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"Pseudo-Cationic" Trifluoromethylation of Enol Esters with Sodium Trifluoromethanesulfinate.

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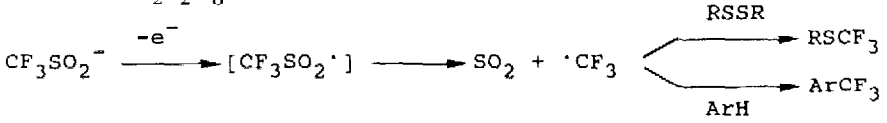
Key Words : trifluoromethylation ; enol esters ; sodium trifluoromethanesulfinate ; t-butyl hydroperoxide ; copper(II) catalyst

Abstract : Enol esters are converted into corresponding trifluoromethylated ketones and/or enol esters with sodium trifluoromethanesulfinate and t-butyl hydroperoxide in the presence of catalytic amounts of Cu(II).

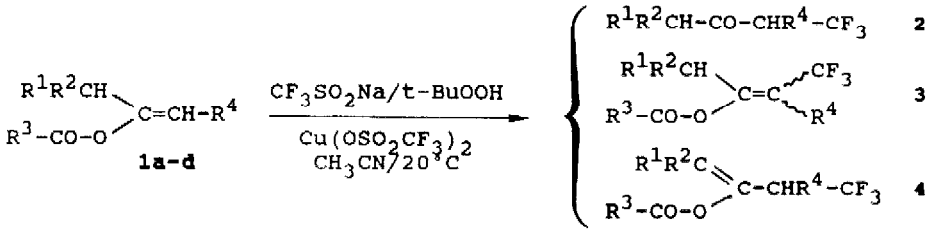
The trapping of the electrophilic radical $\cdot CF_3$ by electron-rich substrates, like olefins[1], aromatics[2] or disulfides[3], is a tool of growing interest in organofluorine chemistry. This radical can result from the homolysis of rather sophisticated reagents like CF_3-N(NO)-SO_2CF_3 (TNS-Tf)[4] but is more commonly generated by reduction of bromotrifluoromethane with precursors of the sulfur dioxide radical-anion[2,3]. We have recently reported that $\cdot CF_3$ can be also produced by monoelectronic oxidation of sodium trifluoromethanesulfinate with aqueous t-butyl hydroperoxide. Under these conditions, $\cdot CF_3$ is trapped by disulfides[5] and aromatic compounds[6] and, for that purpose, t-BuOOH was found to be a more suitable oxidizer than $K_2S_2O_8$ or cerium ammonium nitrate[5].

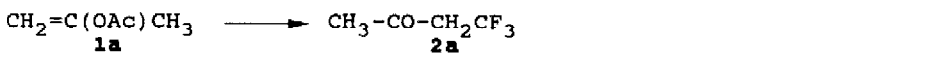


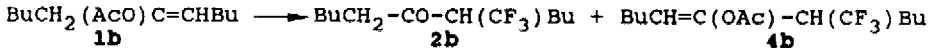
Our study has been extended by examining the behaviour of CF_3SO_2Na (available from CF_3Br and sodium dithionite[7] or Zn/SO_2[8]) towards enol esters in the presence of aqueous t-butyl hydroperoxide. This system did not deliver cleanly the expected trifluoromethylated ketone or enol ester from isopropenyl acetate : numerous products were detected by ^{19}F NMR, among which some ones could result from a radical coupling. Indeed, Huang *et al.* reported, during the course of our work, the bromo-substitutive perfluoroalkylation of allyl and propargyl bromides with sodium perfluoroalcanesulfinates and $(NH_4)_2S_2O_8$ (chosen as the best oxidizer)[9], in which the radical nature of the process was proven by the by-production of R_fCO_2H and R_fCF_2Br, sometimes in significant yields:

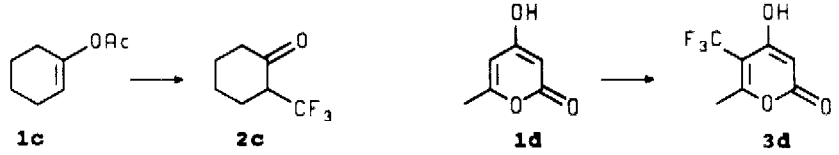
$$CH_2{=}CHCH_2Br \xrightarrow[(NH_4)_2S_2O_8]{R_fCF_2SO_2Na} R_fCF_2CH_2CH{=}CH_2 \quad (+\ R_fCO_2H + R_fCF_2Br)$$

Our bad result from isopropenyl acetate could be related to the fact that t-BuOOH does not oxidise efficiently the carbon-centered radicals. As Cu^{2+} is known to be very effective in the oxidation of such radicals[10,11], the further experiments were performed in the presence of a catalytic amount of cupric trifluoromethanesulfonate. Under these conditions, trifluoromethylated ketones and/or enol esters were cleanly obtained, depending on the substrate[12] :







