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Trifluoromethylation of 1-Aryl-3,3-diisopropyltriazenes

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Abstract: A new method for the trifluoromethylation of functionalized aromatic diisopropyltriazenes is described. In a facile two-step, one-pot synthesis, various functionalized trifluoromethyl-substituted arenes are accessible in mostly good yields by using methyl iodide as iodination agent and the trifluoromethylation system (trifluoromethyl)trimethylsilane/potassium fluoride/copper iodide. This concept could be expanded to perfluoroethylation as well as ethoxycarbonyldifluoromethylation reactions.

Keywords: copper; perfluoroethylation; triazenes; trifluoromethylation

Over the last years, a lot of effort has been made to find new methods that allow the direct insertion of the trifluoromethyl moiety into organic compounds. Since many pharmaceutical and agrochemical compounds possess aromatic CF_3-groups (Figure 1), arenes are the major target of trifluoromethylation reactions.[1]

Fluorine-containing groups like the CF_3 group show an increased stability against metabolization compared to other electron-withdrawing groups (e.g., other halides, carbonyl substituents, etc.). This is one reason why they are interesting in terms of bioisosteric replacement.[2] To date, the trifluoromethyl group can be directly introduced *via* radical,[3] nucleophilic[4] or electrophilic[5] CF_3 sources. While CF_3 radicals react under simple conditions with aromatic compounds there is often a lack of selectivity. Therefore, nucleophilic or electrophilic trifluoromethylation reactions are still favoured for the selective introduction of the CF_3 moiety. In most common protocols aromatic boronic acids[6] or halides[7] (especially iodides or bromides) are selectively trifluoromethylated using easy to handle liquids like (trifluoromethyl)trimethylsilane (TMS-CF_3) or (trifluoromethyl)triethylsilane (TES-CF_3). While TES-CF_3 is often used in copper[7e] or palladium[7d] catalysed trifluoromethylation reactions of aryl halides due to the increased stability against the formation of difluorocarbenes, TMS-CF_3 has still the advantage of being more affordable.[8] In contrast to TES-CF_3, the lower stability of TMS-CF_3 leads to reduced yields or more perfluoroethylated by-product when used under catalytic conditions. In some cases these drawbacks of TMS-CF_3 in copper-catalysed trifluoromethylation can be avoided by adding stoichiometric amounts of AgF.[7c] Nevertheless, when TMS-CF_3 is used as CF_3 source, stoichiometric amounts of copper together with KF are still the method of choice for the trifluoromethylation of aryl halides.[9]

Our group has been working on triazenes and their applications in solid-phase synthesis as well as "solution" chemistry for years.[10] Aromatic triazenes are easily accessible *via* a simple one-step procedure

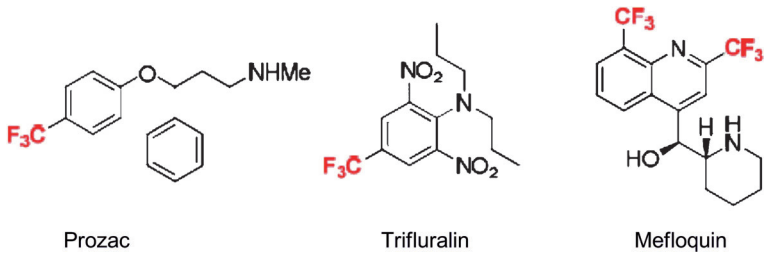


Figure 1. Examples for CF_3-containing drugs and agrochemicals.

starting from commercially available aniline derivatives.[11] They are versatile intermediates in organic synthesis as they can be converted into a whole series of different functionalities.[12] On the other hand, they tolerate several reaction conditions such as cross-coupling reactions and thus allow for the generation of complex structures.[13] Until now, no conversion of this useful group into the corresponding CF_3 moiety is known in literature. Herein, we present a novel and facile two-step, one-pot protocol for the transformation of 1-aryl-3,3-diisopropyltriazenes into the corresponding CF_3-arenes.

