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A deeper insight into direct trifluoromethoxylation with trifluoromethyl triflate

Olivier Marrec [a,b,c,d,e,f], Thierry Billard [a,b,c,d,e,f], Jean-Pierre Vors [g], Sergii Pazenok [g,*], Bernard R. Langlois [a,b,c,d,e,f,**]

[a] ICBMS, Institut de Chimie et Biochimie Moléculaires et Supramoléculaires, Equipe SERCOF, 43 boulevard du 11 novembre 1918, Villeurbanne, F-69622, France
[b] CNRS, UMR5246, Villeurbanne, F-69622, France
[c] Université de Lyon, Lyon, F-69622, France
[d] Université Lyon 1, Lyon, F-69622, France
[e] INSA-Lyon, Villeurbanne, F-69622, France
[f] CPE Lyon, Villeurbanne, F-69616, France
[g] Bayer CropScience AG, Product Technology, Process Research, Building 6550, Alfred-Nobel-Str. 50, 40789 Monheim am Rhein, Germany

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ABSTRACT

Commercially available fluorides (silver fluoride and n-tetrabutylammonium triphenyldifluorosilicate), combined with TFMT, allow a simple generation, in situ, of silver and n-tetrabutylammonium trifluoromethoxides which were able to react with electrophilic substrates. Silver trifluoromethoxide, which is usually more efficient than n-tetrabutylammonium trifluoromethoxide, converts, under mild conditions, primary aliphatic bromides and iodides, as well as primary and secondary benzylic or allylic bromides to the corresponding trifluoromethoxylated compounds. Several trifluoromethyl ethers, which could be valuable building-blocks, were prepared in such a way.

1. Introduction

The intrinsic properties of fluorine atom (small size, high electronegativity, formation of strong C-F bonds) induce dramatic changes in the electronic, steric and hydrophobic parameters of the molecules which bear fluorinated moieties. Thus, their pharmacodynamic and pharmacokinetic properties are deeply modified [1,2]. This is the reason why fluorine chemistry is now so popular in the life sciences.

Among the fluorinated moieties currently used, the trifluoromethoxy group (OCF_3) becomes more and more prominent [3,4]. For example, in addition to trifluoromethoxy-substituted liquid crystals [5] and dyes [6], several trifluoromethoxylated major pesticides and pharmaceuticals are now present on the market [5,7,8] (Fig. 1).

This growing interest for trifluoromethyl ethers is related to the very peculiar characteristics of the CF_3O group. On one hand, this substituent looks like chlorine [9] in the sense that it is electron-withdrawing by induction (χ = 3.7 [10], σ_I = +0.51 to +0.60 [11]), but more than chlorine (σ_I = +0.47 [11a]), and electron-donating by resonance (σ_R = −0.13 to −0.18 [11]), but less than chlorine (σ_R = −0.25 [11a]). For this reason, it has been named "super-halogen" [12] or "pseudo-halogen" [13]. On the other hand, OCF_3 is one of the most hydrophobic substituent, just after SCF_3, as indicated by its Hansch-Leo parameter (Π_R (SCF_3) = +1.44, Π_R (OCF_3) = +1.04, Π_R (CF_3) = +0.88, Π_R (OCH_3) = −0.02) [14]. Thus, such a hydrophobic substituent dramatically increases the bioavailability of the products bearing it.

Another characteristic of the OCF_3 moiety is that the electron density of the non-bonding p-orbitals of oxygen is very low. The first evidence of that came from the study of the UV spectrum of (trifluoromethoxy)benzene, which is very similar to that of (trifluoromethyl)benzene [15,16]. Later, Anderson speculated that "the p atomic orbital of oxygen is drawn towards the CF_3 group by acceptance of its p-electrons into the antibonding orbitals of the perfluoroalkyl group's C–F bonds" [17]. The first consequence is that bonding/non-bonding resonance and ionic limiting structures cannot be written for OCF_3, despite tiny differences in bond lengths sometimes observed between experiment and calculation (the accuracy of which were not precised). As far as aryl trifluoromethyl ethers are concerned, the second consequence is that oxygen non-bonding orbitals are not conjugated with the aromatic nucleus, as

* Corresponding author. Tel.: +49 2173384808; fax: +49 2173384880.
** Corresponding author at: ICBMS, Institut de Chimie et Biochimie Moléculaires et Supramoléculaires, Equipe SERCOF, 43 boulevard du 11 novembre 1918, Villeurbanne, F-69622, France.
E-mail addresses: sergiy.pazenok@bayercropscience.com (S. Pazenok), Bernard.Langlois@univ-lyon1.fr (B.R. Langlois).

