdrawing groups generally leading to the highest yields. In most cases, BTMP provided similar yields of products 3 to those previously reported using reagents A-D. Deviations were observed, however, for benzonitrile 2f and methyl benzoate 2i with the corresponding trifluoromethoxylated arenes being delivered in significantly higher yields (3f = 69%, 3i = 73%), while iodobenzene 2e was much less efficiently converted (4%). The successful synthesis of the halogenated arenes 3c and 3d as well as the boronic ester species 3l is particularly noteworthy as these products can serve as \(\text{OCF}_3\)-containing building blocks for cross-coupling methodologies. The regioselectivity of the photocatalytic trifluoromethoxylolation with BTMP also mirrored that obtained using the previously reported reagents A-D and reflects the inherent electronic properties of the aromatic substrates. In each case, only trace amounts of bis(trifluoromethoxy)arene side-products were observed in the crude reaction mixtures, while waste species derived from the \(\text{OCF}_3\) by-product could be readily removed upon aqueous work-up.

Having developed a set of efficient photocatalytic conditions, we next sought to investigate alternative approaches for activating BTMP, which do not require light irradiation. While initial results had identified metal salts such as CuCl as suitable stoichiometric activators, we were drawn to the recent report from Ngai and co-workers employing catalytic amounts of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) as a single electron shuttle with reagent C.\(^{12}\) TEMPO is significantly less expensive than [Ru(bpy)\(_3\)][PF\(_6\)]\(_2\), while the avoidance of light irradiation brings practical advantages for potential large scale applications.\(^{12}\) Benzene (2a, 5 eq.) and BTMP (1 eq.) were thus reacted with TEMPO (25 mol%) and inexpensive K\(_2\)CO\(_3\) (1 eq.) as a basic additive in MeCN (0.5 M) at rt overnight. Analysis of the reaction mixture by \(^{19}\)F NMR revealed the efficient formation of

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\text{Scheme 2. Scope of the photocatalytic C–H trifluoromethoxylation of arenes using BTMP.} \quad \text{\(^{19}\)F NMR yields using PhCF\(_3\) as an internal standard, ratio ortho-\text/-meta-\text/-para- determined by \(^{19}\)F NMR shown in brackets.} \quad \text{*With 0.1 eq. KF.}
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(trifluoromethoxy)benzene 3a in 70% yield. Furthermore, the low polarity of TEMPO means that the benzene substrate can be used as the only solvent, with 3a being delivered in 61% 19F NMR yield under neat conditions.

The efficiency of the TEMPO-catalyzed trifluoromethoxylation method with a selection of aromatics is shown in Scheme 3. As for the photocatalytic reaction, a range of electron-poor and electron-neutral examples could be successfully employed in generally moderate to good yields up to 81%. While the cyano- and methyl ester-substituted derivatives 3f and 3i could also be prepared in good yields under neat conditions (3f: 81%, 3i: 45%), other examples reacted more efficiently using MeCN as solvent. In most cases, the yields were similar to those obtained under photocatalytic conditions, although nitrobenzene (2m) was less efficiently converted using TEMPO (27% vs. 54%). Interestingly, however, significant differences were observed in the regioselectivities of the trifluoromethoxylation reactions under the two sets of conditions. The halogen-substituted arenes 2b, 2c and 2d, for example, exhibited a notably increased preference for the ortho and, especially, para products under TEMPO catalysis, with this preference increasing in the order 3d < 3c < 3b (i.e. Br < Cl < F). In fact, while the same broad regioselectivity trends were observed under both sets of conditions, TEMPO catalysis led to a higher selectivity for the para-(OCF3)-substituted products with each aromatic substrate tested. The observation that different activation modes lead to different product distributions is both potentially synthetically useful and mechanistically interesting as it implies that the regioselectivity is not simply a reflection of the substrate properties.

At this stage of the study, we sought to explore BTMP as a practical reagent for the direct synthesis of hitherto under-explored OCF3-containing building blocks. Given the importance of nitrogen heterocycles in pharmaceuticals, (trifluoromethoxy)pyridines are highly desirable motifs for incorporation into new drug targets. Currently, however, these species are generally accessed via indirect methods. In comparison to benzene derivatives, such approaches entail additional synthetic steps as the (hydroxy)pyridine starting materials required for de novo construction of the OCF3 moiety are not widely available. Furthermore, the key halogen step can only be achieved on α-chloropyridine derivatives using the unattactive fluorinating agent SbF5.[13] In 2016, the groups of Zou, Wu and Wu reported a trifluoromethylation approach towards trifluoromethoxylated pyridines and pyrimidines. However, the use of the expensive Togni II reagent and the restriction to 2-OCF3-substituted derivatives limits its applicability for the synthesis of diverse building blocks.[14,15]

