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Short communication

CF_3 radicals from triflic anhydride and collidine: Their trapping by a trimethylsilylenolether

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ABSTRACT

The interaction of triflic anhydride with *s*-collidine in the presence of the (trimethylsilyl)enolether of acetophenone led to duplication products the structure of which could only be explained by the formation of CF_3 radicals.

1. Introduction

Improving or finding new methods for the introduction of fluorine in organic compounds, and especially in heterocycles, is an important target since many of the selling drugs appearing on the market contain at least one fluorine atom [1]. During our investigations directed towards the synthesis of new heterocycle-fused lactones *via* halolactonization reactions, [2] we were intrigued by a surprising yet possibly important, if improved, reaction. Indeed, we observed that the interaction of pyridine **1** with bis(trimethylsilyl) ketene acetals **2** (trimethylsilyl = TMS) in the presence of an excess of triflic anhydride Tf_2O **3** ($Tf_2O = (CF_3SO_2)_2O$) led directly to the trifluoromethyllactone **6** (Scheme 1) [3].

During this transformation, triflic anhydride not only activates as expected the pyridine nucleus towards bis(trimethylsilyl) ketene acetal nucleophiles **2** *via* the pyridinium triflate **4** to give dihydropyridines **5**, but delivers also an electrophilic CF_3 group which induces the lactonization reaction of **5**. A mechanism for the last step **5** → **6** involving *pseudocationic CF_3 species* was tentatively suggested [3]. Such species might originate upon electron transfers from the dihydropyridines, known reducing agents, [4] to triflic anhydride, also known as an oxidant [5] in some special cases [6,7].

This result prompted us to re-examine the first and sole other transformation in which triflic anhydride appeared to be the source of CF_3 moieties in order to try to get more insight into the transformation **5** → **6**. Indeed, Binkley and Ambrose observed the formation of two unexpected products **10** and **11**, yet in low yield, from triflic anhydride **3** reacting with *s*-collidine **7** [8]. According to these authors, the expected yet unstable trifyl triflate **8** might lead to the anhydrobase **9** upon deprotonation and then, in the case of either a non-concerted cationic **A** or radical **B** pathway, to **10**, and with loss of SO_2 to **11** (Scheme 2). Negative results from CIDNP experiments led them however to eliminate the second pathway, the formation of radical pairs and to conclude for the involvement of carbocationic CF_3 species.

The purpose of this communication is to show that although not detectable by the CIDNP technique, CF_3 radicals are in fact formed at least to some extend during the interaction of collidine with triflic anhydride. They could however only be directly trapped by the (trimethylsilyl)enolether **12** leading to duplication products **13** which were fully characterized by X-ray crystallography, and also to the corresponding α-trifluoromethylketone **15**. Besides, the low yield of formation of these products might be assigned to a fast, competitive, direct, triflic anhydride induced transformation of (trimethylsilyl)enolethers into vinyl triflates.

2. Results and discussion

Many ways to trap radical species are known. Among them, their interaction with enol ethers or esters appeared to be useful both on a mechanistic and on a synthetic point of view since they can lead to α-substituted ketones [7b,9]. For that purpose, we choose, as a first example, (trimethylsilyl)enolethers which appeared to survive partially under such harsh conditions. Thus

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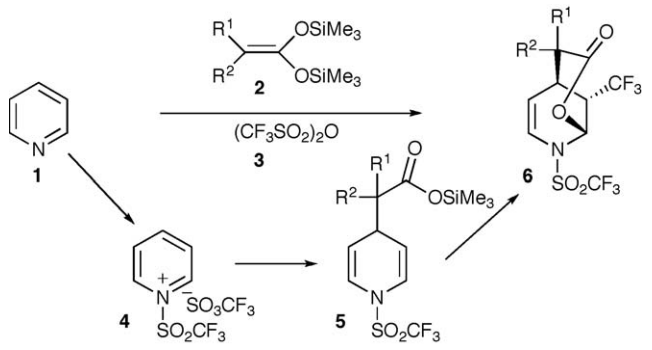


Scheme 1.