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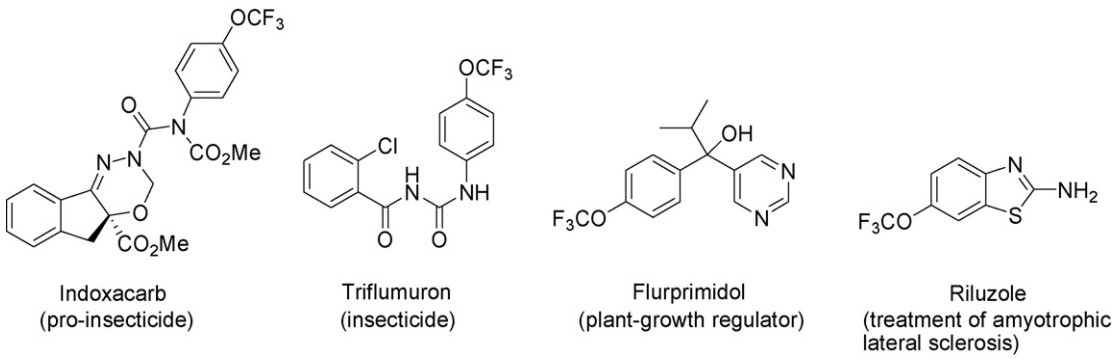
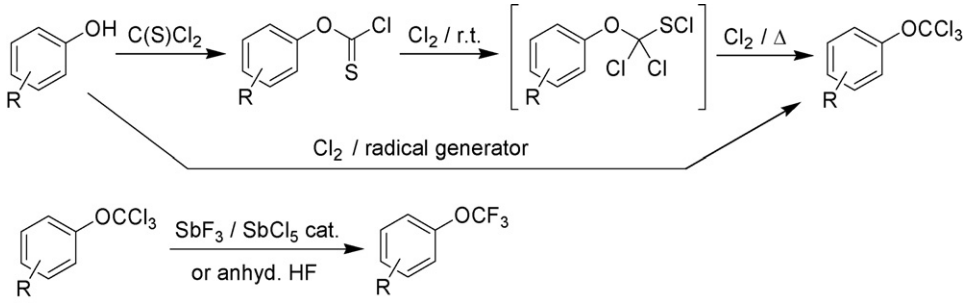


Fig. 1. Some bioactive trifluoromethoxylated products.



Scheme 1. Chlorination/fluorination sequence of phenol derivatives.

also deduced from molecular photoelectron spectroscopy [18] or dipole moments studies [19,20,11b]. Thus, the O–CF_3 group of Ar–OCF_3 can rotate freely out of the nucleus plane. Consequently, in order to minimize electronic repulsions, (trifluoromethoxy)benzene adopts a conformation in which the O–CF_3 bond is orthogonal to the nucleus plane (Fig. 2). Such a conformation was first anticipated from modelling studies [11b] and NMR spectroscopy [21], then directly observed by X-ray spectroscopy [22,23].

Of course, this conformation is suspected to be important in the interaction between trifluoromethoxylated substrates and their biological receptors. Moreover, it could explain the strong para-orientating effect observed in electrophilic substitution of (trifluoromethoxy)benzene. For the previously mentioned reasons, such an orientating effect cannot be due to conjugation between oxygen and the Π-system, though sometimes written. More probably, as the very electronegative fluorine atoms are surrounded by an intense electric field, a strong coulombian repulsion occurs between the fluorine atoms (one of which being always close from the nucleus) and the mobile Π-electrons which are repelled as far as possible ($+I_{\Pi}$ effect), that means towards the para-position of the cycle which, consequently, exhibits the higher electron density (Fig. 2). Through-space field interactions were effectively anticipated by Sheppard from measurements of the Dewar constant (*F*) of the OCF_3 group [12].

Until now, essentially aryl trifluoromethyl ethers are described. Their different preparations have been recently reviewed [7] and can be divided into five methods that are, chronologically, chlorine/fluorine exchange on trichlorinated precursors, action of sulfur tetrafluoride on fluoroformates (Sheppard's method), Hiyama's oxidative fluorodesulfurization, electrophilic trifluoromethylation of hydroxyl functions, and nucleophilic trifluoromethoxylation.

Chlorination/fluorination was developed as soon as 1955 by Yagupolskii et al. [24], a research group which remained on the fore front of CF_3O chemistry until now. This method was improved when Yarovenko and Vasileva, from the same Ukrainian laboratory, discovered a new access to aryl trichloromethyl ethers from aryl thionochloroformates [25] (Scheme 1). However, this chlorination/fluorination technique, which is currently employed on the industrial scale, can be only applied to aromatics. Moreover, Yarovenko's modification is difficult to scale-up because of the high percutaneous toxicity of aryl thionochloroformates [26].

The three following methods can be, in principle, applied to aromatic as well as aliphatic substrates (Scheme 2). Though deoxyfluorination of fluoroformates [27,11a] is greatly deserved by the high toxicity of SF_4 (and that of fluorophosgene when fluoroformates are prepared from it), oxidative fluorodesulfurization [28] opened a new access to trifluoromethyl ethers, which can be used without specific equipment and successfully applied to

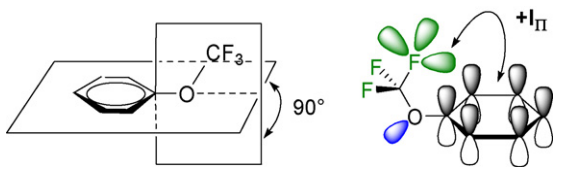
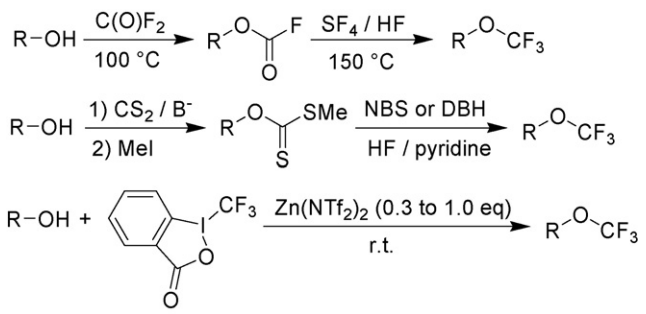
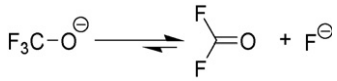


