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Direct N-Trifluoromethylation

Direct Electrophilic N-Trifluoromethylation of Azoles by a Hypervalent Iodine Reagent**

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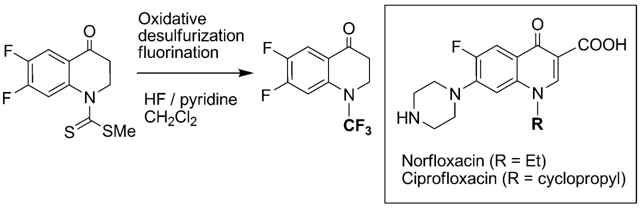
The importance of fluorinated molecules in the chemical sciences has been rapidly increasing in recent years. It is estimated that the share of active ingredients containing at least one fluorine atom in newly marketed crop protection agents and pharmaceuticals amounts to 30–40% and nearly 20%, respectively. Furthermore, half of the top ten best-selling prescription drugs in 2005 are fluorinated molecules.[1] However, an extended database search showed that less than ten N-trifluoromethylated compounds have been tested as biologically active compounds for humans,[2] and the CCDC reveals only 54 crystallographically characterized NCF_3 derivatives,[3] most of which are perfluorinated alkyl amines. In view of the strongly electron-withdrawing nature of the trifluoromethyl group, trifluoromethylamines are anticipated to be much less basic and less nucleophilic than the corresponding methylamines.[4] Hence, their physical, chemical, and/or biological properties should be remarkably different.

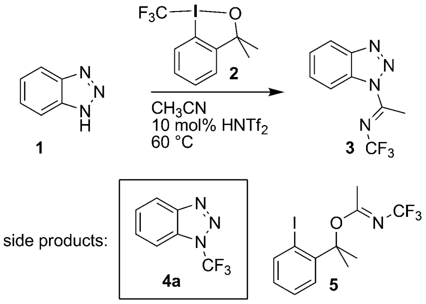
In a stand-alone medicinal chemistry contribution Asahina et al.[5] formally replaced the alkyl substituent on the 4-quinolone nitrogen atom of Norfloxacin and Ciprofloxacin, two important chemotherapeutical antibacterial agents, by a CF_3 group, thereby showing that, in this case, the trifluoromethyl group exerts an effect comparable to that of a simple methyl group with respect to the antibacterial properties. The CF_3 substituent was introduced by an oxidative desulfurization–fluorination procedure on a corresponding dithiocarbamate (see Scheme 1).

This method, first described by Hiyama et al.,[6] is rather convenient for the generation of the NCF_3 unit because it uses fluoride sources as mild as $TBAH_2F_3$ (TBA = tetrabutylammonium), though more aggressive reagents such as HF/pyridine may be required. However, it is safe to say that N-trifluoromethylated compounds are still rather rare and scarcely studied. In 2007 Umemoto and co-workers reported the direct trifluoromethylation of amines, anilines, and pyridines[7] as the first example of a direct N-trifluoromethylation. However, the electrophilic CF_3 source used in such reactions is an unstable and very reactive *O*-(trifluoromethyl)dibenzofuranium salt with inherent shortcomings.



Scheme 1. A rare example of an N-trifluoromethyl intermediate used in the preparation of corresponding derivatives of biologically active compounds.

We recently reported the discovery of a Ritter-type reaction leading to the formation of N-trifluoromethylated imines by the acid-catalyzed electrophilic trifluoromethylation of nitriles in the presence of azoles such as benzotriazole (**1**), indazole, and pyrazoles.[8] The trifluoromethyl group is transferred by a hypervalent iodine reagent (**2**) under straightforward reaction conditions, as illustrated by the example in Scheme 2. Compounds of type **2** have been previously shown to be the reagent of choice for the electrophilic trifluoromethylation of a variety of substrates[9] and are being used increasingly by several research groups.[10]



Scheme 2. Synthesis of **3** under acid-catalyzed conditions.