At first, we tested the direct trifluoromethylation of the triazene group. In general, the triazene moiety is cleaved by using a reactive electrophile (e.g., H^+ or Lewis acids) to generate the corresponding diazonium salt which can then be further reacted. These conditions were not suitable for trifluoromethylation reactions using a nucleophilic CF_3 source since acids also protonate the CF_3 nucleophile to fluoroform (pK_a = 28), which is inert to further conversions under the reaction conditions used. Therefore, we looked for an alternative reaction pathway. It is known that the triazene moiety can be used as a masked iodide group.[14] So we proposed a transformation based on a simple two-step, one-pot procedure. The first step should be the iodination of the triazene group followed by direct trifluoromethylation under known conditions.

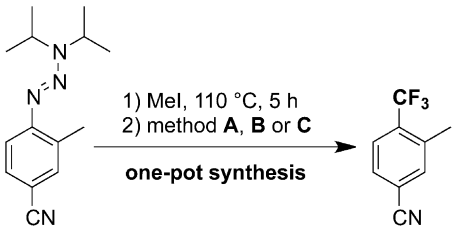
Starting from triazene **1a**, we first tested different iodination reactions and it was possible to achieve quantitative conversion using methyl iodide at 110 °C for 5 h. The remaining methyl iodide was removed under reduced pressure and we tested the trifluoromethylation conditions without further purification. We investigated stoichiometric as well as catalytic transformation protocols[7e] starting from triazene **1a**. With catalytic amounts of CuI and TES-CF_3 as CF_3 source quantitative conversion was observed, but besides the desired product **2a**, perfluoroethylated by-product (~4%) was detected, too (Table 1, A). As expected, the yields as well as the selectivity of the catalytic trifluoromethylation dropped down (23%) when we changed the CF_3 source to TMS-CF_3 (Table 1, B). Lastly, when stoichiometric amounts of CuI together with TMS-CF_3 were used under our optimized conditions, product **2a** was synthesized in quantitative yields (Table 1, C).

The results of methods A and C are comparable to known trifluoromethylation protocols starting from iodoarenes, which indicates a quantitative generation of ammonium salts in the first step, that neither affect the selectivity nor the yields of the following trifluoromethylation reaction. Therefore, both reaction protocols are suitable for this conversion, but because of the less expensive TMS-CF_3 we tested further conversions with method C. With our reaction conditions in hand we synthesized other aromatic triazenes and functionalized them by using MeI and the trifluoromethylation system TMS-CF_3/CuI/KF to the corresponding CF_3-arenes (Table 2). Most interestingly, electron-poor substrates like **1b** and **1d** showed no conversion at all, but when an additional electron-donating group was available, quantitative conversion was observed as in case of **2a** and **2c**. This shows one drawback of this reaction. On the one side, electron-rich triazenes reacted smoothly with MeI to furnish iodoarenes in quantitative yields, while electron-poor triazenes are less reactive or do not react at all.

On the other side, trifluoromethylation of aromatic halides is favoured for electron-poor arenes. These considerations as well as the steric hindrance of *ortho* substituents explain the conversions observed. Nonetheless, most aromatic triazenes could be trifluoromethylated in good yields.

Copper-mediated perfluoroethylation as well as ethoxycarbonyldifluoromethylation are also known in the literature.[9a,15] Therefore, we wondered whether such transformations are also possible under our conditions. When we tested the perfluoroethylation using CuI/TMS-C_2F_5/KF in DMF (in NMP only poor conversions were observed) triazene **1a** as well as **1c** could be converted into their corresponding C_2F_5-products (Table 3, left), but with reduced yields compared to the trifluoromethylation protocol. In 2011,

Table 1. Catalytic and stoichiometric trifluoromethylation.[a]



