EurJOC European Journal of Organic Chemistry

SHORT COMMUNICATION

DOI: 10.1002/ejoc.201402225

O-Trifluoromethylation of *N*,*N*-Disubstituted Hydroxylamines with Hypervalent Iodine Reagents

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Keywords: Synthetic methods / Trifluoromethylation / Chemoselectivity / Hypervalent compounds / Iodine

A mild trifluoromethylation reaction of *N*,*N*-disubstituted hydroxylamines that is tolerant towards a variety of functional groups, including nitriles, alcohols, ketones, esters, amides, imides, and nitrogen heterocycles, is reported. The key feature of this reaction is the activation of the CF_3 reagent with either trimethylsilyl triflate or $LiClO_4$ and partial or full deprotonation of the substrate with tetramethylguanidine or lithium diisopropylamide. Products were obtained in up to 80 % yield. Preliminary mechanistic studies suggested that the reaction follows a radical pathway in which the deprotonated hydroxylamine and a Lewis or Brønsted acid activated CF_3 reagent engages in a single-electron-transfer step to generate a pair of radicals that recombine to afford the desired product. The trifluoromethylation procedure was successfully used in the modification of secondary nitrogen groups of pharmaceutically relevant targets (Fluoxetine and Mefloquine), which afforded new derivatives containing a novel *N*-trifluoromethoxy moiety.

Introduction

Organofluorine chemistry has recently witnessed increased interest from the synthetic community. Among other fields, medicinal and crop protection chemistry could take advantage of new and more efficient methodologies for the introduction of rare or even so far unknown fluorinated functional groups.[1] Despite the growing significance of trifluoromethoxy-containing molecules in such research areas, methods for direct and chemoselective *O*-trifluoromethylation are still underdeveloped. Herein, we describe the trifluoromethylation of *N*,*N*-dialkylhydroxylamines by using hypervalent iodine(III) reagents **1** and **2**, which were developed several years ago in our group[2] (Figure 1).

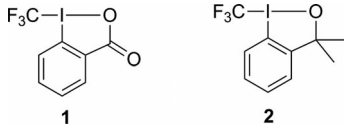

Figure 1. Iodobenzoic acid derived CF_3 reagent **1** ("acid reagent") and iodophenyl propyl alcohol derived reagent **2** ("alcohol reagent").

Several recent studies on trifluoromethylation reactions with **1** and **2** demonstrated the ability of these reagents to produce the CF_3 radical through single-electron transfer (SET) in the presence of a one-electron donor.[3] The formation of this radical was proven by its trapping with a persistent radical such as (2,2,6,6-tetramethylpiperidine)-*N*-oxyl (TEMPO). The coupling product TEMPO–CF_3 could be detected by both GC–MS and ^{19}F NMR spectroscopy.[4] A recent report by Studer et al. revealed the ability of the TEMPO sodium salt to engage in tandem radical fluoroalkylation–aminooxylation of styrene derivatives.[5] These findings prompted us to examine the reactivity of hypervalent iodine reagents **1** and **2** towards *N*,*N*-dialkylhydroxylamines in the absence of any other reactive alkene species.

Results and Discussion

Thus, upon adding Hünig's base (1 equiv.) to a well-stirred suspension of *N*,*N*-dibenzylhydroxylamine (**3a**) and **1** (1.4 equiv.) in CH_2Cl_2 at room temperature, an exothermic reaction ensued, which led to a yellowish solution. TLC examination of the reaction mixture revealed full consumption of the substrate. Analysis by ^{19}F NMR spectroscopy indicated the formation of a new compound that was confirmed to be *N*,*N*-dibenzyl-*O*-trifluoromethylhydroxylamine (**4a**).

Pleased by this initial successful experiment, we embarked on an optimization study to find the most suitable CF_3 reagent, temperature, solvent, mode of addition, and additives. The corresponding results are collected in Table 1.

It is apparent that better results were obtained if **2** rather than **1** was used as the CF_3 source (Table 1, entry 1 vs. 3). Moreover, **2** could be used under neutral conditions,

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201402225.

Table 1. Optimizing the conditions for the trifluoromethylation of **3a**.

