Trifluoromethylation

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Ortho-Trifluoromethylation of Functionalized Aromatic Triazenes**

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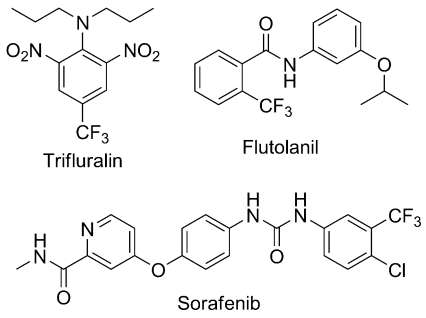
Fluorine containing organic agents play a crucial role in the search for new active pharmaceutical and agrochemical compounds. Owing to their fluorine moieties, these compounds have unique chemical and physical properties. For example, they can increase the metabolic stability or the lipophilicity, which can enhance the biological activity of a drug.[1]

For these reasons, the CF_3 group is an essential moiety of numerous commercially available aromatic and non-aromatic biological active agents. Therefore, the research on new



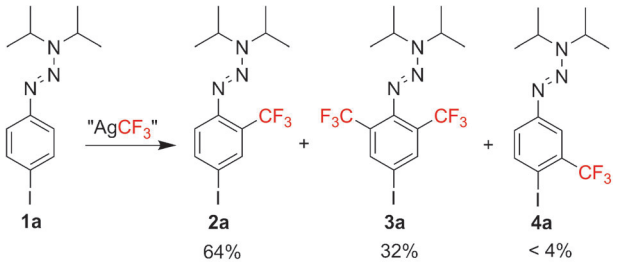
synthetic routes for introducing this group to aromatic systems is an important field of modern organic chemistry.

Over the last years, numerous synthetic examples for the direct trifluoromethylation of aromatic compounds were developed. Most of these routes are based on aromatic halides (mainly iodides), which are converted into the corresponding trifluoromethylated compound using a transition metal (Cu or Pd) and (trifluoromethyl)trimethylsilane ("Ruppert–Prakash reagent").[2,3] The substitution of aromatic boronic acids is also known.[4]

In contrast to these routes, the direct trifluoromethylation by C–H substitution has hardly been investigated. To date, this kind of reaction succeeds only with electrophilic CF_3 reagents[5] or on a few heteroaromatic compounds.[6] Recently, independently of our work, Sanford et al. reported a new trifluoromethylation reaction by C–H substitution. However, the synthetic application is limited, because an excess of the required aromatic compound is needed and only a low regioselectivity is achieved.[7]

For years, our group has been working on triazenes[8] and their application in solid-phase synthesis, as well as the investigation of new efficient cleavage reactions of triazenes.[9] Starting from commercially available aromatic aniline derivatives, a variety of functionalized aromatic triazenes are accessible by a simple one-step procedure.[9] Note that the toxicity of triazenes can be significantly reduced by using diisopropyl-substituted triazenes.[10]

During our investigation for a new cleavage method for triazenes in the presence of Ag_2CO_3, KF, and TMS-CF_3 we did not obtain the desired product but the *ortho*-trifluoromethylated triazene **2a** in 31% yield. This reaction probably occurred via in situ generated $AgCF_3$.[11] By optimizing the reaction conditions we were able to increase the yield to up to 64%. In this case, a second substitution was observed which led to the di-*ortho*-substituted triazene **3a** in 32% yield (Scheme 1).



Scheme 1. Trifluoromethylation of triazenes **1a**. Reaction conditions: **1a** (0.40 mmol), TMS-CF_3 (0.80 mmol), AgF (1.60 mmol), C_6F_{14} (1 mL), 100 °C, 4 h.

In addition to our preferred solvent perfluorohexane, the reaction could be also performed in acetonitrile, but gave lower yields (48%, 60 °C, 16 h). Furthermore, when higher temperatures (100 °C) were applied in acetonitrile, byproducts were obtained, through the formation of difluorocarbene. This result indicates the in situ generation of $AgCF_3$.

Changing the solvent to dichloroethane, which was used by the Sanford group, resulted in a conversion of **1a** into **2a** in only 20% yield. To investigate the scope of the reaction, we synthesized further aromatic triazenes and trifluoromethylated these compounds under analogous conditions (Scheme 2). When *para*-substituted triazenes were used, we always obtained a very high *ortho* selectivity. In all cases only small amounts (< 4%) of *meta* substituted byproduct were detected by GC-MS analysis.