1a 2a

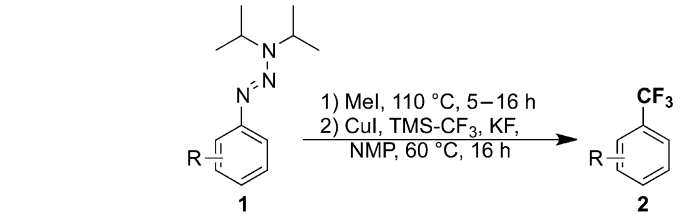
Method	CF_3 source (equiv.)	CuI (equiv.)	Additive (equiv.)	Yield of **2a**
A	TES-CF_3 (2.00)	0.10	phen (0.10)	95%[b]
B	TMS-CF_3 (2.00)	0.10	phen (0.10)	23%[c]
C	TMS-CF_3 (1.20)	1.50	–	>99%

[a] *Reaction conditions:* **1a** (0.40 mmol), MeI (2.40 mmol), 110 °C, 5 h, then under argon atmosphere: CuI, CF_3 source, KF (mmol equal to the CF_3 source), additive, NMP (1.50 mL), 60 °C, 16 h. Yields determined by ^{19}F NMR using *ortho*-fluoronitrobenzene as internal standard.

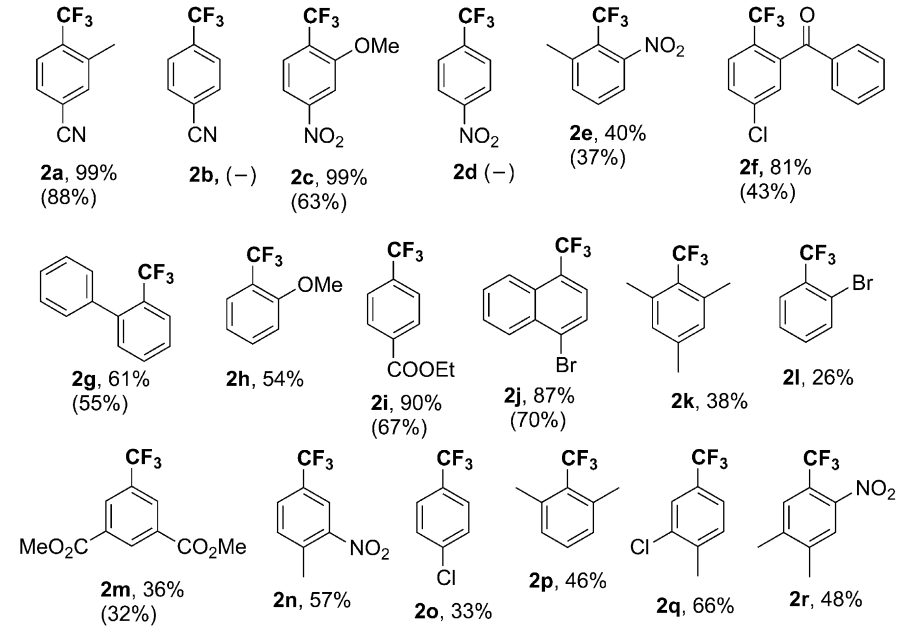
[b] Conversion was quantitative but 4% perfluoroethylated by-product was observed.

[c] 4% perfluoroethylated by-product was also observed.

Table 2. Trifluoromethylation of functionalized aromatic triazenes.

