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Heterocycles

Transition Metal-Free Trifluoromethylthiolation of N-Heteroarenes

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Abstract: A general and efficient methodology for the direct transition metal free trifluoromethylthiolation of a broad range of biologically relevant N-heteroarenes is reported employing abundant sodium chloride as the catalyst. This method is operationally simple, exhibits high functional group tolerance, and does not require protecting groups.

N-Heteroarenes comprise the core structure of numerous natural products, pharmaceuticals, and agrochemicals.[1] The cholesterol-lowering Atorvastatin (Lipitor) and the $GABA_A$ receptor agonist Zolpidem are prominent examples of bioactive compounds containing an N-heteroaromatic core (Figure 1). In this context, the development of efficient and selective methods for the functionalization of N-heterocycles such as pyrroles, indoles, and related ring systems is highly desirable.

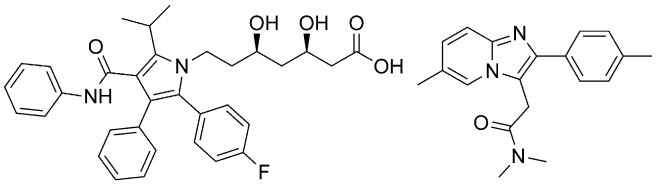

Figure 1. Examples of N-heteroarenes in pharmaceutical chemistry.

Incorporation of fluorinated functionalities is an important strategy to improve the properties of bioactive compounds in the pharmaceutical and agrochemical fields.[2] Thus, new efficient catalytic methods for the introduction of fluorinated moieties to diverse molecules are highly desirable. Furthermore, transformations must be robust and broadly applicable since high-throughput experimentation is frequently applied in these fields. Due to the strict restrictions concerning the metal contamination of drugs, transition metal-free procedures are particularly attractive. In this context, much attention is being focused on the trifluoromethylthio group (CF_3S), due to its electron-withdrawing effect and high lipophilicity, which can improve metabolic stability and the transmembrane permeation of drugs, respectively.[2,3] Different strategies have been developed over the years to incorporate the trifluoromethylthio group into molecules.[4] Traditional methods, such as, trifluoromethylation of sulfur-containing compounds,[5] halogen–fluorine exchange reactions,[6] and coupling of halides[7] or boronic acids,[8] require prefunctionalized substrates. Alternatively, the direct transformation of a C–H bond into a CF_3S group appears to be the most efficient and practical synthetic approach towards trifluoromethylthiolated heteroarenes. Recently, trifluoromethylthiolation of heteroarenes by means of C–H activation were reported, however directing groups were required.[9] Early work in the field of electrophilic trifluoromethylthiolation employed gaseous trifluoromethylsulfenyl chloride (CF_3SCl) as an electrophilic reagent. However, its high toxicity and corrosive properties limit its use.[10] Recently, shelf-stable electrophilic CF_3S reagents have been developed, in part also to avoid handling of CF_3SCl (Figure 2).

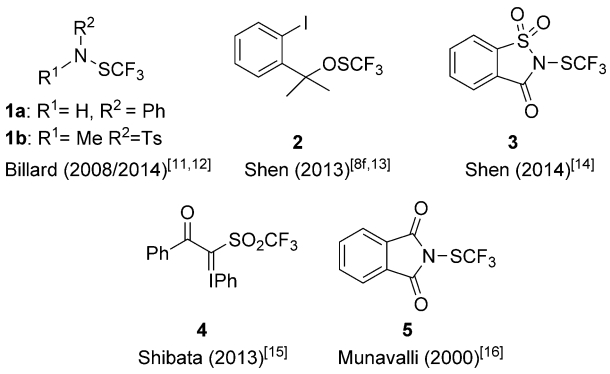

Figure 2. Shelf-stable electrophilic trifluoromethylthiolation reagents.