when triflic anhydride **3** (1.5 eq.) was added to a dichloromethane solution of collidine **7** (2 eq.) and 1-phenyl-1-trimethylsiloxyethylene **12** (1 eq.) at room temperature, the mixture turned rapidly deep red. After 12 h, water was added and the organic layer washed with aqueous potassium hydroxide. After evaporation of the volatiles, the residue was chromatographed on silica gel, leading, besides unreacted collidine, to five new compounds (Scheme 3). Elution with light petroleum ether/dichloromethane (97/3) led successively to two crystalline, difficult to separate compounds in almost equal amounts in a low 5% yield. Extended NMR experiments allowed to establish the structures of these two compounds. The ^{1}H NMR spectrum of the less polar product **13a**, m.p. 168 °C, disclosed a signal at δ 0.09 ppm, corresponding to a TMS group, at δ 1.89 ppm and δ 3.30 ppm as two doublets of quartets (J = 11 and 16 Hz), each for one proton, and at δ 7.36 to 7.49 ppm for five aromatic protons.

Both the ^{19}F NMR and ^{13}C NMR spectra confirmed the presence of fluorine, hence of a CH_2CF_3 group, giving in the ^{19}F spectrum a triplet at δ −54.88, (J = 11 Hz) and in the ^{13}C spectrum a quartet at δ 126.33 ppm (J = 276 Hz) for the CF_3 group, and a quartet at δ 39.28 ppm (J = 26 Hz) for the CH_2 linked to the CF_3 group. Crystals suitable for an X-ray structure determination were grown from heptane solutions at low temperature. As can be seen on the ORTEP view (Fig. 1), compound **13a** results from the combination of two C(Ph)(OSiMe$_3$)(CH_2CF_3) units. Having a plane of symmetry, it is a *meso* compound.

Such a combination can however give rise besides the *meso* form to a pair of *d,l* enantiomers: [10] the slightly more polar compound **13b** corresponds clearly to the *d,l* isomer. Indeed, its ^{1}H NMR spectrum is only slightly different from that of **13a**, showing up signals at δ 0.28 for the TMS group, at δ 2.86 ppm and 3.12 (dq, J = 16 and 11 Hz) for the two diastereomeric hydrogens of the methylene groups, and at δ 7.13 to 7.20 ppm signals for five aromatic protons. Three more polar compounds could although be isolated: first a liquid the NMR data of which were in all respect identical with those of the known vinyl triflate **14**, [11] with typical

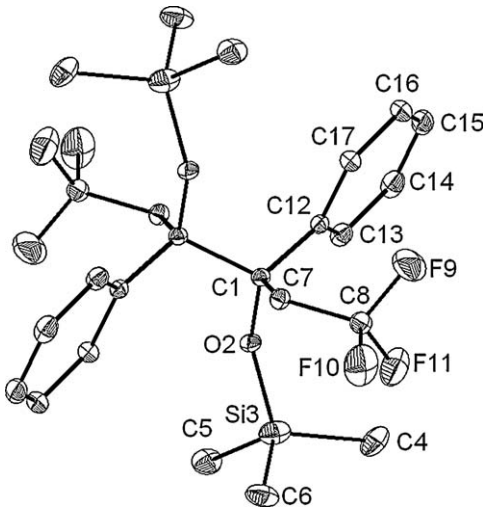
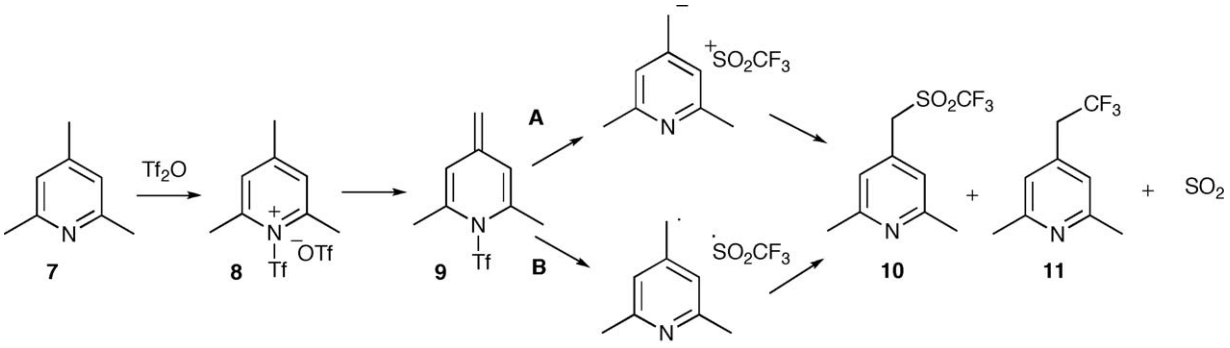


