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A Facile and Inexpensive Way to Synthesize N-trifluoromethyl Compounds

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A facile way to introduce CF_3 groups on a large variety of secondary amines has been developed, avoiding expensive and hazardous reagents. The advantage of the method could be demonstrated by obtaining crystalline *tert*-butyl 4-(trifluoromethyl)piperazine-1-carboxylate, a compound that previously only had been obtained as an oil. A major problem is the extreme sensitivity of these compounds towards moisture.

Introduction

Fluorination of organic compounds has become important over the last years, mainly due to applications in pharmaceutical chemistry.[1] Even though many of these compounds contain nitrogen, it is quite surprising that trifluoromethyl amines so far received little attention. As pointed out recently by Schoenebeck and co-workers, this might be a consequence of the lack of safe, general and highyielding methods to access these compounds together with difficulties regarding their purification.[2] While trying to solve a problem in our research, the stabilization of high valent metal oxido complexes, we established a useful and facile synthetic method to substitute amine hydrogen atoms with CF_3 groups that we report herein.

Results and Discussion

When ozone was reacted with tmc transition metal complexes (tmc = 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclo-tetradecane, Figure 1a, **1**),[3] we observed hydroxylation of one of the methyl groups of tmc (Figure 1b, **2**). To avoid this, we decided to substitute the methyl groups with CF_3 groups (Figure 1c, **3**) and developed a synthetic strategy to achieve this.

Being aware of quite expensive and/or hazardous reagents to perform the fluorination reaction and the need of bulk amounts of ligand, we looked for an alternative synthetic procedure to achieve this substitution.[1b] Our first approach, a combination based on previous work by the groups of Tyrra and Tamejiro (method a, Scheme 1)[4] worked to some extent.

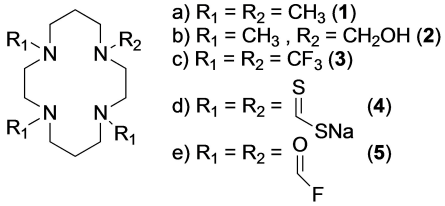
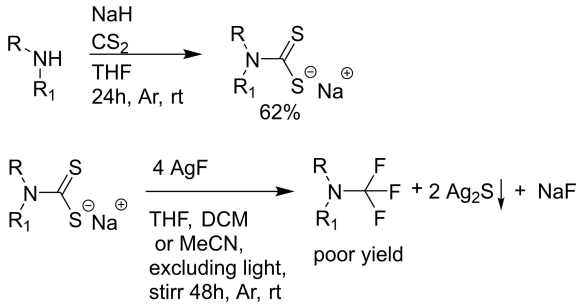


Figure 1. Derivatives of the macrocycle cyclam ($R_1 = R_2 = H$) discussed in the text.



Scheme 1. Method a, based on a combination of previous work by Tyrra and Tamejiro.[4] R, R_1 = different carbon chains.

However, the yield of the product was very low and serious problems with side products were observed.

During the synthesis, it was possible to crystallize the intermediate, the sodium dithiocarbamate-salt (Figure 1d, **4**), and its molecular structure is reported in the Supporting Information (Figure S1). Several water molecules were found in the crystal lattice. In an effort to improve the synthesis, we furthermore tried to methylate the dithiocarbamate with methyl iodide[5] to stabilize the leaving group as a thiomethylate silver salt,[1b,4b] but this method (method b) also only worked to a very small extent, due to over methylation of the whole cyclam scaffold which cannot be avoided under these conditions.

It turned out to be quite difficult to find the right conditions for to obtain **3** in good yields. Trying to improve the synthesis, we at first applied diisopropylethylamine (DIPEA) as an additional base (a known procedure applied previously), but it

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turned out that in this case too many side reactions occurred. However, we observed that instead of using an amine base, the fluoride anion of silver(I) fluoride already could act as a base. Furthermore, while the reaction in principle is a one pot synthesis, it is important to conduct the reaction in two consecutive steps when adding silver(I) fluoride. Otherwise, decomposition was observed, and mainly side products formed. However, by applying chlorodithiophenylformiate as an electrophile (method c, Scheme 2) we successfully obtained **3** in decent yields.

The molecular structure of **3** is presented in Figure 2 (crystallographic data are reported in the Supporting Information).

While being successful with the synthesis of **3**, it unfortunately turned out, that it was not useful as a ligand for our purpose. The trifluoromethylation of the cyclam ligand had decreased the Lewis basicity of the ligand to such an extent that no complex formation with transition metal salts could be achieved anymore.

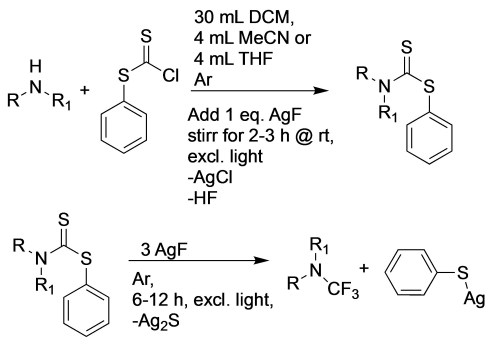
Furthermore, in the process to work with this compound, it was observed that **3** was extremely sensitive towards moisture leading to lower yields already in the synthesis. During our first preparation of the ligand and being unaware of the sensitivity to moisture, the glassware was not heated prior to the reaction. As a consequence, **3** was hydrolyzed and formed an amino-fluoro carbonyl compound instead (Figure 1e, **5**). This observation could be furthermore supported by adding water to dry **3** with the same outcome. The molecular structure of **5** is presented in Figure 3 (crystallographic data are reported in the Supporting Information).