Entry	[**3a**]	Solvent	CF_3 source (equiv.)	Additive (equiv.)	*T* [°C]	Yield [%]
1	0.45	CH_2Cl_2	**1** (1.4)	$(iPr)_2NEt$ (1)	r.t.	61
2[a]	0.45	CH_2Cl_2	**1** (1.4)	–	r.t.	48
3	0.45	CH_2Cl_2	**2** (1.4)	–	r.t.	87
4	0.45	CH_2Cl_2	**1** (1.4)	$(iPr)_2NEt$ (1)	0	43
5	0.45	CH_2Cl_2	**2** (1.2)	–	r.t.	78
6	0.45	CH_2Cl_2	**2** (1.2)	–	0	66
7	0.32	MeOH	**2** (1.5)	–	r.t.	74
8	0.45	DMSO	**2** (1.5)	–	r.t.	34
9	0.45	MeCN	**2** (1.5)	–	r.t.	80
10[b]	0.47	AcMe	**2** (1.5)	–	r.t.	56
11[b]	0.47	THF	**2** (1.5)	–	r.t.	26
12[b]	0.47	$CHCl_3$	**2** (1.5)	–	r.t.	59
13[b]	0.47	EtOAc	**2** (1.5)	–	r.t.	60
14	0.11	CH_2Cl_2	**1** (1.4)	$LiClO_4$ (0.2)	0	0
15	0.11	CH_2Cl_2	**1** (1.4)	$Mg(ClO_4)_2$ (0.2)	0	0
16	0.11	CH_2Cl_2	**1** (1.4)	$Zn(NTf_2)_2$ (0.2)	0	0
17	0.45	CH_2Cl_2	**1** (1.4)	$(iPr)_2NEt$ (0.1)	r.t.	63
18[c]	0.23	THF	**1** (1.4)	*n*BuLi (1)	–80	27
19	0.23	THF	**1** (1.4)	LiOH (1)	0	22
20	0.23	THF	**1** (1.4)	LiO*t*Bu (1)	0	54
21[b]	0.47	CH_2Cl_2	**1** (1.5)	pyridine (0.1)	r.t.	58
22[b][c]	0.47	THF	**1** (1.5)	LDA (1)	–70 to r.t.	23
23[b]	0.27	MeCN	**2** (1.5)	$CuBr{\cdot}SMe_2$ (0.05)	–20	60

[a] Reaction time was 1 h. [b] The reaction was conducted on a 200 mg scale. [c] The CF_3 reagent was added last.

whereas for **1** the presence of an additional base proved to be crucial (Table 1, entry 1 vs. 2). We suspect that the dormant alkoxide base incorporated in **2**, albeit with reduced basicity owing to coordination to the iodonium center (pK_a of **2** in 2-methoxyethanol/water is 5.04[6]) contributes to a higher reaction rate. Subsequently, variation of the CF_3 reagent/substrate ratio showed that the reaction proceeded better if **2** was present in an excess amount and that the optimum loading lay in the range of 1.4–1.5 equiv. (Table 1, entry 3 vs. 5).

Independent of the CF_3 reagent used, the highest yields were observed at room temperature (Table 1, entries 1 and 3). If the reaction was started at a lower temperature, significantly worse results were obtained (Table 1, entries 4 and 6). The difference in the yields of reactions started at 0 and –80 °C was not significant. Furthermore, a slightly higher temperature (35 °C) did not improve the outcome. These trends are in contrast to those observed for the electrophilic trifluoromethylation of thiols in which the reaction must be performed at –80 °C to avoid oxidative coupling of the starting material.[7]

Although reactions performed in CH_2Cl_2 gave very good initial results, we felt that a systematic examination of the solvent effects on the system was needed. Experiments showed that moderate to good yields were achieved if the reaction was conducted in polar solvents (Table 1, entries 7–13). Interestingly, the yield decreased upon changing from CH_2Cl_2 to $CHCl_3$ (Table 1, entry 3 vs. 12), whereas DMSO and THF turned out to be unsuitable (Table 1, entries 8 and 11). The latter probably undergoes α-hydrogen abstraction under the reaction conditions, although we could not detect the corresponding α-trifluoromethylation product.

