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Regioselective electrophilic trifluoromethylation of substituted anilines and derivatives in superacid

Sébastien Debarge, Bruno Violeau, Nohair Bendaoud, Marie-Paule Jouannetaud* and Jean-Claude Jacquesy

Laboratoire 'Synthèse et Réactivité des Substances Naturelles', UMR 6514, 40, Avenue du Recteur Pineau, F-86022 Poitiers Cedex, France

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Abstract—In a one pot procedure, treatment of chloro or methyl substituted acetanilides in $HF/SbF_5/CCl_4$ followed by addition of HF/pyridine yields trifluoromethyl derivatives with high regioselectivity.

1. Introduction

Trifluoromethylated aromatics are of major importance and have found a large number of uses as pharmaceutical and agrochemical agents.

Trifluoromethylation of aromatics can be carried out by conversion of a substituted methyl group ($-CCl_3$, $-C(SMe)_3$, CO_2H) to a trifluoromethyl group, by use of trifluoromethyl radicals or trifluoromethylcopper, or by trifluoromethyl dibenzothiophenium salts and their seleno analogues.[1] One pot direct trifluoromethylation can be performed when an aromatic substrate is reacted with carbon tetrachloride in the presence of HF and a Lewis acid.[2]

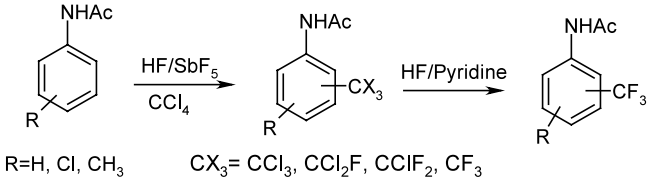
We have previously reported the electrophilic bromination or hydroxylation of anilines, and anilides in a superacid.[3–5]

We would like to report in this paper the electrophilic trifluoromethylation of these substrates in HF/SbF_5 in the presence of carbon tetrachloride, followed by the treatment of the resulting mixture with the fluorinating agent HF/pyridine to complete the halogen exchange (Scheme 1).

2. Results

In a typical experiment, to a mixture of HF (6 mL) and antimony pentafluoride SbF_5 (3 mL) magnetically stirred at −20°C in a teflon reactor, was firstly added the substrate (2 mmol), then carbon tetrachloride (0.58 mL, 3 equiv.). The mixture was maintained at 0°C for 0.5–2 h, according to the substrate (see Tables 1 and 2). The mixture was then cooled at −78°C and HF/pyridine 70/30 (v/v) (2 mL) was carefully added. The reaction mixture was then kept at 0°C overnight, then very carefully poured into a vigorously stirred mixture of Na_2CO_3, H_2O and ice. After extraction with ethyl acetate (three times) and usual work-up, the reaction mixture was evaporated to dryness.

The results reported in Table 1 deserve several comments: anilines **1a–d** are too deactivated by *N*-protonation to react.[6] This result reflects the poor electrophilic power of 'CCl_3^+' obtained from CCl_4, the same substrates yielding the three hydroxyanilines when treated with $HF/SbF_5/H_2O_2$.[4] On the other hand, with toluidi-



R=H, Cl, CH_3 CX_3= CCl_3, CCl_2F, $CClF_2$, CF_3

Scheme 1.

* Corresponding author. Tel.: +33-(0)5-4945-3702; fax: 33-(0)5-4945-3501; e-mail: marie.paule.jouannetaud@univ-poitiers.fr

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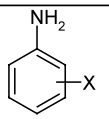
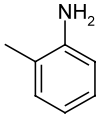
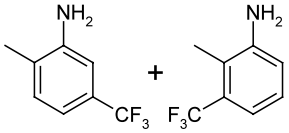
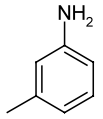
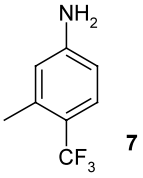
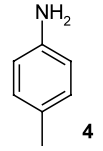
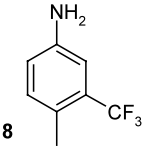
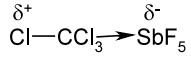
Table 1. Trifluoromethylation of anilines

Substrate	Product(s)	Time (h)	Yield (%)
 **1** a-d *	No reaction	4	
 **2**	 **5** + **6** (4/1 ratio)	0.5	82
 **3**	 **7**	0.5	81
 **4**	 **8**	0.5	85

* **1a**: X=H, 1b: X=2-Cl, 1c: X=3-Cl, 1d: X=4-Cl

nes **2**–**4**, which are activated by a methyl substituent, trifluoromethylation is observed in *ortho* and/or *para* to the methyl group. Trifluoromethylation of toluidine **4** in the presence of trifluoromethyl bromide, zinc and SO_2 has been reported to yield the trifluoromethyl derivative, *ortho* to the amino group in low yield.[7]