While monitoring the reaction with MS, when water still was present, the decomposition of the N-trifluoromethyl groups could be observed according to a well know mechanism (see Supporting Information).[1c,6]

While not being successful for achieving our goal to stabilize high valent oxido complexes by introducing CF_3-groups in our ligand system, we think that our method is useful in general for the synthesis of trifluoromethyl amines. In contrast to previously published and improved methods[1b,2] our synthesis was facile and is based on a commercially available and an inexpensive electrophile that is easily handled in combination with AgF as the fluorinating agent.

To test our method (method c), we applied e.g. *N*-methyl aniline, proline *tert*-butyl ester, indoline and 1-(tert-butoxycarbonyl)piperazine and observed the *N*-CF_3-formation in MS spectra. However, isolation and purification turned out to be difficult due to the general problem of hydrolysis of such compounds.[1c] In addition, side products were observed by the reaction of the electrophile with its own decomposition product thiophenolate and subsequent CF_3-methylation that could be observed in MS spectra (see Supporting Information, compounds **6a**–**6d**). Observed side products are presented in Figure 4. Compounds **6a**–**6d** also formed already by heating (ca. 50 °C) solely the electrophile with four equivalents of AgF in a mixture of THF and acetonitrile.

The unexpected CF_3-substitution of the side products in aryl position (Figure 4) motivated us to test some further substrates for aryl CF_3 methylation. Based on our observation together with a previous publication on the substitution of aryl-substrates with chlorodithiophenylformiate and a Lewis acid,[7] we decided to apply method c (Scheme 2), slightly modified. $Zn(OTf)_2$ or AgOTf were used in a first step as a Lewis



Scheme 2. Method c, improved new method for the synthesis of trifluoromethyl amines (R, R_1 = different carbon chains, any secondary amine).

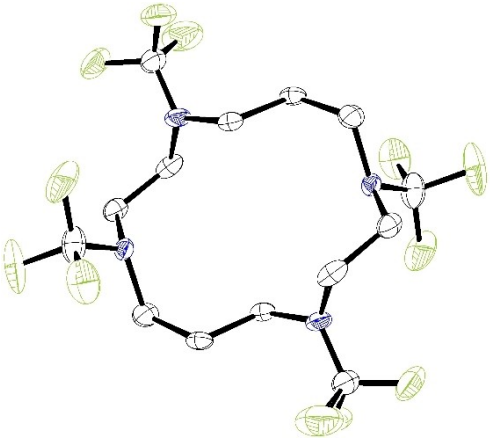


Figure 2. Molecular structure of **3** (Figure 1c).

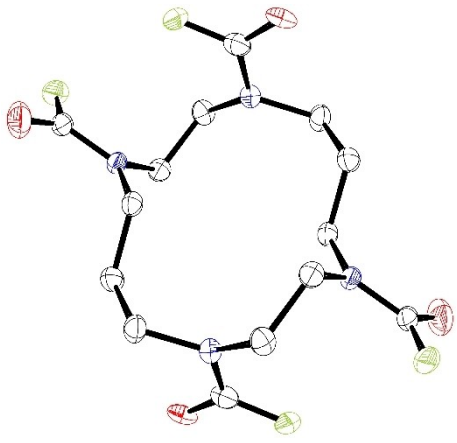


Figure 3. Molecular structure of **5** (Figure 1e).

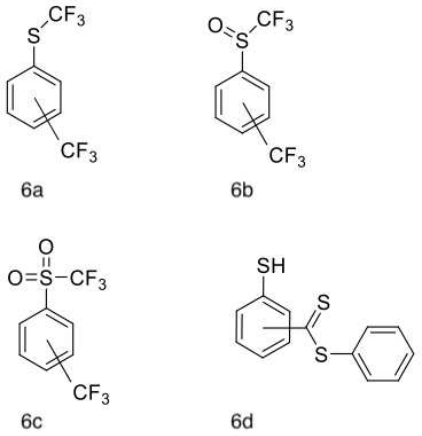


Figure 4. Side products derived from the reaction of the electrophile chlorodithiophenyformiate: trifluoromethylphenyl trifluoromethyl sulfane (**6a**), trifluoromethylphenyl trifluoromethyl sulfoxide (**6b**), trifluoromethylphenyl trifluoromethyl sulfone (**6c**) and 1-thiophenyl 4-methylbenzenecarbodithioate (**6d**).

acid for different substrates such as e.g. *N,N*-dimethylaniline, 1,3-dimethoxybenzene, 1-chloro-3,5-dimethoxybenzene, and 3-methoxytoluene. According to MS measurements, C–CF_3 analogues for all substrates were observed (see Supporting Information for compounds **7a**, **8a**, **9a** and **10a**). However, while the reaction worked, in principle, again side products were observed, and the products could not be isolated yet. An optimization of the synthesis would be necessary to obtain these products. The problem with the side reactions might be caused by water contamination that intervenes with the fluorination step. For all these substrates, the intermediates (dithioesters) were identified (see Supporting Information **7b**, **8b**, **9b** and **10b**) and in some cases even amino carbonyl fluorides could be observed.