Finally, the influence of different additives was studied. It turned out that the presence of Lewis acids, even in substoichiometric amounts, completely inhibited the reaction (Table 1, entries 14–16; Tf = triflate). As mentioned above, a base was crucial for cases in which reagent **1** was used. However, the addition of an amine (10 mol-%) was enough to substantially improve the yield (Table 1, entry 17). Neutral nitrogen-centered bases (Table 1, entries 1, 17, and 21) worked well, but no significant difference was observed upon changing to lithium *tert*-butoxide (Table 1, entry 20). Interestingly, inferior results were obtained if *n*-butyllithium (Table 1, entry 18), lithium hydroxide (Table 1, entry 19), and lithium diisopropylamide (LDA; Table 1, entry 22) were used. In the first and last cases, however, the high reactivity of the base made it necessary to start the reaction at low temperature, and this very aspect mainly contributed to the failure of the reaction. Finally, if the reaction was performed with **1** in the presence of a catalytic amount of copper(I) (Table 1, entry 23), slightly inferior results were obtained, as compared to the additive-free case.

With these optimized conditions in hand, that is, **2** (1.4 equiv.) and Hünig's base (1 equiv.) in CH_2Cl_2 at room temperature, we examined the trifluoromethylation of additional substrates and focused on cyclic hydroxylamines. However, the reaction with *N*-hydroxy-1,2,3,4-tetrahydroisoquinoline (**3b**) gave an unexpected result. Under the standard conditions, **3b** not only underwent *O*-trifluoromethylation to **4b1** but also additional benzylic trifluoromethylation to give **4b2**, which was eventually isolated in 35% yield with 90% purity.

To overcome the double trifluoromethylation problem, an alternative procedure was needed. The idea behind such a modified protocol was to activate **1** or **2** with a suitable

Table 2. Screening of the activation conditions for the CF_3 reagent and substrate **3b** (*N*-hydroxy-1,2,3,4-tetrahydroisoquinoline).[a]

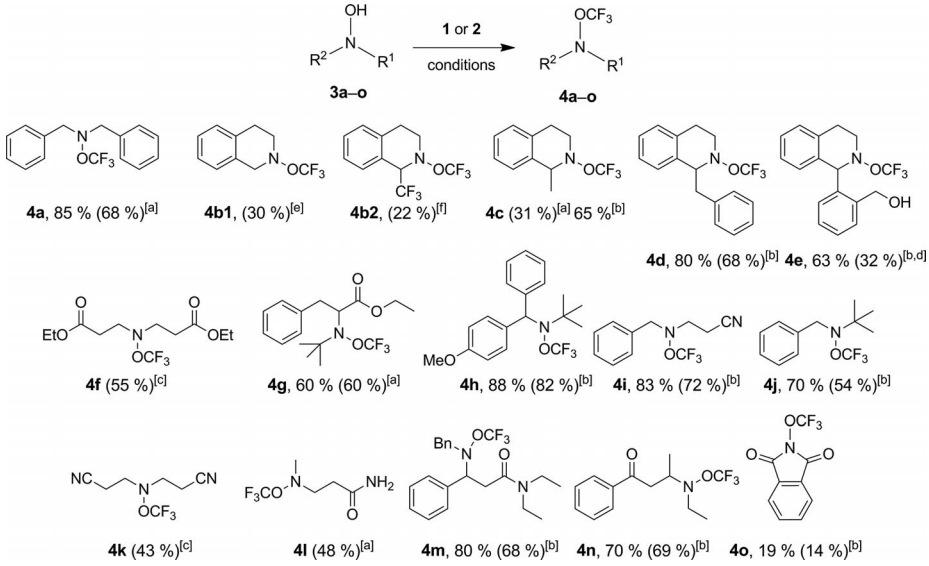
Entry	Solvent	CF_3 source (equiv.)	Additive (equiv.)	*T* [°C]	Yield [%] **4b1**	**4b2**
1[b]	THF	**2** (1.5)	LDA (1), $LiClO_4$ (1)	–20 to r.t.	4	0
2[b]	THF	**1** (1.5)	LDA (1), $LiClO_4$ (1)	–20 to r.t.	27	0
3[c]	CH_2Cl_2	**2** (1.5)	(iPr)$_2$NEt (1), TMSOTf (1.5)	–20 to r.t.	55	7
4[c]	CH_2Cl_2	**2** (1.1)	TMG (1.1), TMSOTf (1.1)	–78 to r.t.	62	4

[a] [**3b**] = 0.5 M. Activator was added to **1** or **2** followed by stirring for 5 min at the given temperature. [b] Lithiated **3b** was added to a solution of the activated CF_3 reagent. [c] A mixture of **3b** and the base was added to a solution of the activated CF_3 reagent.

