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Metal-Free Radical Perfluoroalkylation of (Hetero)Arenes

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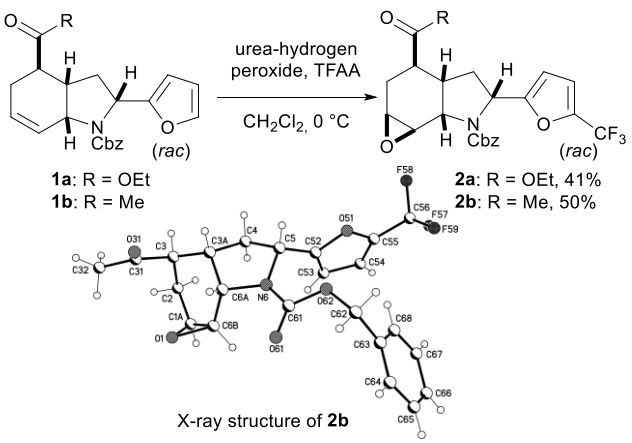
We report a metal-free radical perfluoro¬alkylation method which uses inexpensive and commercially available perfluorocarboxylic anhydrides as an easy to use source of perfluoroalkyl radicals. This approach allows the perfluoroalkylation of different arenes, such as benzene derivatives, furans, thiophenes, and pyrroles, including highly functionalized compounds.

Although fluoroorganyls are very rare in nature, fluorinated compounds play an important and crucial role in modern life and material science.[1] Due to the unique properties of carbon-fluorine bonds such as their high stability, low polarization and strong electron withdrawing effects, the fluorine substituent is a common structural motif in various commercially important compounds, especially in pharmaceuticals and agrochemicals.[2] Over the last years, there has been a lot of attention towards the research of new perfluoroalkylation methods, as perfluoroalkyl groups can be regarded as a superior fluorine substituent, with similar but mostly distinctly increased effects.[3] Nowadays, several different approaches for the introduction of perfluoroalkyl groups into organic compounds are known allowing straightforward routes to functionalized perfluoroalkylated compounds.[4] However, most routes still require expensive perfluoroalkyl sources like (perfluoroalkyl)trimethylsilanes,[5] (perfluroalkyl)dibenzothiophenium salts (Umemoto's reagents)[6] or perfluoroalkyl benziodoxole derivatives (Togni's reagents).[6,7] In contrast to these perfluoroalkylating agents, perfluoroalkylic anhydrides are a cheap and readily available perfluoroalkyl source.

In the course of our studies towards the total synthesis of thiodiketopiperazine natural products,[8] we attempted to epoxidize the double bond in our key intermediates **1a** or **1b**. We discovered that using a combination of urea–hydrogen peroxide (UHP) and trifluoroacetic anhydride[9] led to compounds **2a** and **2b**, where trifluoromethylation occurred at the 2-position of the furan moiety (Scheme 1). The structure of **2b** was confirmed by X-ray analysis.



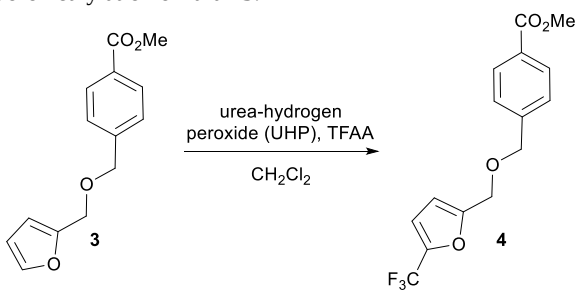
Scheme 1. Epoxidation/trifluoromethylation of furyl hexahydroindoles and molecular structure of **2b** (one of the two crystallographic independent molecules is shown).

Inspired by the simplicity of this trifluoromethylation reaction we then started investigations towards a general perfluoroalkylation protocol using the reagent combination UHP/TFAA. In an earlier publication, Sawada and co-workers generated bis(trifluoroacetyl)peroxide (BTFAP) by oxidation of TFAA with 30 wt.-% hydrogen peroxide, and the resulting solution was stored and used for trifluoromethylation of various arenes.[10] This is based on a radical reaction: Homolytic cleavage of the peroxide and CO_2 extrusion generates trifluoromethyl radicals, which are able to attack several (hetero-)arenes. However, the yield of BTFAP was only 30%

and needed Freon 113 (1,1,2-trichloro-1,2,2-trifluoroethane) as solvent, which should be avoided due to its ozone-depleting and environmentally harmful properties. Furthermore, the reactant solution contained pure and explosive BTFAP, for which particular caution is necessary during handling. The products were analyzed by GC-MS and were not isolated, possibly due to high volatility of trifluoromethylated products. In addition, perfluoroalkylations with those conditions were carried out successfully on a number of arenes and heteroarenes described in a variety of articles by Yoshida, Sawada and Kobayashi.[11]