That chlorodithiophenylformiate is a useful electrophile for these reactions was observed by crystallizing one of the intermediates (dithiocarbamate), **11**, and its molecular structure is shown in Figure 5.

A similar process had been observed previously for the synthesis of CF_3-ethers,[4b,8] however, to the best of our knowledge, the reaction of monomeric N-dithiocarbamate-organyls and their conversion via AgF to N-CF_3 groups had not been reported so far.[1b]

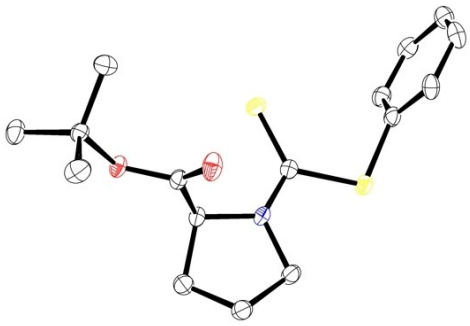


Figure 5. Molecular structure of *tert*-butyl 1-(phenylthiocarbonothioyl)-1*H*-pyrrole-2-carboxylate (**11**).

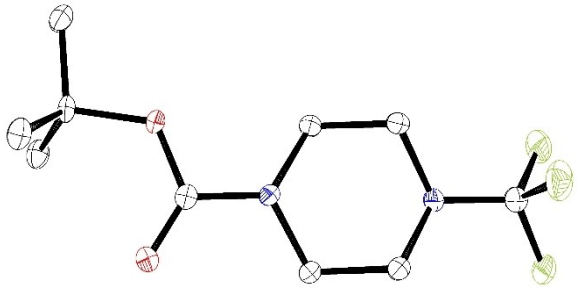


Figure 6. Molecular structure of *tert*-butyl 4-(trifluoromethyl)piperazine-1-carboxylate (**13**).

For a real test of our procedure, we chose t*ert*-butyl piperazine-1-carboxylate (**12**) that had been used previously,[2,9] and successfully obtained the *N*-trifluoromethyl analogue **13** in decent yields with our method. In contrast to the former reports, in which the product was described as an oil, we could isolate it as a crystalline colorless substance, clearly demonstrating one of the advantages of our method for this particular substrate. The molecular structure of this compound is presented in Figure 6 (crystallographic data are reported in the Supporting Information). Here as well (as described above for **3**), moisture immediately did cause a reaction with water. The corresponding amino-fluoro carbonyl compound (**14**) that was formed could be structurally characterized (crystallographic data are reported in the Supporting Information).

Conclusion and Outlook

The main advantage of our method (to introduce CF_3 groups on a large variety of secondary amines) in comparison with synthetic protocols in the literature, is that we don't need to synthesize the CF_3 containing agent prior to its use. The precursor electrophile is commercially available and inexpensive. Furthermore, silver(I) fluoride that more recently has been recognized as a fluorinating agent is not expensive as well.[9–10] Sodium fluoride as a source of fluoride was intentionally excluded due to its ability to hydrolyze protective groups. In some cases, the reaction can be boosted by the application of suitable Lewis's acids, such as e.g. silver(I)-triflate[11] or Zn-$(OTf)_2$[12] might be used in combination with silver(I)-fluoride in a first step. We believe that it should be possible to improve the overall reaction, by variation of temperature and fluorination agents such as ZnF_2, which also could be applied.

Different to synthetic protocols described previously starting materials are inexpensive, less toxic and atom efficient with regard to the fluorination agent. Furthermore, we obtained *tert*-butyl 4-(trifluoromethyl)piperazine-1-carboxylate (**13**) as a crystalline solid in contrast to oils that had been reported previously demonstrating a clean reaction procedure. Quite important, it is not necessary to use corrosive gases and

common glass equipment can be applied without further special safety issues.

With regard to our experience, it should be pointed out that substrates containing a carbonic acid group need to be protected by a *tert-butyl* group instead of a methyl group. Otherwise, cleavage is observed.

As an outlook, we believe it should be possible to reverse the polarity by turning the electrophile to a nucleophile in a Grignard reaction and herewith open further applications.

Deposition Numbers 2151922–2151927 contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint deposition service of the Cambridge Crystallographic Data Center and Fachinformationszentrum Karlsruhe http://www.ccdc.cam.ac.uk/structures.

Supporting Information Summary

The supporting information provides experimental details, crystallographic data as well as spectroscopic characterizations (NMR and ESI-MS spectra).

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Amines · Cyclam · Fluorinated Ligands · Macrocycles · *N*-trifluoromethyl compounds

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