In the case of mono-*ortho*-substituted triazenes, the *ortho* trifluoromethylated triazenes **2f**, **2g**, and **2h** were obtained as

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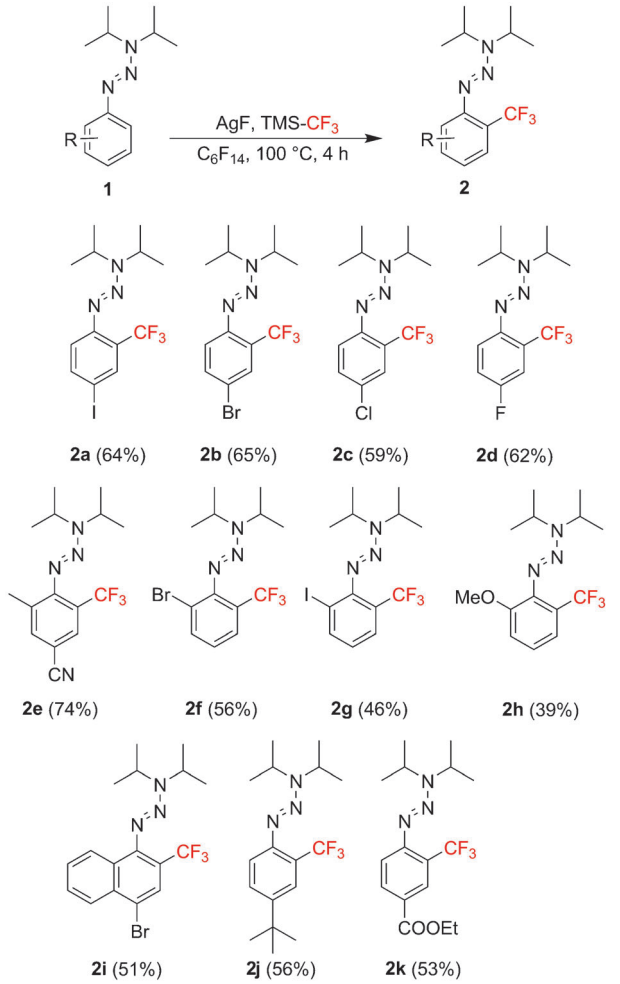


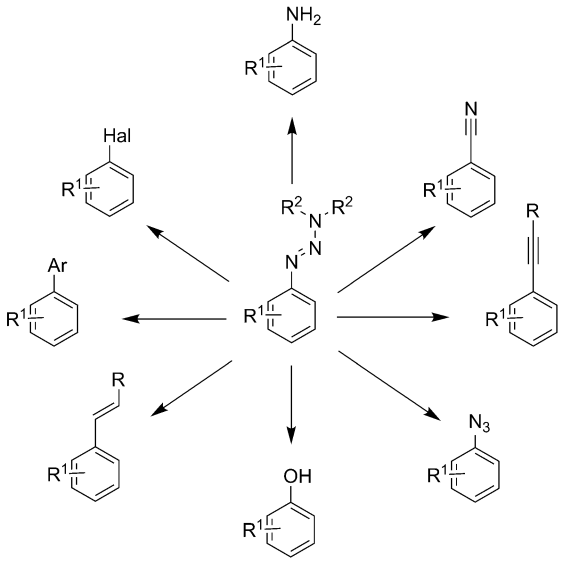
Scheme 2. Trifluoromethylation of different functionalized triazenes. Yields of the isolated *ortho*-substituted product.

the main products. However, best yields could be obtained when one *ortho* as well as the *para* position were blocked for a C–H substitution (**2e**). Overall, the trifluoromethylation reaction occurred mostly in good yields.