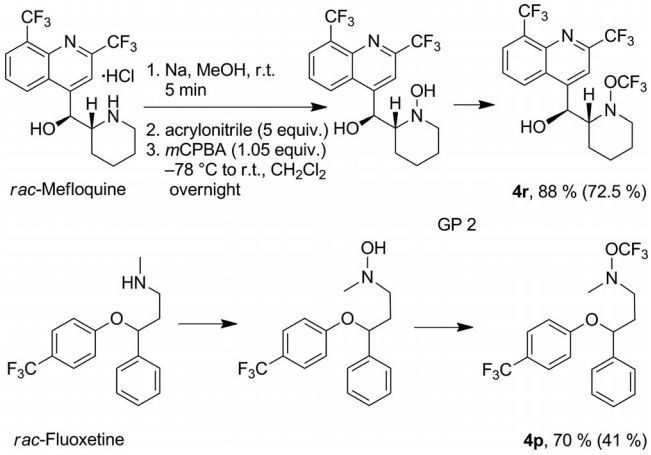
Lewis acid and simultaneously deprotonate the substrate with a stoichiometric amount of base. The results of the corresponding screening are summarized in Table 2. In an initial attempt, the use of LDA as the base and $LiClO_4$ as the activating agent for **2** gave a poor yield (Table 2, entry 1). Changing to more electron-deficient **1** led to a drastic increase in reactivity, and to our delight, the formation of side product **4b2** was fully inhibited (Table 2, entry 2), although a poor yield of **4b1** was still obtained. Activation of **2** with the powerful silylating agent trimethylsilyl triflate (TMSOTf) in combination with a strong amine base appeared to be a key improvement (Table 2, entry 3). Pleasingly, the use of tetramethylguanidine (TMG, 1.1 equiv.) in combination with **2** (1.1 equiv.) gave 62% yield of desired product **4b1**, as determined by ^{19}F NMR spectroscopy, with only a small amount of benzylic trifluoromethylation (Table 2, entry 4).

Having found improved conditions for the trifluoromethylation of cyclic *N*,*N*-disubstituted hydroxylamines, we turned our attention towards the synthesis[8] and trifluoromethylation of other substrates. The results are shown in Scheme 1. The discrepancy between the yields determined by ^{19}F NMR spectroscopy and those of the isolated products is mostly due to challenging purification conditions (see the Supporting Information for details).

As shown in Scheme 1, several classes of hydroxylamine substrates were efficiently trifluoromethylated. Substituted cyclic *N*-hydroxytetrahydroisoquinolines, which resemble natural alkaloid motifs, were trifluoromethylated in moderate to good yields (see **4b**–**e**). Ester as well as nitrile functionalities were tolerated (see **4f**, **4i**, **4k**). Compound **4g** can be perceived as a modified derivative of an amino acid and might thus be of particular interest for the life sciences. Both primary and tertiary amide substrates as well as ketones were successfully trifluoromethylated (see **4l**, **4m**, **4n**) in moderate to good yields. Primary and secondary alcohol groups were also shown to be compatible with the protocol (see **4e**, **4r** in Scheme 2). The trifluoromethylation method is not sensitive to steric bulk, as **4g**, **4h**, and **4j** were trifluoromethylated in good yields. Activation of **2** according to GP 2 led to an appreciable extent of trifluoromethylation of *N*-hydroxyphthalimide (**3o**) to give crystalline **4o** in 14% yield. The modest reactivity of **3o** may be due to the lack of the α-effect, as a result of the delocalization of the lone pair of electrons on the nitrogen atom.