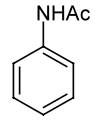
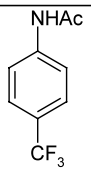
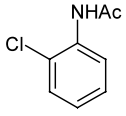
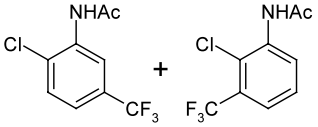
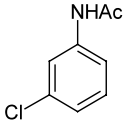
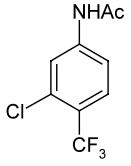
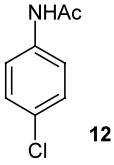
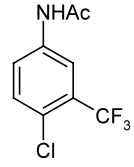
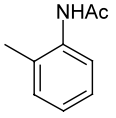
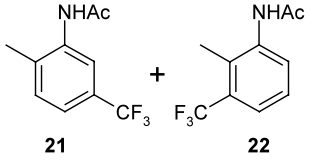
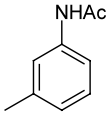
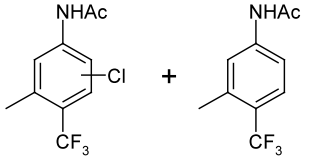
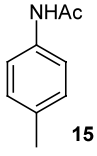
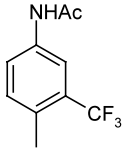
Table 2 shows that selective *para*-trifluoromethylation is observed with acetanilide **9** to yield compound **16** (65%), the more stabilized *O*-protonated substrate being more reactive than the anilinium ion (vide supra). This result has to be compared to the trifluoromethylation of acetanilide **9** by a source of trifluoromethyl radical leading to a mixture of the three trifluoromethyl derivatives.[8] Chloroacetanilides **10**–**12** give trifluoromethyl derivatives in excellent yields. A chlorine substituent is directing the substitution, leading for compounds **11** and **12** to a single isomer (**19** and **20**, respectively), and for compound **10** to two isomers **17** and **18**.[8,9] For compound **11**, no trifluoromethylation is observed in *para* of the chlorine because of steric hindrance and electronic repulsion between the electrophile and the *O*-protonated function. A similar substitution pattern is observed in the trifluoromethylation of compounds **13** to **15** activated by a methyl group. But surprisingly, the reaction of the *meta*-isomer **14** yields a mixture of chloro-derivatives **23** as major products and only traces of the expected *para*-substituted isomer **24** which is recovered unchanged when submitted again to the same reaction conditions. This implies that chlorination should occur on the trichloro (or partially fluorinated) intermediate, carbon tetrachloride acting as a chlorinating agent.[10]



Hydrogenolysis by H_2/Pd of the mixture of compounds **23** and **24** yields quantitatively compound **24** (global yield 70%). Similarly, treatment of compounds **19** and **20** gives compounds **16** and **26**, respectively, in excellent yield (Scheme 2).

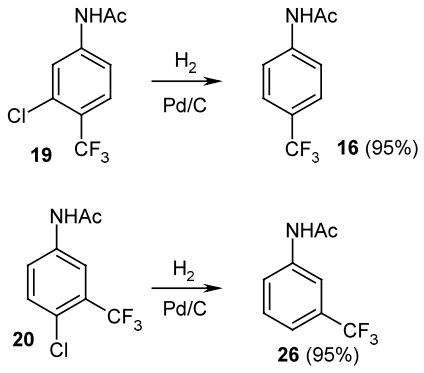
To conclude, aniline and chloroanilines **1a**–**d** appear to be too deactivated by protonation to react with the poorly electrophilic trichloromethyl ion, whereas hydroxylation of the same substrates was observed with protonated hydrogen peroxide in similar conditions. On the other hand, all the acetanilides studied yield trifluomethylderivatives with high regioselectivity and good yields. Whereas acetanilide yields directly the *para*-

Table 2. Trifluoromethylation of acetanilides

Substrate	Product(s)	Time (h)	Yield (%)
 **9**	 **16**	0.5	65
 **10**	 **17** + **18** (7/3 ratio)	2	82
 **11**	 **19**	2	84
 **12**	 **20**	2	85
 **13**	 **21** + **22** (4/1 ratio)	0.5	74
 **14**	 **23** major + **24**	0.5	70*
 **15**	 **25**	0.5	65

* yield of compound **24** obtained after hydrogenolysis of the mixture of products **23** and **24**

trifluoromethyl analog, *meta*-trifluoromethylation of *para*-chloroacetanilide followed by hydrogenolysis leads selectively to a *meta*-trifluoroacetanilide, the chlorine atom acting as an efficient auxiliary group. The selective synthesis of these trifluoro derivatives appears to be superior to those previously reported.



Scheme 2.

Acknowledgements

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