To assess the feasibility of direct C-H trifluoromethylation of pyridine building blocks using BTMP, picolinonitrile 4a was selected as a representative substrate featuring a functional group amenable to subsequent conversion into other useful moieties (e.g. through hydrolysis to a carboxylic acid). Reacting 4a with BTMP under the optimized conditions with TEMPO provided the (trifluoromethoxy)pyridine 5a in a 19F NMR yield of 35% as a mixture of three regioisomers favoring the 5-(trifluoromethoxy)picolinonitrile (23% of 5ab, Scheme 4). While the yield is only moderate, the direct synthesis of this species in a single step from 4a represents a significant improvement on previously reported routes, which involved at least 6 steps from 2-aminopyridine.[16]

A selection of further substrates featuring halogen, cyano and amino substituents were then reacted under both sets of optimized conditions and the product distribution was analyzed by 19F NMR and GC-MS (Scheme 5). In all cases, the desired (trifluoromethoxy)pyridines 5 were obtained in mostly moderate yields with TEMPO catalysis generally proving more efficient. Only with the 2-chloro-5-amino-substituted pyridine 4f was a higher efficiency observed under photocatalytic conditions with 5f being produced in 39% 19F NMR yield (cf. 30% using TEMPO). To the best of our knowledge, the successful conversion of substrates 4e and 4f represents the first time amino substituents have been tolerated in radical trifluoromethylation reactions. The more electron deficient

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**Scheme 3.** Scope of the TEMPO-catalyzed C-H trifluoromethylation of arenes using BTMP. 19F NMR yields using PhCF3 as an internal standard, ratio ortho-/meta-/para- determined by 19F NMR shown in brackets. *TEPLO (5 mol%), no MeCN.* a) Aroene (10 eq.).

**Scheme 4.** Synthesis of 5-(trifluoromethoxy)picolinonitrile 5ab. a) Current approach: multi-step indirect synthesis. b) TEMPO-catalyzed trifluoromethoxylation with BTMP. 19F NMR yields (internal standard = PhCF3), isolated yields in parentheses.
Scheme 5. C–H Trifluoromethoxylation of pyridines with BTMP. \(^{19}\)F NMR yields, isolated yields in parentheses. A: TEMPO catalysis conditions (Substrate (5 eq.), BTMP (1 eq., 0.5 mmol), TEMPO (25 mol%), Na\(_2\)CO\(_3\) (0.4 M), neat at 30 \(^\circ\)C for 6 h). B: photocatalysis conditions (see Scheme 2). \(^{a}\) 6 mmol scale. \(^{b}\) 3 mmol scale. \(^{c}\) 0.5 mmol scale. \(^{d}\) neat at 30 \(^\circ\)C. \(^{e}\) 0.2 M. \(^{f}\) in MeCN (2.0 M). \(^{g}\) in MeCN (0.4 M). \(^{h}\) in MeCN (0.2 M). \(^{i}\) 6 h.

pyridine motif likely inhibits undesired direct electron transfer steps, which are thought to take place between electron rich aromatics and OCF\(_3\) reagents.\(^{17}\) The product regioisomers could be separated from the unreacted substrate and from each other via normal-phase column chromatography while, in no case, were bis(trifluoromethoxy) side-products resulting from double addition observed by GC-MS.\(^{18}\) As chromatography is unattractive for large scale applications, differential scanning calorimetry (DSC) analysis was performed to assess the potential isolation of each regioisomer by fractional distillation. As shown in Scheme 5, a significant decrease in the boiling point was observed upon trifluoromethoxylation (up to 45.7 \(^\circ\)C for 5fa), while for most examples, meaningful differences in the boiling points of each product regioisomer were measured (up to 33 \(^\circ\)C for 5ea and 5eb). These results suggest that radical trifluoromethoxylation with BTMP could prove useful as a practical one-step method for the preparation of (trifluoromethoxy)pyridine building blocks with final product isolation being achieved via well-established and inexpensive distillation techniques.

In conclusion, BTMP has been employed as a source of OCF\(_3\) radicals in C–H trifluoromethoxylation reactions of aromatic compounds. Using either visible light photoredox catalysis or TEMPO as a catalytic electron shuttle, valuable trifluoromethoxylated arenes could be prepared under mild conditions, while direct radical trifluoromethoxylation of underexplored pyridine derivatives was achieved. Given the ready availability of BTMP from inexpensive bulk compounds, we believe these methods could serve as useful routes to OCF\(_3\)-containing building blocks.

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