Scheme 1. *O*-Trifluoromethylation of hydroxylamines, yields in parentheses refer to the yields of the isolated products; otherwise, yields determined by ^{19}F NMR spectroscopy ($PhCF_3$ as an internal standard) are given. Details concerning general procedures (GP) are provided in the Experimental Section. [a] GP 1. [b] GP 2. [c] GP 3. [d] Hünig's base used instead of tetramethylguanidine, **2** (1.5 equiv.), and TMSOTf (1.5 equiv.) were used. [e] Substrate (1 equiv.), $LiClO_4$ (1 equiv.) as activator for **1**, and LDA (1 equiv.), THF, –20 °C to r.t., 10 min. [f] As GP 1 but **2** (3 equiv.) was used.



Scheme 2. Synthesis of Mefloquine- and Fluoxetine-derived hydroxylamines and subsequent trifluoromethylation; *m*CPBA = *m*-chloroperoxybenzoic acid.

Medicinally interesting substrates such as Fluoxetine and Mefloquine were transformed into the corresponding hydroxylamines,[9] and these were further trifluoromethylated in good to excellent yields (see **4r** and **4p**, Scheme 2).

Crystalline compounds **4o** and *N*-trifluoromethoxy-substituted Mefloquine (**4r**) were subjected to an X-ray crystallographic study. In the solid state (see Figure 2), phthalimide derivative **4o** displays a significant degree of pyramidalization of the nitrogen atom as expressed by the sum of the angles around it of 350.5° and by the distance of 0.25 Å from the plane defined by its neighbouring atoms. Remarkably, both compounds show the same orientation of the OCF_3 group with respect to the CNC unit. The corresponding conformation is best described by the F1–C–O–N torsion angles of 179.8 and 176.4°, respectively. This is probably due to a hyperconjugative interaction between the lone pair of electrons on the nitrogen atom and the antibonding orbital of the C–F fragment[10] antiperiplanar to the O–N bond.

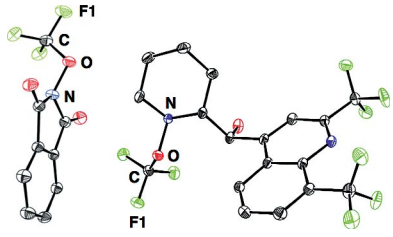


Figure 2. ORTEP drawings of the X-ray structure of *N*-(trifluoromethoxy)phthalimide (**4o**) and Mefloquine derivative **4r**. Hydrogen atoms are omitted for clarity; thermal ellipsoids are set to 50% probability.

This hyperconjugation may also be responsible for the existence of two diastereomers in products containing a chiral backbone.[11] This phenomenon was observed in the ^1H NMR and ^{19}F NMR spectra of **4g**, **4h**, and **4p**. In the case of OCF_3-Fluoxetine, detailed analysis was performed. Thus, upon cooling, the initial broad signal of the OCF_3 group in the ^{19}F NMR spectrum split into two sharp signals with a 6:4 area ratio. Splitting was also observed for the aromatic CF_3 signal and for the aliphatic protons. A subsequent ^1H–^{19}F HOESY experiment indicated that the CF_3 group was close in space to both the methyl and methylene protons, which suggested that it lies in the plane bisecting the CNC angle, as observed in the solid state. In this way, the n(N)–σ*(CF) interaction increases the inversion barrier of the nitrogen atom, which thereby generates two observable stereoisomers (Figure 3).