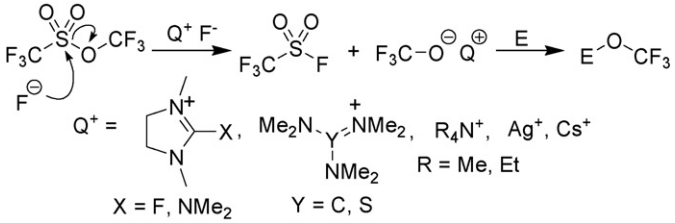
Fig. 2. Conformation and through-space interactions in (trifluoromethoxy)benzene.



Scheme 2. Conversion of alcohols into trifluoromethyl ethers.



Scheme 3. Decomposition of the trifluoromethoxide anion.



Scheme 4. Generation of trifluoromethoxide from TFMT.

phenols, primary and even secondary alcohols. Nevertheless, this latter method is not tolerant with many functional substituents. Electrophilic trifluoromethylation of alcohols and phenols has been first reported by Umemoto et al. [29], using O-trifluoromethyl dibenzyl furanium salts, but these trifluoromethylating agents cannot be isolated and must be prepared in situ and at low temperature from trifluoromethylated biphenyls. An outstanding breakthrough in electrophilic trifluoromethylation has been recently brought by Togni et al. [30] with easily accessible trifluoromethyl-containing iodine (III) reagents. When opposed to phenols, aromatic trifluoromethylation competes with O-trifluoromethylation [31] but, in the presence of sub-stoichiometric amounts of zinc triflimide, such reagents allow trifluoromethylation of aliphatic alcohols [32], though a large excess of the latter is required.

Obviously, the best synthesis of trifluoromethyl ethers would be the direct introduction of the whole OCF_3 moiety. Apart the addition of trifluoromethyl hypofluorite upon olefins [33], which is highly hazardous and toxic, numerous attempts to generate trifluoromethoxide salts failed since, generally, this anion collapses into fluoride and fluorophosgene, even at low temperature (Scheme 3).

Several teams tried to draw this equilibrium towards CF_3O^- and demonstrated that, if fluorides are associated with rather bulky cations (CsF [34,35], $(Me_2N)_3S^+$ $Me_3SiF_2^-$ [36,37a]), the resulting trifluoromethoxide could be stable enough, in solution, to react with reactive electrophiles such as benzyl bromide [35] as well as primary triflates and bromides [37]. Nevertheless, the development of this reaction is limited by the high toxicity of gaseous fluorophosgene which must be used under pressure.

Recently, Kolomeitsev et al. [38] have described, during our own work on the same topics, a more convenient generation of trifluoromethoxide salts from trifluoromethyl triflate (TFMT), which is a volatile liquid, far less toxic than fluorophosgene. It is usually prepared from triflic acid or anhydride [17,39] and is commercially available on the bench scale. Indeed, it was known for more than two decades that, in contrast to other triflates, TFMT is not an electrophilic trifluoromethylating agent and is attacked by nucleophiles, especially hard ones, at its harder electrophilic site, that is sulfur (VI). For example, fluorides gave rise to trifluoromethanesulfonyl fluoride and CF_3O^-, which usually collapses into $C(O)F_2$ and F^-, so that catalytic amounts of F^- can cause the complete decomposition of TFMT [39c]. Taking advantage of this observation, Kolomeitsev et al. performed the same reaction with bulky fluorides in order that the generated trifluoromethoxide salt was stable enough to substitute some leaving groups on reactive substrates (Scheme 4).

Several trifluoromethoxides were generated from several fluorides but their relative stabilities were not rationalized and their reactivities are very difficult to compare since, if different substrates were opposed to some of them, only ethyl 2-(trifluoromethanesulfonyloxy)-propionate has been reacted with all the prepared trifluoromethoxide. Thus, the scope of the method does not seem very clear and other potentialities have to be explored.

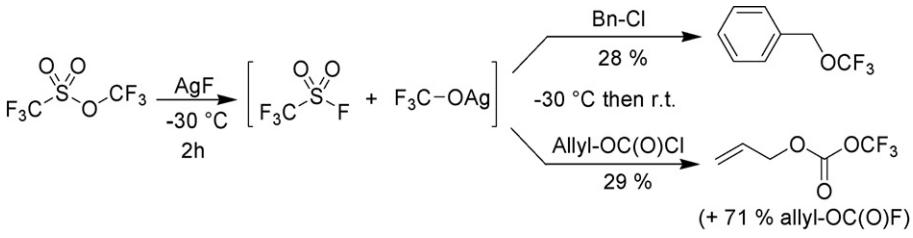
As already mentioned, we started working on the same reaction, concomitantly but totally independently, more than 1 year before Kolomeitsev's paper appeared. Our major goal was to compare the reactivities of different trifluoromethoxides, prepared from TFMT and different nucleophiles, towards different classes of electrophiles, especially alkyl halides which are more accessible and less expensive than alkyl triflates.