These reagents have been shown to require a catalyst/activator for the direct C–H functionalization of heteroarenes. Importantly, the type of catalyst/activator significantly influences the general applicability of the transformation and its functional group tolerance. Reagents **1a**,[11] **1b**,[12] and **2**[8f,13] (Figure 2) were reported to be activated by Brønsted or Lewis acids preventing their application for the trifluoromethylthiolation of pyrroles due to their sensitivity towards polymerization under acidic conditions.[11b] Comparable limitations are valid for reagent **3**, which is known to require Lewis acids, so few structurally or electronically specific pyrrole derivatives could be trifluoromethylthiolated by employing this reagent.[14] For re-

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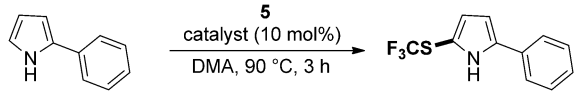
agent **4**, copper salts were reported to be effective in activation, however high catalyst loadings of the transition metal were required.[15]

To address the demands for synthetic procedures made by the pharmaceutical and agrochemical fields, we envisaged the development of a transition metal-free method for trifluoromethylthiolation that is robust, operationally simple, and generally applicable to pyrroles, indoles, and related heteroarenes. We chose compound **5** (Figure 2) as the electrophilic reagent,[16] due to its high stability and ease of synthesis, as reported by Rueping and co-workers.[8d] Additionally, to date, this reagent has not been applied in the C–H functionalization of heteroarenes. Employing 2-phenylpyrrole (**6a**) as the model substrate, we initially attempted the reaction without catalyst. However, the desired product was only formed in trace amounts (Table 1, entry 1). We therefore commenced searching for a catalyst that was effective at activating reagent **5** and, most importantly, still compatible with highly sensitive pyrroles. Based on previous reports on the activation of thiophthalimide reagents by halide ions,[17] we investigated different halide sources as catalysts. Fluoride and iodide sources showed no catalytic activity (Table 1, entries 2–4), whereas product formation in low to moderate yields was observed on employing bromide sources (Table 1, entries 5–7). To our delight, alkali chlorides were very effective for this transformation (Table 1, entries 8–10), with sodium and potassium chloride as the most active catalysts, despite previous reports that they were catalytically inactive.[17a] To rule out catalysis by the alkali cation, the reaction was performed with tetrabutylammonium chloride as catalyst, also leading to an excellent yield (Table 1, entry 11; see the Supporting Information for more results). We chose sodium chloride as a very cheap and effective catalyst for further reactions. Undertaking solvent screening, the reaction occurred only in very polar solvents (similar yields in dimethylacetamide, DMF, and DMSO), with DMF (p.a. grade) giving the most consistent results. Therefore, DMF was chosen as the optimal solvent.

Table 1. Catalyst screening.[a]