Main advantages of replacing 30 wt.-% aqueous H_2O_2 with UHP are its convenient handling (the crystalline solid can be stored at room temperature) and the release of pure H_2O_2 upon treatment with TFAA, leading to a potentially higher yield and concentration of H_2O_2 and therefore BTFAP. Because of *in situ* generation of BTFAP, an isolation of this explosive reagent can be avoided, which is a major advantage compared to the previous method. Furthermore, we used the more common CH_2Cl_2 instead of Freon as solvent.

Table 1. Screening of the reaction conditions for the trifluoromethylation of furan **3**.



entry	equiv. UHP	equiv. TFAA	time	temp.	yield
1	6	6	0.5 h	0 °C	12% (^{19}F)
2	6	12	2.0 h	0 °C	15% (^{1}H)
3	10	20	1.0 h	0 °C	49% (isol.)
4	15	30	2.0 h	0 °C	32% (^{1}H)
5[a)]	10	10	1.5 h	0 °C	0%
6[b)]	10	20	1.0 h	0 °C	23% (^{1}H)
7[c)]	10	20	1.5 h	0 °C	11% (^{1}H)
8	10	20	1.0 h	rt.	0%
9[d)]	10	20	2.5 h	0 °C	11% (^{1}H)
10[e)]	10	20	1.0 h	0 °C	47% (^{1}H)

TFAA was added over 10 min if not stated otherwise. The reactions were performed on a 0.2 mmol scale. a) TFAA was added in one portion; b) TFAA was added over 6 min; c) TFAA was added over 30 min; d) concentrated reaction mixture (2 mL); e) inverse experimental procedure: TFAA was added to UHP in CH_2Cl_2 (4 mL) at 0 °C over 10 min. It was stirred for another 6 min before a solution of **3** in CH_2Cl_2 (2 mL) was added over 20 min.

In order to isolate the trifluoromethylated products and to avoid problems arising from high volatility, we chose substituted furan **3** as substrate, easily accessible by etherification of furfuryl alcohol.[12] Several reaction conditions were screened (Table 1). We observed that changing the UHP/TFAA ratio from 1:1 (6:6 equivalents, entry 1) to 1:2 (6:12 equivalents, entry 2) led to a minor improvement of yield from 12% to 15%. Furthermore, the yield was higher when increasing the reagent equivalents to 10:20 (entry 3), but another increase to 15:30 equivalents resulted again in decrease of yield (entry 4). The TFAA addition rate is also important: when added in one portion, no product was obtained (entry 5). By fast addition over 6 min (entry 6) or slow addition over 30 min (entry 7) the yield was significantly lower than with TFAA addition over 10 min (entry 3). When the temperature was raised to room temperature (entry 8), no product was found after the reaction, and a more concentrated substrate solution affected the yield adversely (entry 9). Interestingly, there was no significant change of yield when the reaction procedure was reversed (entry 10). We were pleased to see that trifluoromethylation occurred selectively at the 2-position of the furan moiety with UHP/TFAA in CH_2Cl_2 in up to 49% isolated yield. The best results were obtained with 10 equivalents of UHP and 20 equivalents of TFAA (addition over 10 min) at 0 °C (entry 3).

Next, we investigated the substrate scope of the UHP/TFAA trifluoromethylation (Figure 1). We were able to trifluoromethylate another furan derivative (→ **5**), a thiophene derivative (→ **6**), benzofuran (→ **7**), Boc-protected indole (→ **8**), and a pyrrole derivative (→ **9**) at the 2-position. Furthermore, the reaction was successful on a variety of electron-rich benzene derivatives, including [2.2]paracyclophane (→ **10**). Product **10** was separated from the crude mixture along with double and triple trifluoromethylated side products of unknown regioselectivity and ratio.