2. Results and discussion

The first attempt to activate TFMT with phosphines, instead of fluoride, was unsuccessful: if triphenylphosphine was able to react with TFMT, as expected, this reaction led exclusively to Ph_3PF_2. Also, activation of TFMT with chlorides was not satisfying. For example, it was expected that benzyltriphenylphosphonium chloride, prepared in situ from benzyl chloride and triphenylphosphine, could generate triflyl chloride and CF_3O^- $(BnPPh_3)^+$ and, finally, provide benzyl trifluoromethyl ether. The result was different since triflyl fluoride was the major product, along traces of triflyl chloride but not any trace of $BnOCF_3$ was detected. That means that the benzyltriphenylphosphonium cation, though bulky, is not able to stabilize CF_3O^- and, maybe, that bulkiness is not the only parameter involved in the stabilization of CF_3O^-.

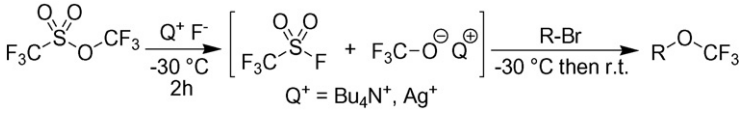
Thus, we focused our efforts on the use of n-tetrabutylammonium triphenyldifluorosilicate (TBAT, DeShong's reagent), a commercially available, cheap, anhydrous and bulky fluoride which was not used by Kolomeitsev, as we remarked later. Silver fluoride was also evaluated since, as our goal was to substitute alkyl halides, it was anticipated that precipitation of silver halides could contribute to success.

Indeed, the corresponding methoxides (Bu_4N^+ CF_3O^-, Ag^+ CF_3O^-) were formed but they were not reactive enough towards chlorides, except benzyl chloride and allyl chloroformate which reacted with CF_3OAg in a medium yield (Scheme 5). Other chlorides, such as aroyl chlorides, benzenesulfonyl chloride and chlorotrimethylsilane, led quite exclusively to the corresponding fluorides. Probably, silver trifluoromethoxide was too soft to react



Scheme 5. Reaction of CF_3OAg with chlorides.

Table 1
Trifluoromethoxylation of alkyl bromides with nBu$_4$NOCF$_3$ or AgOCF$_3$



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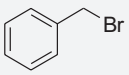
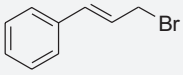
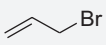
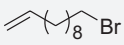
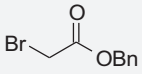
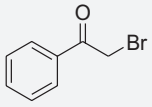
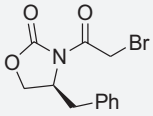
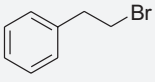
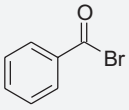
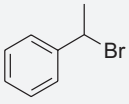
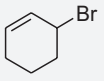
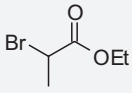
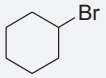
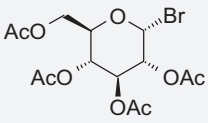
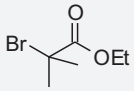
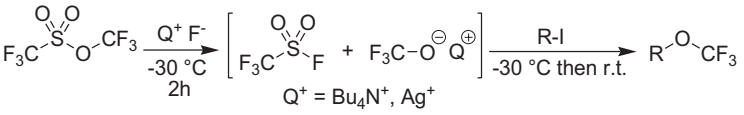
Entry	Substrate	Method A nBu$_4$N$^+$ $^-$OCF$_3$		Method B Ag$^+$ $^-$OCF$_3$	
		Substrat eq.	Yield[a]	Substrat eq.	Yield[a]
1		1 eq., 1.5 eq., 2 eq.	45%, 60%, 75%	0.9 eq., 1.5 eq.	100% (76%), 100%
2		1.5 eq.	53%	0.9 eq.	57% (47%)
3		Not examined	0.9 eq.	80%	
4		1.5 eq., 2 eq.	1%, 2%	0.9 eq.	50%
5		0.9 eq.	36%	0.9 eq.	70% (45%)
6		0.9 eq.	41%	0.9 eq.	47%
7		0.9 eq.	58%	0.9 eq.	60% (58%)
8		1.5 eq.	1%[c]	Not examined	
9		1.5 eq.	100%	0.9 eq.	92% (42%), Mono-F 8%[b]
10		0.9 eq.	11%	0.9 eq.	74% (50%)
11		0.9 eq.	40%	0.9 eq.	44%
12		Not examined	0.9 eq.	11%	
13		1.5 eq.	0%	0.9 eq.	2%
14		1.5 eq.	α: 3%, β: 24%	0.9 eq.	β: 97% (75%)

Table 1 (*Continued*)

Entry	Substrate	Method A $nBu_4N^+ {}^-OCF_3$		Method B $Ag^+ {}^-OCF_3$	
		Substrat eq.	Yield[a]	Substrat eq.	Yield[a]
15		Not examined	0.9 eq.	0%	

[a] Crude yield determined from ^{19}F NMR with $PhCF_3$ as internal standard. Isolated yield in parentheses.
[b] Mono-F = monofluorinated compound without any CF_3O moiety.
[c] Elimination reaction may predominate since styrene has been detected.