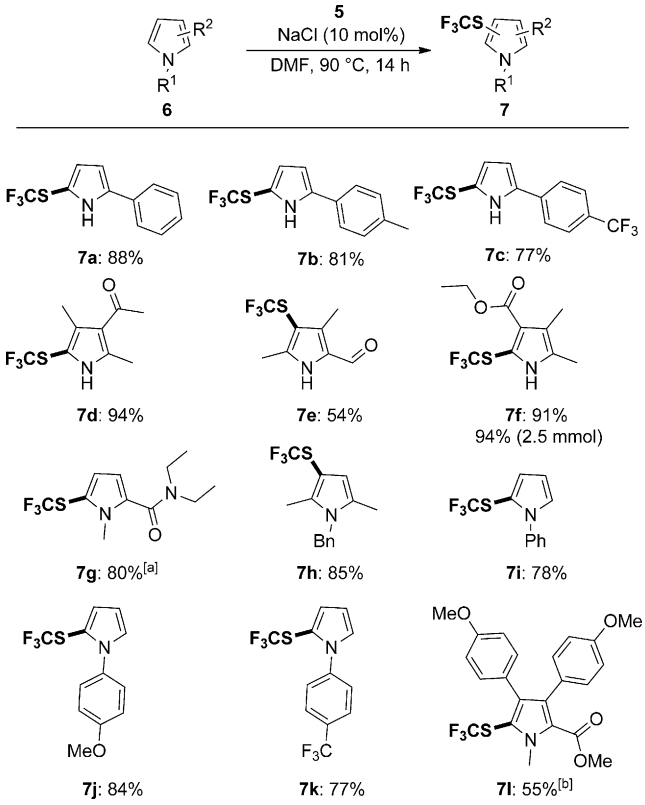


6a **7a**

Entry	Catalyst	Yield [%][b]
1	–	trace
2	KF	trace
3	NaI	trace
4	KI	trace
5	LiBr	60
6	NaBr	52
7	KBr	24
8	LiCl	85
9	**NaCl**	**94**
10	KCl	89
11	NBu_4Cl	92

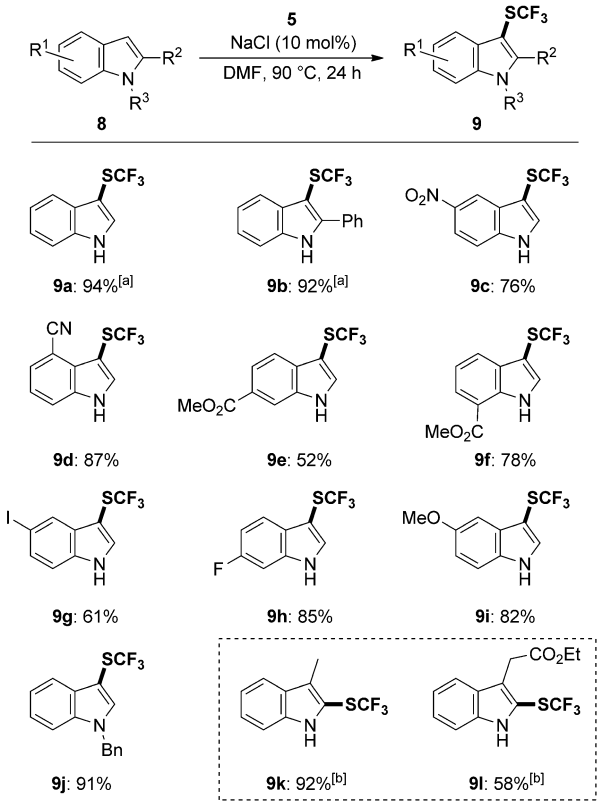
[a] Reaction conditions: Pyrrole **6a** (0.1 mmol), reagent **5** (1.1 equiv), catalyst (10 mol%), DMA (0.5 mL), 90 °C, 3 h; [b] GC yield. DMA = dimethylacetamide.

With the optimized conditions in hand, we next investigated the scope of the reaction. Electronically and structurally diverse pyrrole derivatives were selectively converted into the desired trifluoromethylthiolated products in excellent yields employing only a slight excess of the reagent **5** (Scheme 1). The reaction was observed to exhibit a broad functional group tolerance. Aliphatic as well as electronically diverse aryl substituents were well tolerated (Scheme 1, **7a**–**f**). Furthermore, substrates bearing different carbonyl groups (ketone, aldehyde, ester and amide) attached directly to the pyrrole core were efficiently trifluoromethylthiolated (Scheme 1, **7d**–**g**). Importantly, the reaction did not require a protecting group on the pyrrole nitrogen. However, aliphatic, benzylic, and electronically diverse aromatic substituents at the nitrogen atom were tolerated (Scheme 1, **7g**–**l**), which is significant as *N*-substituted pyrroles represent core structures in many natural products[1a] and bioactive compounds.[1e]



Scheme 1. Trifluoromethylthiolation of pyrrole derivatives. Reaction conditions (unless otherwise stated): Pyrrole (0.5 mmol), reagent **5** (1.0–1.1 equiv), sodium chloride (10 mol%), DMF (2.5 mL), 14 h, 90 °C. DMF = dimethylformamide. Yields of isolated product are given. [a] 1.3 equivalents of **5**. [b] Pyrrole (0.1 mmol), DMF (0.5 mL), 24 h.