Fig. 1. X-ray structure of compound **13a**.

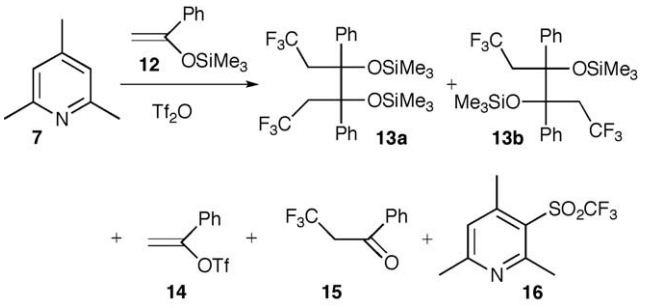
signals at δ 5.60 (d, J = 4 Hz) and 5.37 (d, J = 4 Hz)ppm, each for one proton, then a low-melting solid (5%), the NMR data of which agreed with those of the known trifluoromethyl acetophenone **15**, disclosing in the ^{1}H NMR spectrum a signal at δ 3.78 ppm for the two CH_2CF_3 protons, as a quartet (J = 10 Hz) and in the ^{19}F NMR spectrum, a triplet (J = 10 Hz), at δ −61.98 ppm [6f]. Finally, a more polar product (10%), eluted with PE/dichloromethane (60/40), as a yellow oil. Its spectroscopic data as well as its mass spectrum agreed with structure **16**. Indeed, the ^{1}H NMR spectrum disclosed a singlet, at δ 7.02 ppm for one proton, and δ 2.51, 2.62 and 2.84 ppm for three methyl groups. Both the ^{19}F and the ^{13}C NMR spectra confirmed the presence of a $-SO_2CF_3$ group on the collidine ring with a singlet at δ −79.33 ppm and a quartet at δ 120.38 ppm, J = 325 Hz. Deprotection to the corresponding diols **17a,b** was achieved upon treatment of **13a,b** with NBu_4F, H_2O [12]. The NMR data of the diols fully agreed with such structures with the typical series of doublets of quartets for the CH_2CF_3 groups and the disappearance of the signals for the $SiMe_3$ groups (Scheme 4).

This confirms thus that CF_3 species can be formed from triflic anhydride reacting with collidine, but that these species are in fact free radicals escaping from the solvent cage. (Scheme 2, route **B**) The intermediate stabilized radicals **18**, obtained upon their interaction with the enol ether **12** can either undergo a dimerization reaction to give the observed pinacol ethers **13a,b** or might undergo a further oxidation to **19** to afford the trifluoromethylketone **15** *via* **19** (Scheme 5). As far as the product **16** is concerned, its structure is not unexpected and is the result of the sulfination of the collidine ring.

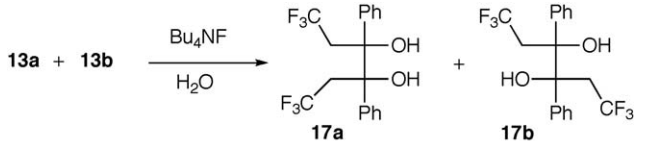
When however the enol ether of cyclohexanone was used, neither of the expected addition products was observed. Instead, a



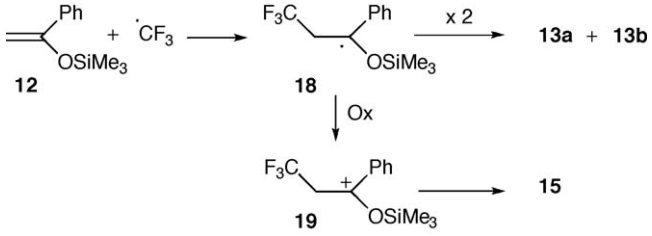
Scheme 2.