The observation of *N*-trifluoromethylbenzotriazole (**4a**)[11] as a side product of the Ritter-type reaction indicates that the direct N-trifluoromethylation of an azole with reagents of type **2** is indeed possible. Such a reaction is potentially useful and desirable, but still unknown as a viable synthetic protocol.

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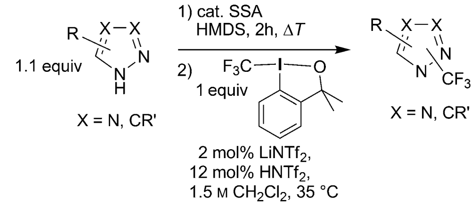
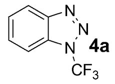
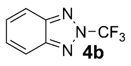
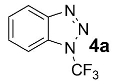
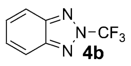
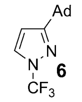
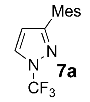
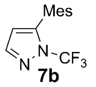
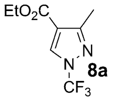
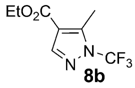
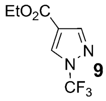
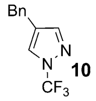
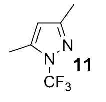
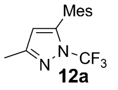
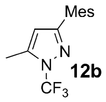
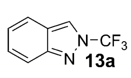
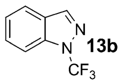
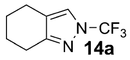
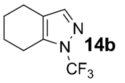
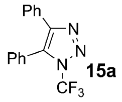
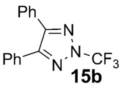
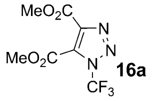
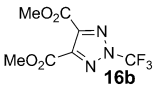
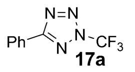
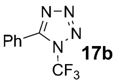
We disclose here an efficient route for the direct N-trifluoromethylation of azoles. Optimization of the reaction conditions for benzotriazole (vide infra) led to the formation of **4a** as the main product in excellent yield. Optimized conditions consist of the in situ silylation of the substrate by 1,1,1,3,3,3-hexamethyldisilazane (HMDS) in the presence of catalytic silica sulfuric acid (SSA),[12] followed by trifluoromethylation in highly concentrated CH_2Cl_2 solution at 35 °C in the presence of a catalytic amount of $HNTf_2$ and $LiNTf_2$ (Tf = trifluoromethanesulfonyl). These conditions were successfully applied to a variety of different azoles, such as indazoles, pyrazoles, triazoles, as well as tetrazoles, as shown in Table 1.

Table 1: Product scope for the direct N-trifluoromethylation of azoles.



Entry	Major product	Minor product	Yield[a] [%] major/minor product	
1	 **4a**	 **4b**	84:2	(64:–)
2[b]	 **4a**	 **4b**	48:46	(44:24)
3	 **6**		69	(62)
4[c]	 **7a**	 **7b**	34:28	(30:25)[d]
5	 **8a**	 **8b**	35:7	(33:–)[e]
6[b]	 **9**		26	(<13)
7	 **10**		69	(66)
8[f]	 **11**		68	(15)
9	 **12a**	 **12b**	48:20	(40:12)
10	 **13a**	 **13b**	68:2	(39:–)[g]
11	 **14a**	 **14b**	49:29	(30:12)[h]
12	 **15a**	 **15b**	42:11	(21:11)
13	 **16a**	 **16b**	46:10	(24:–)[i]
14[j]	 **17a**	 **17b**	42:18	(18:10)

[a] Yields were calculated based on the integration of ^{19}F NMR signals using $C_6H_5CF_3$ as an internal standard. Yields of isolated products are given in brackets (significant differences are mainly due to losses during isolation because of volatility). [b] 5 mol% $BF_3{\cdot}Et_2O$ instead of $LiNTf_2$ and $HNTf_2$. [c] 14 mol% $HNTf_2$. [d] **7b** contained 3% **7a**, 15% yield as single regioisomer after sublimation. [e] **8a** contained 5% **8b**. [f] Synthesized from 1-trimethylsilyl-3,5-dimethylpyrazole. [g] **13a** contained < 2% **13b**. [h] **14b** contained ≤ 5% **14a**. [i] **16a** contained 8% **16b**. [j] RT instead of 35 °C, no $HNTf_2$ addition.