Table 2
Trifluoromethoxylation of alkyl iodides with nBu_4NOCF_3 or $AgOCF_3$



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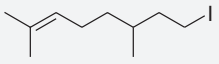
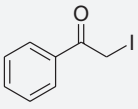
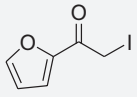
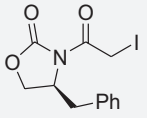
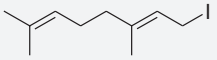
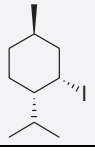
Entry	Substrate	Method A $nBu_4N^+ {}^-OCF_3$		Method B $Ag^+ {}^-OCF_3$	
		Substrat eq.	Yield[a]	Substrat eq.	Yield[a]
1		0.9 eq.	4%	0.9 eq.	64% (56%)
2		0.9 eq.	33%	0.9 eq.	85% (69%)
3		0.9 eq.	35%	0.9 eq.	60% (40%)
4		Not examined	0.9 eq.	84% (80%)	
5		0.9 eq.	40%	0.9 eq.	22%
6		Not examined	0.9 eq.	0%	

[a] Crude yield determined from ^{19}F NMR with $PhCF_3$ as internal standard. Isolated yield in parentheses.

with chlorinated substrates. It can be also noticed that with benzeneselenenyl chloride as substrate, decomposition was only observed.

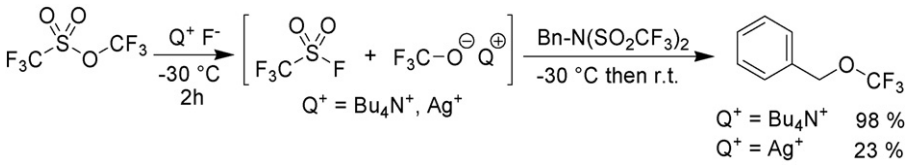
The results were far more satisfying with alkyl bromides, as shown in Table 1.

Generally speaking, alkyl bromides reacted more efficiently than alkyl chlorides and, as expected, silver trifluoromethoxide offered better yields than n-tetrabutylammonium trifluoromethoxide.

Indeed, excellent yields were obtained from primary bromides (entries 1–7), except phenethyl bromide for which β-elimination was probably the major reaction (entry 8). Obviously, primary benzyl and allyl bromides were the most reactive (entries 1–3) but, interestingly, primary bromine atoms in α position to a carbonyl function could be substituted in a satisfactory way (entries 5–7). The resulting products could be valuable starting materials for more sophisticated trifluoromethoxylated compounds.

Both silver trifluoromethoxide and n-tetrabutylammonium trifluoromethoxide were able to substitute secondary benzylic bromides (entry 10) and secondary allylic bromides (entry 11), though with lower yields, but very poor yields were obtained from secondary aliphatic bromides (entries 12 and 13) and no reaction was observed with tertiary bromides (entry 15).

It can be also mentioned that, in sharp contrast with benzoyl chloride, benzoyl bromide led to trifluoromethyl benzoate in good yields, through an addition-elimination process, whatever the trifluoromethoxide employed (entry 9). The reaction with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (entry 14) is worthy to mention since this substrate has been already reacted with $TAS^+ CF_3O^-$ [37a] and, under these conditions, delivered the expected



Scheme 6. Trifluoromethoxylation of N-benzyl trifluoromethanesulfonimide.

β-trifluoromethyl glucoside (14%) along a far larger quantity of β-glucosyl fluoride (34%). In our hands, this substrate gave a higher yield of β-trifluoromethyl glucoside with n-tetrabutylammonium trifluoromethoxide (27%, $\alpha:\beta$ = 1:8) and an excellent yield with silver trifluoromethoxide which, on the other hand, offered a complete stereoselectivity in favor of the β stereomer.

The reactivity of alkyl iodides was also examined (Table 2).

As usual, alkyl iodides delivered better results than alkyl bromides (i.e. Table 2, entry 2 *vs.* Table 1, entry 6; Table 2, entry 4 *vs.* Table 1, entry 7) and, again, CF_3OAg was more efficient than CF_3ONBu_4, except with geranyl iodide (entry 5). This apparent contradiction could be related to the moderate stability of this substrate which would be decreased by the Lewis acidity of the silver cation. The same kind of reason could explain that substitutive trifluoromethoxylation was slightly better with benzyl and allyl bromides than with the corresponding iodides. As far as neomenthyl iodide is concerned, a hindered secondary iodide, no reaction occurred.

After bromides and iodides, the reactivity of some other leaving groups towards Q^+ CF_3O^- ($Q^+ = Bu_4N^+$, Ag^+) was examined. Aromatic nucleophilic substitution of 2-fluoropyridine and pentafluoropyridine failed but N-benzyl trifluoromethanesulfonimide was quite quantitatively transformed by n-tetrabutylammonium trifluoromethoxide into benzyl trifluoromethyl ether. In must be noticed that, in this case, silver trifluoromethoxide provided a far lower yield than n-tetrabutylammonium trifluoromethoxide (Scheme 6). This result contrasts with those of the substitutive trifluoromethoxylation of alkyl halides with the same reagents.