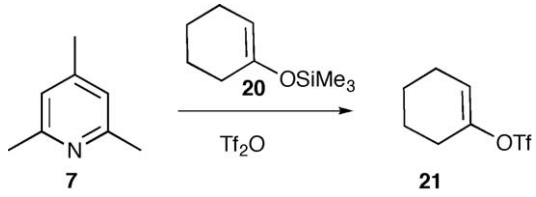
Scheme 3.



Scheme 4.



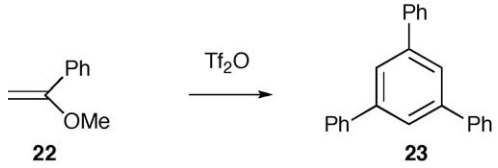
Scheme 5.



Scheme 6.

quantitative transformation of the TMS enol ether **20** into the corresponding vinyl triflate **21** took place (Scheme 6).

A similar transformation could be achieved in the absence of collidine, by simply mixing the enol ether **20** in dichloromethane, at room temperature, with triflic anhydride. Moreover, under such conditions, the enol ether **12** behaved similarly: it gave, as sole product, the vinyl triflate **14** with the exclusion of any products **13** and **15** arising from radical reactions [14,15]. This observation is thus in agreement with the partial transformation of **12** into **14** during the transformation depicted in the Scheme 3 and with the involvement of both picoline and triflic anhydride for the formation of CF_3 radicals [13]. Alkylenolethers such as **22** which might also be used as radical scavengers proved even more reactive towards triflic anhydride: a fast, undesired reaction led only to **23**, 1,3,5-triphenylbenzene, a triflic anhydride induced elimination-trimerization product [16] (Scheme 7).



Scheme 7.

3. Conclusion

The results reported herein provide clear-cut evidence for the formation of electrophilic CF_3 radicals upon the interaction of methyl-substituted pyridines with triflic anhydride. In spite of our efforts, there remains however a considerable drawback to these quenching reactions: the high reactivity of triflic anhydride towards all of the unsaturated scavengers used so far. Work is progressing to the use of such substrates in the transformation depicted in the Scheme 1.

4. Experimental

All commercially available reagents were used without further purification. ^1H, ^{13}C, ^{19}F NMR spectra were recorded on a Bruker Avance 400 spectrometer. CH_2Cl_2 was distillated on CaH_2 before use.

4.1. Reaction of (trimethylsilyl)enolether **12** *with triflic anhydride in the presence of collidine* **7**

To a solution of collidine (1 g, 8.32 mmol, 1.1 mL) and 1-phenyl-1-trimethylsiloxyethylene (0.8 g, 4.16 mmol, 852 μL) in dichloromethane (50 mL) was added slowly at room temperature triflic anhydride (1.7 g, 6.24 mmol, 1.1 mL) with syringe. The mixture turned rapidly deep red. After 12 h, water was added and the organic layer washed with aqueous potassium hydroxide. After evaporation of the volatiles, the residue was chromatographed on silica gel. Elution with light petroleum ether/dichloromethane (97/3) led successively to two crystalline, difficult to separate compounds in almost equal amounts **13a** and **13b** (56 mg, 5% yield).