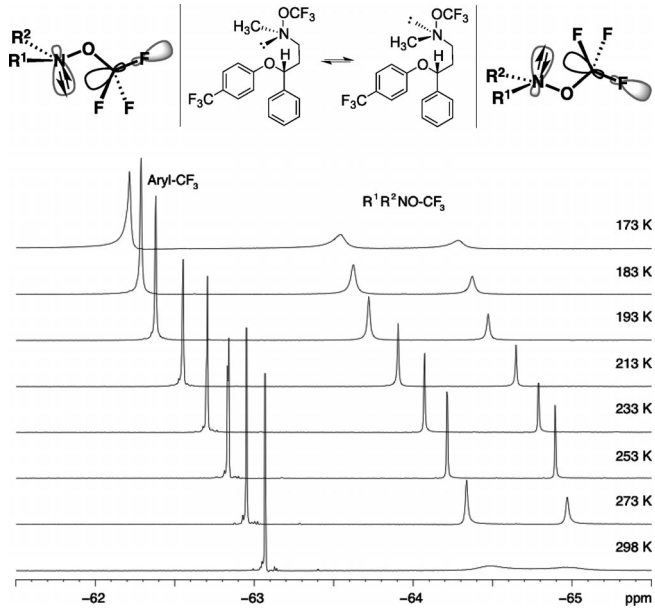


Figure 3. 658.8 MHz ^{19}F variable-temperature NMR spectroscopy analysis of **4p** in [D_4]methanol/TMS (9:1) and the proposed n(N)–σ*(CF) hyperconjugative interaction.

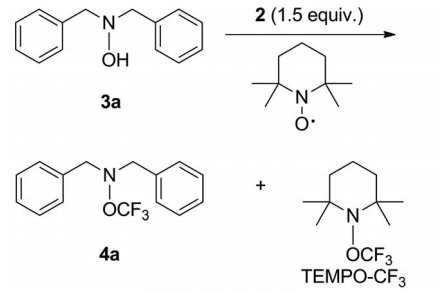
Hyperconjugation may lead to hindered rotation of the CF_3 group, which would render the F atoms diastereotopic. Although several examples of hindered CF_3 group rotation have been reported,[12] it could not be resolved in the cases that were examined down to 173 K.

We originally anticipated that during the trifluoromethylation reaction, CF_3 radicals were formed. To verify this hypothesis experimentally, we conducted the reaction in neat styrene to force the addition of the CF_3 radical to the double bond. Analysis of the reaction mixture by ^{19}F NMR spectroscopy showed the expected product of the radical β-trifluoromethylation of styrene[13] formed in 126% yield on the basis of ^{19}F NMR spectroscopy with respect to dibenzylhydroxylamine in addition to the desired product (26% yield).

Another experiment in which toluene was used as the solvent showed that aromatic trifluoromethylation took place under the applied reaction conditions. Apart from the desired product, a mixture of *o*-, *p*-, and *m*-trifluoromethyltoluene was observed (67% combined yield). The low regioselectivity is typical for radical aromatic substitution reactions.[14]

To get further evidence for the radical nature of the process, the more powerful radical scavenger TEMPO was added to the reaction mixture in a stoichiometric amount.

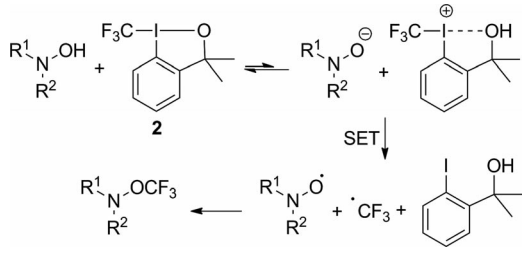
As shown in Scheme 3, competitive trifluoromethylation of the excess amount of TEMPO completely suppressed the formation of **4a**. We consider this result as a strong indication for a radical pathway with a CF_3 radical as the key intermediate. Unfortunately, trifluoromethylation of the potential radical clock 1-allyl-3,4-dihydroisoquinolin-2(1*H*)-ol failed to provide a single product.



TEMPO (1 equiv.): **4a**, 20 %; TEMPO-CF_3, 94 %
TEMPO (1.5 equiv.): **4a**, 12 %; TEMPO-CF_3, 125 %
TEMPO (3 equiv.): **4a**, 2.5 %; TEMPO-CF_3, 130 %
TEMPO (10 equiv.): **4a**, 0 %; TEMPO-CF_3, 115 %
all yields are based on **3a**

Scheme 3. CF_3 radical quenching experiment with TEMPO.

As shown in Scheme 4, a plausible mechanism for the reaction would thus involve a proton transfer pre-equilibrium between the hydroxylamine and **2** followed by a SET step. This affords a pair of radicals leading to the desired product upon recombination (see the Supporting Information for a detailed discussion).



Scheme 4. Proposed reaction mechanism.