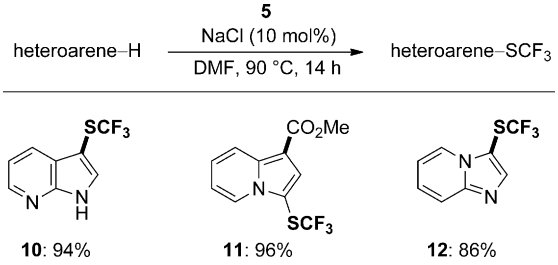
Next, we applied our procedure to the trifluoromethylthiolation of indoles in order to examine the generality of our method. Gratifyingly, a broad range of indole derivatives could be converted to the desired products in excellent yields



Scheme 2. Trifluoromethylthiolation of indole derivatives. Reaction conditions (unless otherwise stated): Indole (0.5 mmol), reagent **5** (1.1 equiv), sodium chloride (10 mol%), DMF (2.5 mL), 90 °C, 24 h. Yields of isolated product are given. [a] reaction time = 14 h. [b] $PdCl_2$ (5 mol%) as catalyst.

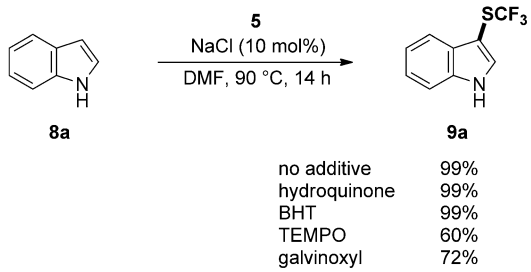
(Scheme 2). Again, no protecting group was required and both electron-withdrawing (Scheme 2, **9c**–**h**) and electron-donating substituents (Scheme 2, **9i**) were well tolerated. Notably, substitution of the benzo moiety, in any position, did not negatively influence the reaction (Scheme 2, **9c**–**i**). However, whereas a 2-substituted indole was smoothly converted to the desired product (Scheme 2, **9b**), no product was observed in the case of 3-substituted indole derivatives. Since the latter represent an important structural motif in pharmaceuticals and natural products,[1b–e] we conducted a brief screening of chloride sources with other metal cations for the additional activation of the indole core. To our delight, palladium(II) chloride and gold(III) chloride both displayed high catalytic activities. Thus, employing palladium(II) chloride as the catalyst, under otherwise identical conditions, 3-methylindole (Scheme 2, **8k**) and ethyl-3-indole-acetate (Scheme 2, **8l**) were converted to the desired trifluoromethylthiolated compounds. The latter represents a derivative of indole-3-acetic acid (IAA), a naturally occurring phytohormone that, along with its derivatives, is used in the agrochemical field.[18]

Finally, we turned our attention to the trifluoromethylthiolation of more challenging N-heteroarenes (Scheme 3). To our delight, 7-azaindole and an indolizine derivative provided the desired products (**10**, **11**) in excellent yields. Both heteroarenes constitute important classes of bioactive compounds.[19] Furthermore, we successfully performed the selective trifluoromethylthiolation of imidazo[1,2*a*]pyridine, which represents an important class of drugs acting as $GABA_A$ receptor agonists.[20] giving product **12**.



Scheme 3. Trifluoromethylthiolation of different N-heteroarenes. Reaction conditions: Heteroarene (0.5 mmol), reagent **5** (1.1 equiv), sodium chloride (10 mol%), DMF (2.5 mL), 90 °C, 14 h. Yields of isolated product are given.