Thus, in the case of pyrazoles, the trifluoromethylation reaction tolerates various substitution patterns and a range of different substituents. Alkyl-, aryl-, and alkoxycarbonyl-substituted pyrazoles all undergo the desired reaction. As illustrated by the results in Table 1, entries 5–7, heterocycles with electron-donating groups afford higher yields of N-trifluoromethylated products, whereas electron-withdrawing substituents lead to lower yields. This can be explained by the fact that electron-poor groups lead to slower reactions, allowing side-product formation, mainly decomposition of the reagent, to predominate. Isomeric mixtures that can be resolved by flash chromatography are typically obtained from reactions of nonsymmetrically substituted pyrazoles. Indazoles (Table 1, entries 10 and 11) are preferentially trifluoromethylated at the N2 position. Monocyclic triazoles (Table 1, entries 12 and 13) with aryl or alkoxycarbonyl substituents lead to isomeric mixtures when they are trifluoromethylated under the standard conditions. 5-Phenyltetrazole can also be N-trifluoromethylated; however, the reaction temperature should be lowered to room temperature, and no acid is needed to obtain good yields (Table 1, entry 14).

The structures of the regioisomers of the newly prepared compounds were assigned using 2D heteronuclear NMR spectroscopic techniques. As a representative example, the $^{19}F^{1}H$ HOESY spectra of the major and minor isomer of N-trifluoromethylated 4,5,6,7-tetrahydro-1*H*-indazole are shown in Figure 1. The spectrum of the major isomer **14a** shows the contact of the CF_3 group with the unique proton of the heteroaromatic ring, whereas in the case of the minor regioisomer **14b**, the contact between the trifluoromethyl group and an aliphatic proton is observed.

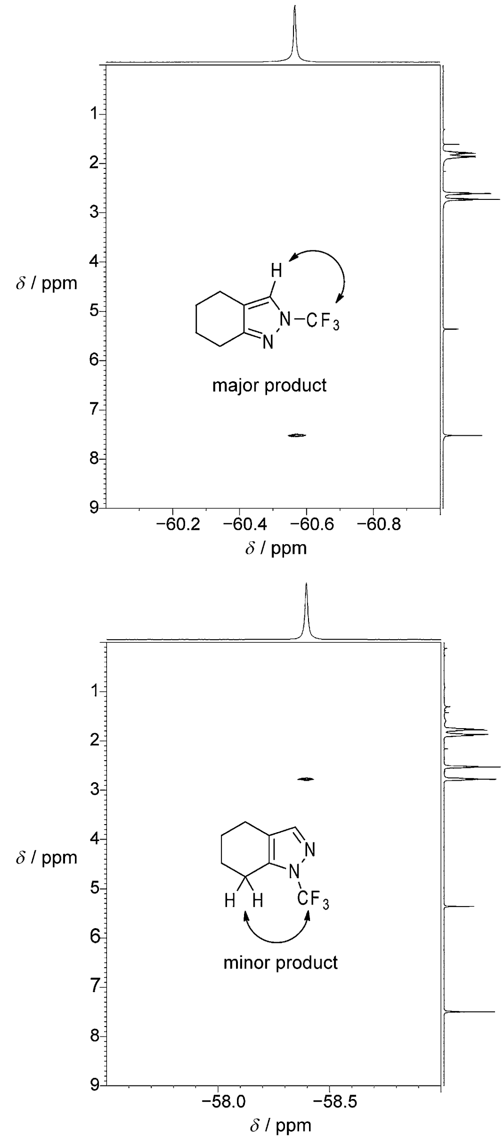


Figure 1. 400 MHz $^{19}F^{1}H$ HOESY spectrum (CD_2Cl_2) of major (**14a**) and minor (**14b**) products from the N-trifluoromethylation of 1*H*-tetrahydroindazole.