This result was rationalized by the fact that, because of the oxophilic character of Ag^+, silver fluoride (which is probably in equilibrium with CF_3OAg) could partly reacted with the triflyl moieties of the $N(SO_2CF_3)_2$ leaving group and generate triflyl fluoride.

So, in order to avoid such a side-reaction, the substitution of cinnamyl acetate and citronellyl mesylate was tested with n-tetrabutylammonium trifluoromethoxide only. Surprisingly, trifluoromethoxylation of these two substrates completely failed. Of course, it could be argued that even Bu_4NF (in equilibrium with CF_3O^- Bu_4N^+) can attack the carbonyl or the sulfonyl moieties of these starting materials, prior attacking the harder and far more electrophilic sulfur (VI) of TFMT, but this hypothesis does not seem very realistic to explain such a sharp drop in the results. It could be also supposed that, instead of substituting acetate or mesylate, CF_3O^- Bu_4N^+ could be quenched by the carbonyl function or the sulfonyl function of these "leaving groups", without evolution of the system until work-up.

Comparatively, it must be reminded that Kolomeitsev et al. [38] reported a successful substitution of alkyl triflates (which bear a more electrophilic sulfur than mesylates) by tetramethylammonium and triethylammonium trifluoromethoxides, which look very similar to n-tetrabutylammonium trifluoromethoxide. However, in Kolomeitsev's experiments, it seems (though not clearly mentioned) that trifluoromethoxides were prepared in situ and separated from triflyl fluoride prior addition of the electrophilic substrate. Because of the announced trifluoromethoxylation yields, this also implies that the preformed trifluoromethoxides were not contaminated at all by fluoride residues. Are these experimental differences significative enough to explain such changes? Nevertheless, such intermediate treatments and purifications make Kolomeitsev's process and equipment more complicated than ours.

In conclusion, the present work confirms that trifluoromethyl triflate can be used as a generator of trifluoromethoxide anions when activated by fluoride anions, of course, but also by chlorides or phosphines. Nevertheless, such trifluoromethoxides, which collapse rapidly into fluoride and fluorophosgene when "free", must be stabilized by bulky counter-cations to have a chance to trifluoromethoxylate electrophilic substrates, through nucleophilic substitution or addition-elimination, and deliver trifluoromethyl ethers. Moreover, the reaction must be carried out in a closed vessel to counterbalance the possible decomposition of CF_3O^- into F^- and gaseous fluorophosgene. Commercially available fluorides (silver fluoride and n-tetrabutylammonium triphenyldifluorosilicate), combined with TFMT, allow a simple generation, in situ, of silver and n-tetrabutylammonium trifluoromethoxides which were able to react with electrophilic substrates. Silver trifluoromethoxide, which is usually more efficient than n-tetrabutylammonium trifluoromethoxide, converts, under mild conditions, primary aliphatic bromides and iodides as well as primary and secondary benzylic or allylic bromides. Several trifluoromethyl

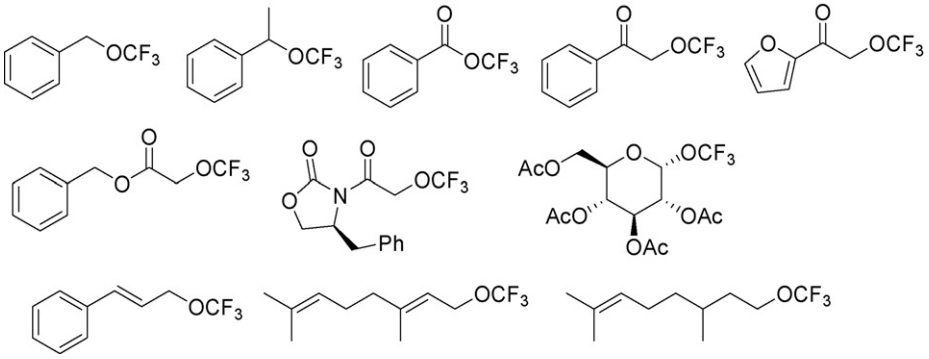


Fig. 3. Prepared trifluoromethyl ethers.

ethers, which could be valuable building-blocks, were prepared in such a way (Fig. 3).

3. Experimental part

THF was distilled over sodium/benzophenone prior to use. Dichloromethane was dried over molecular sieves. Other reagents were used as received.

^{1}H, ^{13}C (CPD and DEPT 135) and ^{19}F NMR spectra were generally recorded in $CDCl_3$ at respectively 300, 75 and 282 MHz, unless specified. Attribution of ^{1}H and ^{13}C NMR peaks have sometimes required 2D NMR experiments (COSY, HSQC, HMBC, NOESY, HOESY). Chemical shifts are given in ppm relative to TMS (^{1}H and ^{13}C) or $CFCl_3$ (^{19}F), used as internal references. Coupling constants are given in Hertz. For ^{19}F NMR titration, $PhCF_3$ has been used as internal standard. The following abbreviations are used: "s" singlet, "bs" broad singlet, "d" doublet, "bd" broad doublet, "t" triplet, "q" quadruplet, "m" multiplet, "Cq" quaternary carbone.

Flash chromatography was performed on silica gel Geduran 60 M (40–60 μm). Melting points (uncorrected) were determined in capillary tubes on a Büchi apparatus.