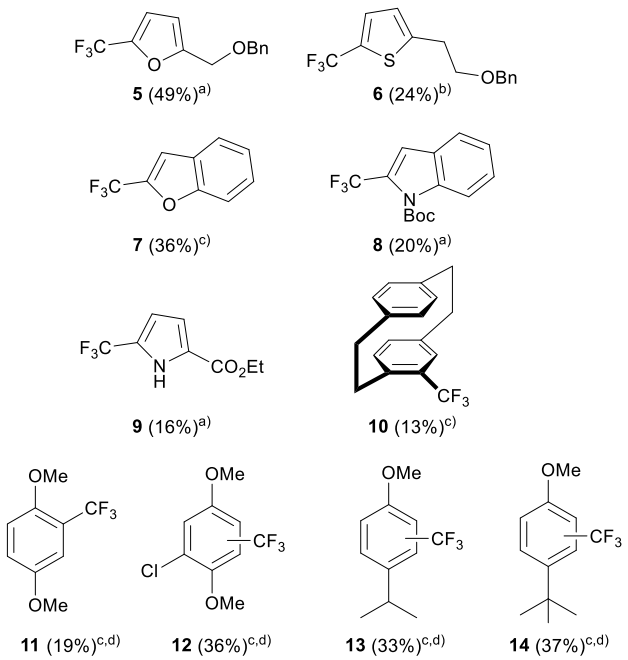
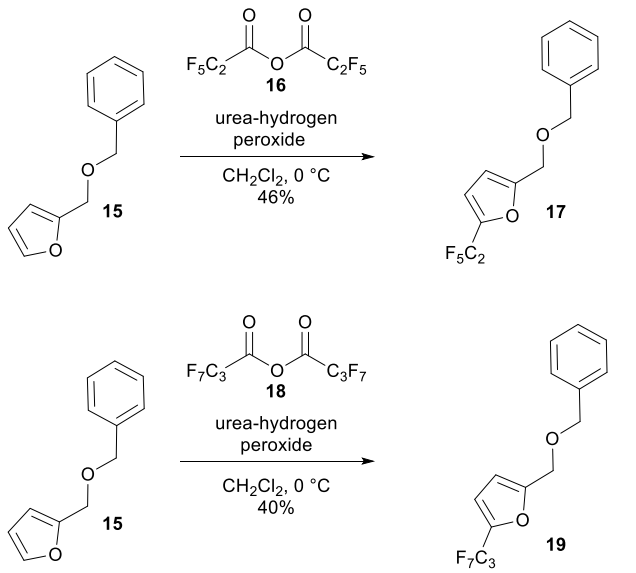


Figure 1. Substrate scope of the UHP/TFAA trifluoromethylation. The reactions were performed on a 0.2 mmol scale (for **5**, **6**, **8–10**), 0.5 mmol scale (for **7**) or a 0.15 mmol scale (for **11**–**14**). a) isolated yield; b) ^{1}H NMR yield with mesitylene as internal standard; c) ^{19}F NMR yield with *o*-fluoronitrobenzene as internal standard; d) inverse experimental procedure: TFAA was added to UHP in CH_2Cl_2 (1 mL) at 0 °C and the solution was stirred for another 10 min before the arene was added (entry 6: as 1 M solution; entries 7–9: neat). Afterwards the reaction mixture was stirred for 2 h at room temperature; isomeric mixtures of mono- and di-trifluoromethylated products were obtained for **11**–**14**.

However, in the case of all other benzene derivatives, attempts to separate the isomeric products from the crude mixture were not successful. Therefore the yields for **11**–**14** were determined from the crude mixture by ^{19}F NMR with *o*-fluoronitrobenzene as internal standard, yet assignment of the different products (regioisomers, double trifluoromethylated products) was not possible.

Having proven that TFAA is a valuable and feasible source of CF_3 radicals, we explored the use of the corresponding longer-chained pentafluoropropionic and heptafluorobutyric anhydride (**16**, **18**). Treatment of furan derivative **15** with these carboxylic anhydrides in combination with UHP gave perfluoroalkylated furans **17** and **19** in 46% and 40% isolated yield respectively (Scheme 2).



Scheme 2. Pentafluoroethylation and heptafluoropropylation of furan derivative **15**.

Conclusions

In conclusion, we showed that the inexpensive reagents trifluoroacetic anhydride (TFAA) in presence of urea–hydrogen peroxide (UHP) can be used as a new source of trifluoromethyl radicals for the trifluoromethylation of electron-rich (hetero-)arenes. The reaction proceeds fast at 0 °C within few hours and can be applied to complex systems, such as functionalized hydroindoles **1a** and **1b**. Furthermore, by using longer-chained perfluoro carboxylic anhydrides instead of TFAA, it is also possible to obtain the corresponding pentafluoroethyl and heptafluoropropyl derivatives.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details, analytical data, and crystallographic data for **2b**. See DOI: 10.1039/c000000x/

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