In addition to $^{19}F^{1}H$ HOESY spectra, $^{19}F^{15}N$ HMBC spectra were measured to confirm the connectivity of the trifluoromethyl group to a ring nitrogen. An added benefit of this method was the unambiguous assignment of the ^{15}N NMR chemical shifts to the corresponding nitrogen atoms and the determination of the $^{2}J(N,F)$ coupling constant in the range of roughly 20 Hz (see the Supporting Information). In some cases, in addition to the NMR analysis, the structure of the products obtained was determined by single-crystal X-ray analysis. This was the case, for example, for **8a** and **7b** (Figure 2).

As mentioned above, the important steps in optimizing this new direct electrophilic N-trifluoromethylation were carried out using the model substrate benzotriazole (Table 2). Obviously, to avoid the formation of Ritter-type products nitrile solvents should not be used.

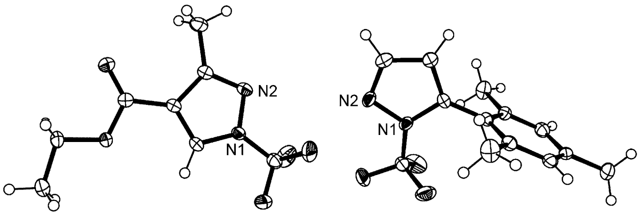
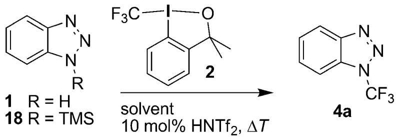


Figure 2. ORTEP representation of the structures of ethyl **8a** (left) and **7b** (right); thermal ellipsoids at the 50% probability level.

Table 2: Reaction optimization for product **4a**.



Entry	Molar ratio **1**(**18**)/**2**	R	Solvent	*T* [°C]	Conc.[a] [M]	**4a**[b] [%]
1[c]	3	H	CH_3CN	60	0.1	16
2[c]	1.5	H	DCE	60	0.1	41
3	1.5	H	CS_2	60	1.5	58
4	1.5	H	CH_2Cl_2	35	0.1	6
5	1.5	H	CH_2Cl_2	35	1.5	16
6	1.5	TMS	CH_2Cl_2	35	0.1	42
7	1.5	TMS	CH_2Cl_2	35	0.5	70
8	1.5	TMS	CH_2Cl_2	35	1.0	79
9	1.5	TMS	CH_2Cl_2	35	1.5	81
10	1.1	TMS	CH_2Cl_2	35	1.5	73
11	1.1	TMS	CH_2Cl_2	35	1.5	87[d]

[a] Concentration of reagent **2**. [b] Yields were calculated based on the integration of ^{19}F NMR signals using $C_6H_5CF_3$ as the internal standard. [c] From Ref. [8]. [d] Addition of $LiNTf_2$ before the addition of reagent and with 12 mol% $HNTf_2$ instead of 10 mol%.