Conclusions

In summary, we developed a method for the chemoselective *O*-trifluoromethylation of *N*,*N*-disubstituted hydroxylamines. Mechanistic and screening experiments indicated that the reaction follows a radical pathway with nitroxyl and CF_3 radicals as relevant intermediates. The method was shown to be suited for a wide variety of substrates, including more complex molecular targets with potential application in medicinal chemistry.

Experimental Section

GP 1: In a dry Schlenk flask under an atmosphere of Ar, CF_3 reagent **2** (1.5 equiv.) was dissolved in dry CH_2Cl_2 to give a 1 M solution that was precooled to –20 °C in a cooling bath (water/ice/ethanol slush). In a separate flask, the hydroxylamine substrate was dissolved in dry CH_2Cl_2 to give a 0.5 M solution. The substrate solution was rapidly injected to the precooled CF_3 reagent solution, and the resulting mixture was immediately taken out of the cooling bath and allowed to reach room temperature.

GP 2: A dry Schlenk flask under an atmosphere of Ar was charged with CF_3 reagent **2** (244 mg, 0.737 mmol, 1.1 equiv.) and cooled to –78 °C in an ethanol/dry ice bath. A solution of trimethylsilyl triflate (0.5579 M in CH_2Cl_2, 1.32 mL, 0.737 mmol, 1.1 equiv.) was then injected within 10 s along the precooled wall whilst stirring. The resulting solution was stirred at this temperature for 5 min. Meanwhile, a solution of the hydroxylamine substrate (0.67 mmol, 1 equiv.) and tetramethylguanidine (92 μL, 84.8 mg, 0.737 mmol, 1.1 equiv.) in CH_2Cl_2 (1 mL) was prepared. After a period of 5 min for the TMSOTf-mediated activation of the CF_3 reagent, the substrate solution was added within 10 s to the solution of the activated CF_3 reagent along the precooled wall of the Schlenk flask. The resulting mixture was stirred at –78 °C for 1 min, and then taken out of the cooling bath and allowed to reach room temperature.

GP 3: In a dry Schlenk flask under an atmosphere of Ar, CF_3 reagent **1** (1.5 equiv.) was suspended in CH_2Cl_2 (0.3 mL of CH_2Cl_2 per mmol of CF_3 reagent) and cooled to an ice bath (0 °C). In a separate flask, the hydroxylamine substrate (1 equiv.) was dissolved in CH_2Cl_2 to give a 0.5 M solution, and it was added dropwise with a Pasteur pipette to the well-stirred suspension of the reagent. Finally, triethylamine (1 equiv.) was injected with a syringe. The ice bath was removed, and the mixture was stirred several minutes at room temperature.

GP 2 was always superior to GP 1 and GP 3, which were used in the early stages of this project. Further details are included in the Supporting Information.

CCDC-978124 (for **4o**) and -978125 (for **4r**) 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.

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures and copies of the ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra.

Acknowledgments

The ETH Zürich is acknowledged for financial support. Dr. Nico Santschi is acknowledged for providing helpful suggestions regarding mechanistic issues. Julie Charpentier and Joël Egloff are acknowledged for their assistance in preparing this manuscript.

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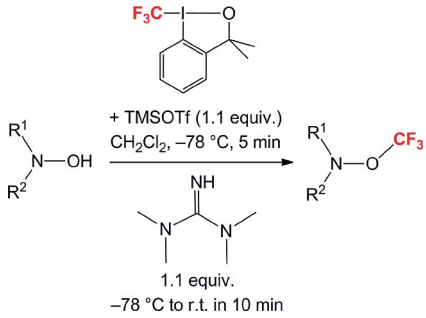
Received: March 7, 2014
Published Online: ■

EurJOC European Journal of Organic Chemistry

Electrophilic trifluoromethylation of dialkyl hydroxylamines with hypervalent iodine(III) reagents gives access to compounds containing the virtually unexplored $NOCF_3$ functional group. Aspects concerning synthesis, properties, and reaction mechanism are presented. The transformation is also applicable to hydroxylamines derived from common drugs and shows a broad functional group tolerance.



Keywords: Synthetic methods / Trifluoromethylation / Chemoselectivity / Hypervalent compounds / Iodine