4(*S*)-Benzyl-3-(bromoacetyl)-1,3-oxazolidin-2-one was prepared according to [40]. Its iodo analog was obtained by exchange with NaI in acetone. 2-Iodoacetophenone and 2-(iodoacetyl)furan were prepared according to [41]. 2,6-Dimethyl-8-iodo-oct-2-ene (citronellyl iodide), (2*E*)-1-iodo-3,7-dimethylocta-2,6-diene (geranyl iodide) and (1*S*,2*S*,4*R*)-2-iodo-1-isopropyl-4-methylcyclohexane (neomenthyl iodide) were prepared according to [42]. N-benzyl triflimide was prepared according to [43].

3.1. Nucleophilic trifluoromethoxylation with TFMT and AgF: general procedure

In a 10 mL round bottomed flask, equipped with a rubber septum and a magnetic stirrer, silver fluoride (1 mmol) was introduced. Under nitrogen atmosphere, anhydrous CH_3CN (2 mL) were added and the heterogeneous mixture was cooled to −30 °C. TFMT (300 μL) was then added, the vessel was tightly closed (autogenous pressure of COF_2 is needed to allow the reaction to proceed) and the reaction mixture was stirred for 2 h at −30 °C. After addition of the electrophile (neat when liquid or dissolved in the minimum of CH_3CN when solid) by the mean of a gas-tight syringe, stirring was continued at −30 °C for 30 min then at r.t. for 24 h (in the dark). Finally, the vessel was depressurised and the reaction mixture was filtered over celite. The filtrate was concentrated in vacuo, the residue was dissolved in dichloromethane, washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by chromatography over silica gel finally afforded the pure corresponding trifluoromethyl ether.

3.1.1. Benzyl trifluoromethyl ether

Colourless oil (76%). ^{1}H NMR: 7.40–7.35 (massif, 5H), 4.99 (s, 2H). ^{13}C NMR: 134.0, 129.1, 128.7, 127.5, 121.8 (q, $^{1}J_{C\text{-}F}$ = 255.4), 69.2 (q, $^{3}J_{C\text{-}F}$ = 3.5). ^{19}F NMR: -60.78 (s). Anal: Calcd for $C_8H_7F_3O$: C (54.55), H (4.01); Found: C (54.34), H (3.90).

3.1.2. 1-Phenylethyl trifluoromethyl ether

Colourless oil (50%). ^{1}H NMR: 7.41–7.30 (massif, 5H), 5.30 (q, 1H, $^{3}J_{H\text{-}H}$ = 6.6), 1.63 (d, 3H, $^{3}J_{H\text{-}H}$ = 6.6). ^{13}C NMR: 140.6, 128.7, 128.5, 125.9, 121.8 (q, $^{1}J_{C\text{-}F}$ = 255.0), 77.3 (q, $^{3}J_{C\text{-}F}$ = 2.6), 23.4. ^{19}F NMR: −58.44 (s). Anal: Calcd for $C_9H_9F_3O$: C (56.85), H (4.77); Found: C (57.01), H (4.89).

3.1.3. Trifluoromethyl benzoate

Colourless oil (50%). ^{1}H NMR: 8.07 (m, 2H), 7.70 (m, 1H), 7.52 (m, 2H). ^{13}C NMR: 159.2, 135.3, 130.7, 129.1, 126.8 (q, $^{4}J_{C\text{-}F}$ = 1.6), 120.1 (q, $^{1}J_{C\text{-}F}$ = 256.3). ^{19}F NMR: −57.48 (s). Anal: Calcd for $C_8H_5F_3O_2$: C (50.54), H (2.65); Found: C (50.22), H (2.36).

3.1.4. (2E)-3-phenylprop-2-en-1-yl trifluoromethyl ether (cinnamyl trifluoromethyl ether)

Colourless oil (47%). ^{1}H NMR: 7.45–7.29 (massif, 5H), 6.72 (bd, 1H, $^{2}J_{H\text{-}H}$ = 15.8), 6.29 (dt, 1H, $^{2}J_{H\text{-}H}$ = 15.8, $^{3}J_{H\text{-}H}$ = 6.4), 4.65 (dd, 2H, $^{3}J_{H\text{-}H}$ = 6.4, $^{4}J_{H\text{-}H}$ = 1.3). ^{13}C NMR: 135.8, 135.3, 128.8, 128.6, 126.9, 121.9 (q, $^{1}J_{C\text{-}F}$ = 255.2), 121.5, 68.1 (q, $^{3}J_{C\text{-}F}$ = 3.5). ^{19}F NMR: −60.54 (s). Anal: Calcd for $C_{10}H_9F_3O$: C (59.41), H (4.49); Found: C (59.53), H (4.40).

3.1.5. Benzyl (trifluoromethoxy)acetate

Colourless oil (45%). ^{1}H NMR: 7.39–7.35 (massif, 5H), 5.25 (s, 2H), 4.52 (s, 2H). ^{13}C NMR: 166.0, 134.8, 128.9, 128.8, 128.7, 121.6 (q, $^{1}J_{C\text{-}F}$ = 256.9), 67.7, 63.2 (q, $^{3}J_{C\text{-}F}$ = 3.5). ^{19}F NMR: −61.86 (s). Anal: Calcd for $C_{10}H_9F_3O_3$: C (51.29), H (3.87); Found: C (51.21), H (4.18).