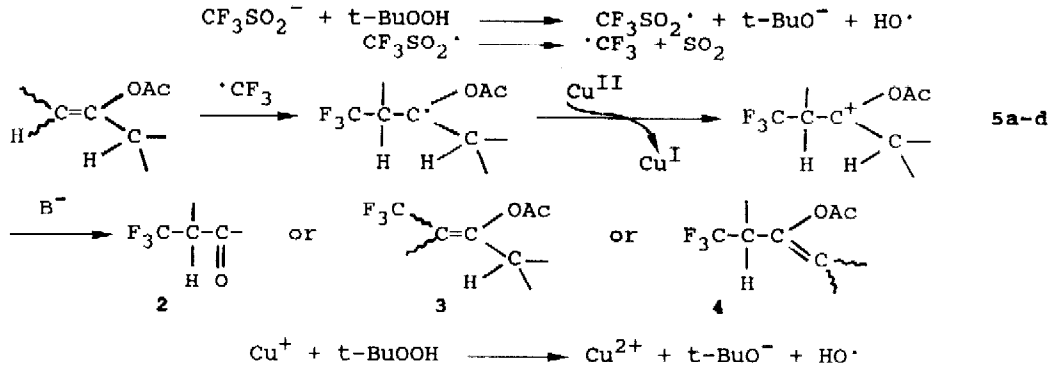


Entry	1	$CF_3SO_2^-$ (eq.)	t-BuOOH (eq.)	Cu^{II} (eq.)	CH_3CN (*)	Product	yields (%) (**)
1	**1a**	1	3	0.1	1.5	**2a**	53[13]
2	**1b**	2	4	0.25	3	**2b** **4b**	22 (19)[14] 2
3	**1b**	4	5	0.25	3	**2b** **4b**	55 (44)[14] 8
4	**1c**	4	5	0.25	3	**2c**	66 (53)[15]
5	**1d**	4	7	0.25	3	**3d**	60 (53)[16]

(*) ml/mmol **1** ; (**) isolated yield into brackets

It appears, from entries 2 and 3, that a sufficient excess of sodium trifluoromethanesulfinate is needed to obtain fluorinated products in fair yields. This is in accordance with the previous observation that $\cdot CF_3$ behaves as a moderately reactive electrophile, very sensitive to steric hindrance[5] (cf. entries 1 and 3). **1d**, which bears a free enolic moiety and an esterified one, was trifluoromethylated on the enol ester only. The apparent unreactivity of the free enol function, which could deliver an α-trifluoromethylated tertiary radical as stable as the observed one, could be attributed to an unfavourable conjugation with the carbonyl group.

From the comparison between the preliminary experiment (without Cu^{II}) and the further ones (with Cu^{II}), it can be assumed that the process implies the formation of a radical which is further oxidised into a cation. Consequently, the following mechanism is proposed :



Thus, the CF_3SO_2Na/t-BuOOH/Cu^{II} system can be considered as a formal "cationic" trifluoromethylating reagent.

Some deprotonation competed with deacetylation from **5** during the trifluoromethylation of 6-acetoxy-5-undecene **1b**. When, under the conditions of experiment 3, one equivalent of sodium acetate was added to CF_3SO_2Na (while keeping other parameters constant), the ratio between deacetylation and deprotonation decreased (**2b/4b** = 23/22 instead of 55/8) and two isomeric **4b** (in the ratio 17/5) were detected by NMR instead of one. However, the total trifluoromethylation yield dropped (45% v.s. 63%). It can be noted that, when the cation **5** bears an hydrogen α to both cationic centre and CF_3 group and another hydrogen α' to the cationic centre, as in **5b** (from 6-acetoxy-5-undecene), deprotonation occurs by the exclusive abstraction of the α' hydrogen : **4b** was formed and **3b** was not. This fact could be explained by the field effect of the strongly electronegative CF_3 moiety which prevents the approach of a base from the α position, though the α hydrogen would be more acidic, on a thermodynamic point of view, than the α' one. When no α' hydrogen is present, as in **5d**, the α one is, nevertheless, expelled.

In conclusion, the present method offers a cheap and mild access to α-trifluoromethylated ketones far more efficient than the electrochemical trifluoromethylation of isopropenyl acetate with CF_3CO_2H[17] and more convenient than the condensation of 2,2,2-trifluorodiazoethane with aldehydes[18] as well as the reaction of CF_2Br_2 (2 steps)[19] or $CF_3Br/Zn/C_5H_5N$ (under pressure)[20] with enamines.

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12. In a typical procedure, 7.8 ml of 63% aqueous t-BuOOH (50 mmol) were dropped at room temperature, within 100 min by the mean of a syringe pump, onto a solution of 6-acetoxy-5-undecene (10 mmol), CF_3SO_2Na (40 mmol) and $Cu(OSO_2CF_3)_2$ (2.5 mmol) in acetonitrile (30 ml). After standing at room temperature for 2,5 hours then treatment with aqueous sodium metabisulfite, an oily layer was separated. The remaining solution was extracted with petroleum ether (3x30 ml). The organic phases were gathered, dried and evaporated. The products were separated by column chromatography on silica.