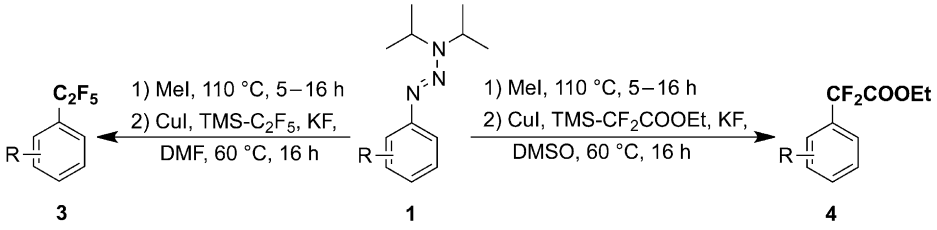


1 2

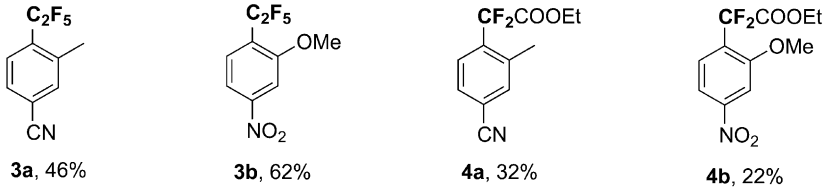


[a] Reaction was conducted with 0.40 mmol of triazene **1**. Yields determined by ^{19}F NMR using *ortho*-fluoronitrobenzene as internal standard. Yields in parentheses are isolated yields.

Table 3. Perfluoroethylation and ethoxycarbonyldifluoromethylation of functionalized aromatic triazenes.[a]



3 1 4



[a] Reaction was conducted with 0.40 mmol of triazene **1**. Isolated yields are given.

Amii and co-workers reported the ethoxycarbonyldifluoromethylation of aromatic iodides.[15] Thus we tested this reaction under similar conditions starting from aromatic triazenes **1a** and **1c**. In both cases only low yields were obtained, despite the fact that stoichiometric equivalents of copper were used (Table 3, right).

In conclusion, we have shown that the trifluoromethylation of the triazene moiety is possible with a facile two-step, one-pot synthesis in mostly good yields. This transformation can also be used for perfluoroethylation as well as ethoxycarbonyldifluoromethylation.

Experimental Section

General

NMR spectra were recorded on a Bruker AM 400, a Bruker Avance 300 or a Bruker DRX 500 spectrometer as solutions. Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane (TMS) and are referenced to residual solvent peaks. All coupling constants (*J*) are absolute values and *J* values are expressed in Hertz (Hz). The description of signals includes: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. The spectra were analyzed according to first order. The signal structure in ^{13}C NMR was analyzed by DEPT and is described as follows: + = primary or tertiary C-atom (positive signal), − = secondary C-atom (negative signal) and C_{quart} = quaternary C-atom (no signal). MS (EI) (electron impact mass spectrometry) was performed by using *a Finnigan* MAT 90 (70 eV). In cases where no (EI) mass spectra could be measured due to the high volatility of the compound, the GC-MS was used for characterization. IR (infrared spectroscopy) was recorded on a FT-IR Bruker alpha. Solvents, reagents and chemicals were purchased from Aldrich, ABCR and Acros. All solvents, reagents and chemicals were used as purchased unless stated otherwise.

General Procedure for Trifluoromethylation of the Triazene Moiety

A vial equipped with a pressure-resistant crimp top and a stirring bar was charged with 0.40 mmol of the triazene. The reaction vessel was closed and 0.15 mL methyl iodide (340 mg, 2.40 mmol) was added *via* syringe under an argon atmosphere. The suspension was stirred at 110 °C. After 5–16 h the suspension was cooled to room temperature and remaining methyl iodide was removed under reduced pressure. Now, 113 mg (0.60 mmol) copper iodide and 35 mg (0.60 mmol) potassium fluoride were added. Then, 1.50 mL dry NMP and 0.07 mL (68 mg, 0.48 mmol) TMS-CF_3 were added under argon and the suspension was heated to 60 °C for another 16 h. The solution was diluted with diethyl ether and washed with NH_3 solution and 2 M HCl. The organic layer was dried over $MgSO_4$. Finally, the solvent was removed under vacuum and the crude product purified by flash column chromatography.

General Procedure for Perfluoroethylation of the Triazene Moiety

The procedure as well as the equivalents were the same as in the general procedure for the trifluoromethylation reactions, except for the solvent (DMF instead of NMP) and the TMS-agent (TMS-C_2F_5 instead of TMS-CF_3).

General Procedure for Ethoxycarbonyldifluoromethylation of the Triazene Moiety

The procedure as well as the equivalents werethe same as in the general procedure for the trifluoromethylation reactions, except for the solvent (DMSO instead of NMP) and the TMS-agent (TMS-CF_2COOEt instead of TMS-CF_3).

Acknowledgements

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