13a: white solid, m.p. 168 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.49 (m, 2H), 7.36 (m, 3H), 3.30 (dq, J = 16, 11 Hz, 1H, CH_2), 1.89 (dq, J = 16, 11 Hz, 1H, CH_2), 0.09 (s, 9H, $SiMe_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.62 (q, arom), 128.84, 127.96, 127.02 (arom), 126.33 (q, J = 276 Hz, CF_3), 83.82 (C–O), 39.28 (q, J = 26 Hz, CH_2), 2.51 ($SiMe_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ −54.88 (t, J = 11 Hz); Analysis for $C_{24}H_{32}F_6O_2Si_2$: calcd, C, 55.15; H, 6.17; found, C, 55.26; H, 6.11.
13b: white solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.20 (m, 2H), 7.13 (m, 2H), 6.70 (m, 2H), 3.12 (dq, J = 16, 11 Hz, 1H, CH_2), 2.86 (dq, J = 16, 11 Hz, 1H, CH_2), 0.28 (s, 9H, $SiMe_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.92 (q, arom), 128.87, 127.96, 126.52 (arom), 126.41 (q, J = 276 Hz, CF_3), 85.94 (C–O), 37.26 (q, J = 26 Hz, CH_2), 3.01 ($SiMe_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ −55.85 (t, J = 11 Hz). Further elution gave a liquid **14** [11] (250 mg). Then **15**: (40 mg, 5% yield) deliquescent solid. ^1H NMR (400 MHz), $CDCl_3$): δ 7.93 (m, 2H), 7.63 (m, 1H), 7.50 (m, 2H), 3.78 (q, J = 10 Hz, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.78 (CO), 135.94, 134.28, 129.03, 128.45 (arom), 124.08 (q, J = 275 Hz, CF_3), 42.15 (q, J = 28 Hz, CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ −61.98 (t, J = 10 Hz). And finally **16**: (158 mg, 10% yield) yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.02 (s, 1H, arom), 2.84 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 2.51 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.63, 162.56, 153.28 (3 C–Me)126.18 (C–H), 123.54 (C–SO_2), 120.38 (q, J = 325 Hz, CF_3), 26.13 (CH_3), 24.47 (CH_3), 22.58 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ −79.33 (s, CF_3); HRMS for $C_9H_{11}O_2NF_3$ ($M+H^+$), calcd: 254.04571; found: 254.04509.

4.2. Deprotection of **13a** *and* **13b** *with* Bu_4NF

To a solution of a mixture (50/50) of **13a** and **13b** (50 mg, 0.17 mmol) in THF (3 mL) was added a solution of Bu_4NF in THF

(1 M, 0.2 mL). After 17 h at room temperature water was added and the organic layer washed several times with water. After evaporation of the volatiles, the residue was chromatographed on silica gel. Elution with light petroleum ether/ethyl acetate (95/5) led successively to two oily, difficult to separate compounds in equal amounts **17a** (18 mg, 30% yield))and **17b** (19 mg, 30% yield)

17a: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (m, 2H), 7.40 (m, 3H), 3.19 (dq, J = 16, 11 Hz, 1H, CH_2), 2.50 (q, J = 2 Hz, 1H, OH), 2.09 (dq, J = 16, 11 Hz, 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.82 (q arom), 128.92, 127.83, 127.78 (arom), 126.45 (q, J = 276 Hz, CF_3), 127.56 (arom), 78.14 (C–OH), 39.36 (q, J = 25 Hz, CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ −58.03 (dt, J = 11, 2 Hz); HRMS calcd for $C_{18}H_{16}F_6O_2Na$: 401.09467, found 401.09418. **17b**:^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (m, 5H), 3.30 (q, J = 2 Hz, 1H, OH), 3.13 (dq, J = 16, 11 Hz, 1H, CH_2), 2.43 (dq, J = 16, 11 Hz, 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.02 (q arom), 128.49 (arom), 126.41 (q, J = 276 Hz, CF_3), 78.94 (C–OH), 37.91 (q, J = 26 Hz, CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.81 (t, J = 11 Hz).

Supplementary material

Crystallographic data (excluding structure factors) for the structural analysis of **13a** have been deposited with the Cambridge Crystallographic Data Centre**:** CCDC No 738546. Copies of the crystallographic data may be obtained free of charge from: The Director, CCDC, 12 Union Road, Cambridge CB2 1Z, UK (fax: +44 123 336033; E-mail: deposit@ccdc.ac.uk or http://www.ccdc.cm.ac.uk).

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