In general, relatively high temperatures were needed for the reaction of unactivated benzotriazole to occur. Thus, moderate yields were observed when the reaction was carried out in 1,2-dichloroethane at 60 °C (Table 2, entry 2). When the reaction was conducted at the same temperature but with high concentrations in CS_2, up to 60% yield was obtained (Table 2, entry 3). Given that reagent decomposition becomes significant at elevated temperatures, it was important to find conditions under which the reaction would still take place at reasonable rates but at temperatures significantly below 60 °C. However, at 35 °C only low yields were observed when the trifluoromethylation was carried out in CH_2Cl_2 (Table 2, entry 4). Slightly higher yields were obtained when the concentration of the reaction mixture was increased by a factor of 15, while maintaining the initial substrate/reagent molar ratio of 1.5 (Table 2, entry 5). Based on previous findings concerning the reaction of silylated phosphines,[9n] the reaction was carried out with silylated benzotriazole (**18**) at 35 °C. This afforded 42% yield (Table 2, entry 6). Increasing the concentration gradually improved the yield of **4a** to an excellent 81% (Table 2, entries 7–9). Finally, using only a slight excess of substrate (1.1 equiv instead of 1.5) led to a minor reduction in yield (Table 1, entry 10)

In order to further optimize the reaction conditions, we monitored the reaction leading to **4a** by ^{19}F NMR spectros-

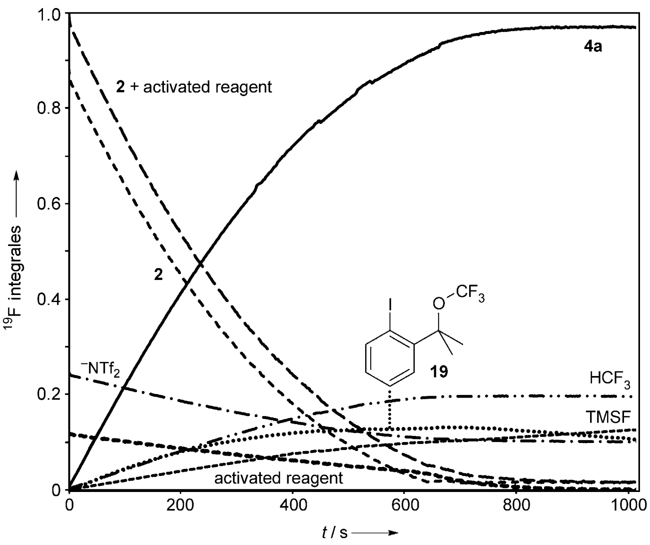


Figure 3. ^{19}F NMR reaction profile (arbitrary integral units) for the electrophilic trifluoromethylation of **18** with 1.5 M **2** in CD_2Cl_2 using 12 mol% $HNTf_2$ as the catalyst.

copy (Figure 3). Thus, both the exponential decay of the reagent as well as the exponential formation of the product were observed. On the basis of the ^{19}F NMR chemical shifts, a species suspected to be protonated or silylated, that is, activated reagent **2**, is present in catalytic amounts during the reaction. A diminishing concentration of this species seems to be related to the formation of trimethylsilyl fluoride (TMSF). Further side products formed during the reaction include HCF_3 as well as the unstable trifluoromethylated benzyl alcohol **19** formed as a decomposition product of **2**. Finally, the concentration of the acid catalyst $HNTf_2$ slightly decreases over the course of the reaction.

Based on the likely correlation between the decay of the activated reagent and the generation of TMSF, we postulate that the formation of fluoride might interfere with the reaction. Therefore, we conducted additional ^{19}F NMR experiments in which the reaction was run using 5 mol% $BF_3{\cdot}Et_2O$ as the catalyst instead of $HNTf_2$ (see the Supporting Information for the corresponding reaction profile). Again, the exponential decay of reagent was observed but instead of the exponential formation of only the N1-substituted product **4a** also the N2-trifluoromethylated benzotriazole **4b** was observed. These two products form at essentially identical rates and the overall yield of N-trifluoromethylated products reached 94%, with less than 6% total yield of side products (see Table 1, entry 2 for the in situ silylation experiment). The most evident difference in the outcome of these trifluoromethylation reactions using different catalysts is the ratio of the two isomeric products. This was to be expected since, in general, the isomeric distributions observed in, for example, alkylation reactions of heterocycles are highly sensitive to the specific reaction conditions.[13,14]