13. Titrated by ^{19}F NMR (CF_3CH_2OH as internal standard) and characterized as 2,4-dinitrophenylhydrazone **6a**.
^{19}F NMR ($CDCl_3$, $CFCl_3$, 56.4 MHz, ϕ_F in ppm, J in Hz) : **2a** : -63.0 (t, J= 10) ; **6a** : -64.3 (t, J= 10).
^1H NMR ($CDCl_3$, TMS, 60 MHz, δ in ppm, J in Hz) : **6a** : 9.0 (d, J= 2, 1H) (H arom.), 8.25 (dd, J= 10, J=2, 1H) (H arom.), 7.85 (d, J= 10, 1H) (H arom.), 3.2 (q, J= 10, 2H) (CH_2CF_3), 2.2 (s, 3H) (CH_3), 2.1 (s, 1H) (NH).
MS (m/e, %) : **6a** : 306 ($M^{+\cdot}$, 65), 79 (83), 78 (64), 77 (53), 43 (63), 42 (99), 41 (93), 39 (74), 30 (100).

14. ^{19}F NMR ($CDCl_3$, $CFCl_3$, 75.2 MHz, ϕ_F in ppm, J in Hz) : **2b** : -67.35 (d, J= 9) ; **4b** : -69.34 (d, J= 9) (minor isomer), -70.20 (d, J= 9) (major isomer).
^1H NMR ($CDCl_3$, TMS, 300 MHz, δ in ppm, J in Hz) : **2b** : 0.83 to 2.16 (m, 18H) (C_4H_9), 2.41 to 2.52 (dt, $^2J_{H^1H^2}$= 18, $^3J_{H^2CH2}$= 7.2, 1H) (CH_2-CH^1H^2-CO), 2.56 to 2.67 (dt, $^2J_{H^1H^2}$= 18, $^3J_{H^1CH2}$= 7.3, 1H) (CH_2-CH^1H^2-CO), 3.12 to 3.26 (qdd, $^3J_{H^3F}$= 9.1, $^3J_{H^3H}$= 4.6 and 9, 1H) (CH_2-CH^3(CF_3)-CO).
GPC/MS (m/e, %) : **2b** : 238 ($M^{+\cdot}$, 3), 99 ($C_5H_{11}CO$, 100), 71 (C_5H_{11}, 46), 56 ($C_4H_8^{+\cdot}$, 13), 55 (22), 43 (C_3H_7, 90), 42 (11), 41 (26), 29 (C_2H_5, 30), 27 (14) ; **4b** : 280 ($M^{+\cdot}$, 0.3), 238 (M - $COCH_3$, 7), 167 ($C_3H_7CH(CF_3)CO$, 13) + same cleavages as **2b** : 99 (41), 56 (14), 55 (48), 43 (100), 41 (12), 29 (13).

15. ^{19}F and ^1H NMR spectra are in agreement, for **2c**, with less precise previous data[19].
^{19}F NMR ($CDCl_3$, $CFCl_3$, 188.2 MHz, ϕ_F in ppm, J in Hz) : -69.40 (d, J= 8).
^1H NMR ($CDCl_3$, TMS, 200 MHz, δ in ppm, J in Hz) : 1.62 to 2.19 (m, 6H) ($[CH_2]_n$), 2.27 to 2.56 (m, 2H) (CH_2CO), 2.98 to 3.19 (qdd, $^3J_{HF}$= 8, $^3J_{HH}$= 5 and 2, 1H) (CH_2-$CH(CF_3)$-CO).
GPC/MS (m/e, %) : 166 ($M^{+\cdot}$, 15), 138 (M - CO, 3), 77 (10), 55 (CH_2=CH-CO, 100), 42 ($C_3H_6^{+\cdot}$, 47), 41 (C_3H_5, 15), 39 (13), 27 (13).

16. ^{19}F NMR ($CDCl_3$, $CFCl_3$, 56.4 MHz, ϕ_F in ppm) : -56.0 (s).
^1H NMR ($CDCl_3$, TMS, 80 MHz, δ in ppm) : 2.22 (s, 3H) (CH_3), 6.12 (s, 1H) (=CH-CO), 10.5 to 12 (m, 1H) (OH).
GPC/MS (m/e, %) : 194 ($M^{+\cdot}$, 34), 166 (M - CO, 20), 91 (36), 85 (35), 55 (10), 69 (166 - CF_3CO, 87), 43 (CH_3CO, 100), 42 (12).
Elemental analyses : calc. for $C_7H_5F_3O_3$: C, 43.31 ; H, 2.60 ; O, 24.73 ; F, 29.36 ; found : C, 43.27 ; H, 2.45 ; F, 29.12 .

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