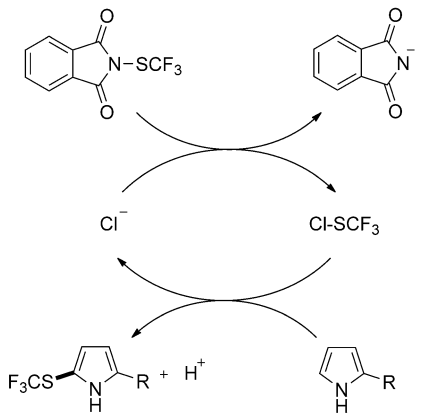
To elucidate the mechanistic aspects of the transformation, we first carried out the trifluoromethylthiolation of indole in the presence of radical inhibitors (Scheme 4). In the case of hydroquinone and 2,6-di-*tert*-butyl-4-methylphenol (BHT), no influence on the yield of the reaction was observed, whereas free radicals, namely 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and galvinoxyl, led to diminished yields. However, no radical coupling products were observed. These results, combined with the observed C3-selective functionalization of indoles, indicate an electrophilic substitution mechanism rather than a radical pathway.



Scheme 4. Trifluoromethylthiolation of indole in the presence of radical inhibitors. Reaction conditions: indole (0.1 mmol), reagent **5** (1.1 equiv), sodium chloride (10 mol%), radical inhibitor (0.5 equiv), DMF (0.5 mL), 90 °C, 14 h. Yields were determined by ^{19}F NMR spectroscopy with (trifluoromethoxy)benzene as internal standard.

In light of previous reports,[17a,21] we propose that catalytic amounts of chloride acting as a Lewis base lead to the in situ formation of highly reactive trifluoromethylsulfenyl chloride (CF_3SCl). The latter subsequently undergoes an electrophilic aromatic substitution reaction with the N-heteroarene, yielding the desired trifluoromethylthiolated product (Scheme 5).[10a]

Monitoring the trifluoromethylthiolation of 2-phenylpyrrole by ^{19}F NMR spectroscopy (470 MHz, [D_6]DMSO), we observed the continuous decrease of the signal from reagent **5** ($\delta = -48.4$ ppm), whereas the signal from the product ($\delta = -44.6$ ppm) increased. However, neither CF_3SCl nor any related intermediate were detected, which may be attributed to its high reactivity. Repeating the reaction in the absence of 2-phe-



Scheme 5. Proposed mechanism (sodium cation omitted for clarity).

nylpyrrole, an equilibrium formed between reagent **5** and CF_3SSCF_3 ($\delta = -45.0$ ppm). Upon addition of an excess of 2-phenylpyrrole to this mixture, product formation occurred with reagent **5** being continuously consumed, while the amount of CF_3SSCF_3 remained constant. Upon complete consumption of reagent **5**, a comparatively very slow conversion of disulfide, with simultaneous formation of the product, was observed. Thus, CF_3SSCF_3, although capable of forming the product, appears not to be the reactive species in this transformation under standard conditions.

In summary, a general transition metal-free method for the trifluoromethylthiolation of a range of diverse biologically relevant N-heteroarenes was developed, employing sodium chloride as a cheap and simple catalyst. The transformation is robust and exhibits a broad functional group tolerance. Thus, it appears to be an appropriate methodology for application in the fields of pharmaceutical and agrochemical chemistry.

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Keywords: electrophilic substitution · N-heterocycles · sodium chloride · synthetic methods · trifluoromethylthiolation

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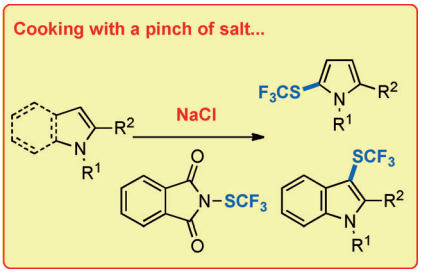
Transition Metal-Free Trifluoromethylthiolation of N-Heteroarenes



A pinch of salt: A general and efficient methodology for the direct transition metal-free trifluoromethylthiolation of a broad range of biologically relevant N-heteroarenes is reported employing abundant sodium chloride as the catalyst. This method is operationally simple, exhibits high functional group tolerance, and does not require protecting groups.