As promising as $BF_3{\cdot}Et_2O$ was as a catalyst for the reaction of **18** with **2**, it was significantly less effective in combination with other N-silylated nitrogen heterocycles. Nevertheless, the application of $BF_3{\cdot}Et_2O$ in the aforementioned experiments demonstrated the beneficial effect of a potential fluoride scavenger. Therefore, we used, as an alternative, the lithium salt $LiNTf_2$ as a less Lewis acidic fluoride scavenger compatible with a wider range of substrates. To this end, an experiment (Table 2, entry 11) was carried out in which 2 mol% $LiNTf_2$ was added to the solution containing **18** prior to the addition of **2** and subsequently $HNTf_2$. The presence of $LiNTf_2$ at the onset of the reaction seems to be crucial for improving the overall yield of N-trifluoromethylation and leads to the formation of **4a** in excellent 87% yield.

Since silylated heterocycles are moisture sensitive, we opted for an in situ reaction sequence in order to avoid having to isolate the silylated intermediates. Thus, **1** was heated at reflux in HMDS with a catalytic amount of silica sulfuric acid (SSA).[12] After this treatment, full derivatization was confirmed by NMR analysis. SSA was readily removed by filtration and the solvent was replaced with CH_2Cl_2 prior to trifluoromethylation. Only a minor decrease in the yield of **4a** was observed when the in situ silylation procedure was used (compare entry 1 in Table 1 to entry 11 in Table 2). On a small scale, the second reaction step was usually carried out in a glovebox for convenience. This simplified the addition of hygroscopic $HNTf_2$ to water-sensitive silylated azoles. However, on a larger scale the reaction may be conducted using standard Schlenk techniques and $HNTf_2$ stock solutions affording similar results.

In conclusion, we have developed a mild and effective method for the direct electrophilic N-trifluoromethylation of a series of variously substituted electron-rich nitrogen heterocycles. Higher yields are obtained when TMS-activated azoles are used as substrates. In situ silylation is a viable simplification, thus allowing the synthesis of the desired N-trifluoromethyl products in moderate to high yields without the isolation of the silylated intermediates. The novel compounds were fully characterized inter alia by 2D NMR spectroscopic methods in order to ascertain the isomeric distribution and, in cases where crystalline products were obtained, X-ray diffraction studies were carried out. We now have ready access to a wide variety of stable NCF_3 compounds which may be of significant interest across the chemical sciences.

Experimental Section

General procedure for the N-trifluoromethylation of azoles: A flame-dried 25 mL two-neck flask with reflux condenser was charged with silica sulfuric acid (SSA, 2.8 mg) and azole (0.55 mmol, 1.1 equiv). HMDS (5.5 mL) was added and the mixture was heated at reflux for 2 h. To remove SSA, the mixture was cooled to 100°C and the solution was filtered off into a 20 mL Young Schlenk by using a filter canula and the original reaction vessel was rinsed with toluene (3 × 0.5 mL). After the collected filtrate and rinses were cooled to room temperature all volatile compounds were removed under reduced pressure (15 mbar, 30 min 10^{-3} mbar). In a glovebox the intermediate, usually a dynamic isomeric mixture of N-silylated heterocycles, was redissolved in CH_2Cl_2 (0.33 mL) and $LiNTf_2$ (2.9 mg, 0.01 mmol, 2 mol%) was added. After the reaction mixture was shaken, **2**[9a] (165 mg, 0.5 mmol) and subsequently $HNTf_2$ (16.9 mg, 0.06 mmol, 12 mol%) were added and the neck of the vessel was rinsed with CH_2Cl_2 (50 μL). The resulting clear solution was then stirred at 35°C (bath temperature) in a closed Young Schlenk for 15 h. The solvent was then removed under reduced pressure (650 mbar, 40 °C).

CCDC 841859, 841860, 841861, 841862 ,and 843429 (compounds **7b**, **6**, **8a**, **12a**, and **15a**, respectively) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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