3.1.6. 2,6-Dimethyl-8(trifluoromethoxy)oct-2-ene (citronellyl trifluoromethyl ether)

Colourless oil (58%). ^{1}H NMR: 5.09 (m, 1H), 4.00 (m, 2H), 1.98 (m, 2H), 1.63–1.12 (massif, 11H); 0.91 (d, 3H, $^{3}J_{H\text{-}H}$ = 6.4). ^{13}C NMR: 131.7, 124.5, 121.9 (q, $^{1}J_{C\text{-}F}$ = 253.6), 66.0 (q, $^{3}J_{C\text{-}F}$ = 3.1), 37.0, 35.7, 29.1, 25.8, 25.5, 19.3, 17.7. ^{19}F NMR: −61.13 (s). Anal: Calcd for $C_{11}H_{19}F_3O$: C (58.91), H (8.54); Found: C (59.12), H (8.45).

3.1.7. Trifluoromethyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside

White solid (75%). M.P.: 120–122 °C. ^{1}H NMR: 5.25–5.07 (massif, 4H), 4.31 (dd, 1H, $^{2}J_{H\text{-}H}$ = 12.5, $^{3}J_{H\text{-}H}$ = 4.8), 4.14 (dd, 1H, $^{2}J_{H\text{-}H}$ = 12.5, $^{3}J_{H\text{-}H}$ = 2.3), 3.82 (ddd, 1H, $^{3}J_{H\text{-}H}$ = 9.8, $^{3}J_{H\text{-}H}$ = 4.8, $^{3}J_{H\text{-}H}$ = 2.3), 2.10 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H). ^{13}C NMR: 170.9, 170.1, 169.3, 169.0, 121.0 (q, $^{1}J_{C\text{-}F}$ = 259.6), 96.9 (q, $^{3}J_{C\text{-}F}$ = 3.3), 72.8, 72.2, 70.2, 67.6, 61.4, 20.6, 20.5, 20.4. ^{19}F NMR: −59.57 (s). Anal: Calcd for $C_{15}H_{19}F_3O_{10}$: C (43.28), H (4.60); Found: C (43.37), H (4.76).

3.1.8. (4S)-4-Benzyl-3-[(trifluoromethoxy)acetyl]-1,3-oxazolidin-2-one

Viscous yellow oil (80%). ^{1}H NMR: 7.38-7.19 (massif, 5H), 5.13 (d, 1H, $^{2}J_{H\text{-}H}$ = 17.3), 5.07 (d, 1H, $^{2}J_{H\text{-}H}$ = 17.3), 4.71 (m, 1H), 4.29 (m, 2H), 3.32 (dd, 1H, $^{2}J_{H\text{-}H}$ = 13.5, $^{3}J_{H\text{-}H}$ = 3.2), 2.86 (dd, 1H, $^{2}J_{H\text{-}H}$ = 13.5, $^{3}J_{H\text{-}H}$ = 9.3). ^{13}C NMR: 165.3, 153.5, 134.6, 129.4, 129.1, 127.7, 121.6 (q, $^{1}J_{C\text{-}F}$ = 256.7), 67.8, 65.7 (q, $^{3}J_{C\text{-}F}$ = 3.3), 54.9, 37.5. ^{19}F NMR: −61.38 (s). Anal: Calcd for $C_{13}H_{12}F_3NO_4$: C (51.49), H (3.99), N (4.92); Found: C (51.73), H (4.22), N (5.21).

3.1.9. 1-Phenyl-2-(trifluoromethoxy)ethanone [α-(trifluoromethoxy)acetophenone]

Yellow oil (69%). ^{1}H NMR: 7.91 (m, 2H), 7.65 (m, 1H), 7.52 (m, 2H), 5.18 (s, 2H). ^{13}C NMR: 190.2, 134.4, 133.8, 129.1, 127.9, 121.8 (q, $^{1}J_{C\text{-}F}$ = 256.3), 68.4 (q, $^{3}J_{C\text{-}F}$ = 2.9). ^{19}F NMR: -61.44 (s). Anal: Calcd for $C_9H_7F_3O_2$: C (52.95), H (3.46); Found: C (53.12), H (3.15).

3.1.10. 1-(2-Furyl)-2-(trifluoromethoxy)ethanone

Colourless oil (40%). ^{1}H NMR: 7.63 (dd, 1H, $^{3}J_{H\text{-}H}$ = 1.8, $^{4}J_{H\text{-}H}$ = 0.6), 7.34 (dd, 1H, $^{3}J_{H\text{-}H}$ = 3.6, $^{4}J_{H\text{-}H}$ = 0.6), 6.60 (dd, 1H, $^{3}J_{H\text{-}H}$ = 3.6, $^{3}J_{H\text{-}H}$ = 1.8), 5.01 (s, 2H). ^{13}C NMR: 179.6, 150.2, 147.4, 121.7 (q, $^{1}J_{C\text{-}F}$ = 254.2), 119.0, 112.0, 67.8 (q, $^{3}J_{C\text{-}F}$ = 3.0). ^{19}F NMR: −61.62 (s). Anal: Calcd for $C_7H_5F_3O_3$: C (43.41), H (2.60); Found: C (43.32), H (2.89).

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