Noteworthy is the high tolerance of various functional groups. Thus, the aromatic trifluoromethylation was applicable in presence of iodides, bromides, chlorides, fluorides, cyanides, as well as in the presence of ester and methoxy groups (Scheme 2). Interestingly, the conversion of the halogenated halides **2a**–**2d**, **2f**, and **2g** was always almost quantitative into the corresponding trifluoromethylated products (*ortho*, di-*ortho* ≫ *para* ≫ *meta*), whereas a substitution of the corresponding halide was never detected. This situation is remarkable, because most common metal-mediated trifluoromethylation reactions substitute halides, especially iodides. Therefore, the new reaction shows a reaction pathway that is orthogonal to common routes.[3]

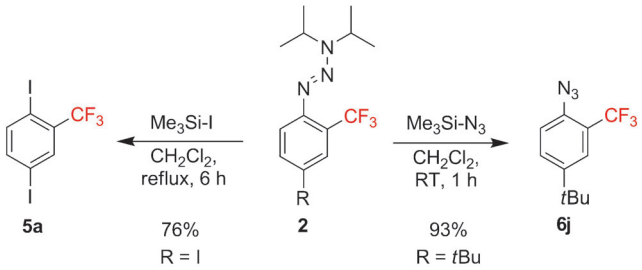
While many applications of $AgCF_3$ in transmetallation reactions are reported,[11] only a few synthetic examples are known in which $AgCF_3$ is used to form new C–CF_3 bonds.[7,12] Therefore, information on the reaction mechanism of silver-mediated trifluoromethylation reactions is limited. Naumann et al. showed by NMR spectroscopy that in aprotic solvents an equilibrium between $AgCF_3$ and $Ag(CF_3)_2^-$ occurs and that $Ag(CF_3)_2^-$ is the reactive species in the trifluoromethylation of mercury(II) chlorides.[13] However, in the aromatic trifluoromethylation reaction, another reactive species seemed to be involved. On the basis of experiments involving the addition of radical initiators/inhibitors, the Sanford group supposed that radical intermediates are involved. Although a radical mechanism seems unlikely owing to the high *ortho* selectivity, similar experiments using radical initiators/inhibitors do indicate the existence of radical species. While a radical initiator such as azobisisobutyronitrile (AIBN) did not have any influence on the reaction, the addition of 2 equivalents of (2,2,6,6-tetramethylpiperidine-1-yl)oxyl (TEMPO) decreased the yield of **2a** to 30% (determined by GC-MS). When 5 equivalents of TEMPO were used, no product could be found at all. As TEMPO is known as a scavenger of CF_3 radicals,[6] this result suggests that the CF_3 radicals are the reactive species. Nevertheless, the high *ortho* selectivity of triazenes is remarkable.

Triazenes are useful equivalents of protected diazonium salts and therefore can be easily transformed into various functional groups. Thus, it is possible to convert the triazene moiety into different halides,[14] into the corresponding azide,[15] nitrile,[16] and phenol[17] or back to the starting amine.[18] A traceless transformation back to the hydrocarbon was also feasible.[19] Furthermore, cross-coupling reactions using triazenes are also known (Scheme 3).[20]



Scheme 3. Transformations of the triazene moiety reported in the literature.

We believe that this versatility together with the high selectivity towards trifluoromethylation makes triazenes useful in the synthesis of new CF_3 building units. To demonstrate this synthetic potential we tested the transformation of the triazene moiety to the corresponding iodide (**5a**) and azide (**6j**). Both reactions succeeded under literature conditions in good to excellent yields (Scheme 4).



Scheme 4. Transformation of an *ortho*-trifluoromethylated triazene into the corresponding iodide (**5a**) and azide (**6j**).

In conclusion, a highly *ortho*-selective trifluoromethylation of aromatic triazenes was reported. This reaction tolerates a broad range of functional groups, especially iodides and bromides. Our further studies will deal with investigating the reaction mechanism as well as exploring the further synthetic scope of $AgCF_3$ mediated trifluoromethylation reactions.

Experimental Section

Representative trifluoromethylation of aromatic triazenes: A vial equipped with a septum and a stirring bar was charged with AgF (202 mg, 1.60 mmol, 4.00 equiv) and the triazene **1a** (133 mg, 0.400 mmol). The reaction vessel was closed and, under argon atmosphere, perfluorohexane (1 mL) was added by syringe. Then TMS-CF_3 (0.120 mL; 114 mg, 0.800 mmol, 2.00 equiv) was added and the suspension was heated to 100 °C. The suspension was stirred for 4 h. Afterwards, the solution was cooled to room temperature and ethyl acetate (3 mL) was added. The layers were separated (in a separating funnel) and the perfluorohexane layer was reextracted with ethyl acetate twice. The combined organic phases were concentrated under reduced pressure. The crude product was purified by flash column chromatography (with cyclohexane on silica gel) and **2a** could be obtained as a yellow oil (101 mg, 64 %).

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