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SYNTHESIS OF ß-CHLORO(TRIFLUOROMETHYL)ACROLEINS AND A SPECIFIC REACTION TOWARDS ß-AMINOTHIOLS

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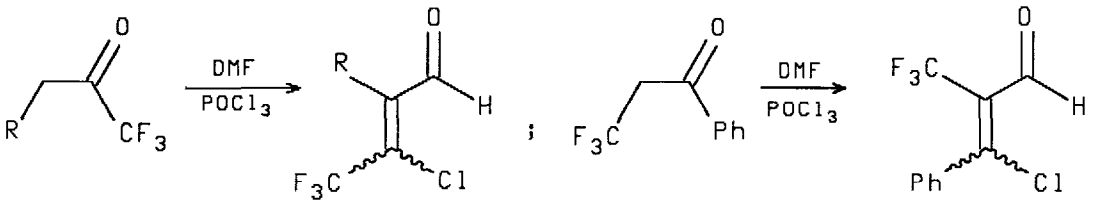
Summary : β-chloro-β-(trifluoromethyl)acroleins and β-chloro-α-(trifluoromethyl)-acrolein have been synthesized through Vilsmeier's reaction. A specific 1,4-addition of the nitrogen atom from β-aminothiols is observed.

An increasing interest is been paid to the chemistry of trifluoromethyl compounds, not only due to their potential biological applications (1, 2) but also for their specific chemical reactivity For example, within the last two years, Meazza (3) proposed a synthesis of 1-aryl-3,3,3-trifluoro-1-propynes, and Uneyama (4) reported on the reactivity of trifluoroacetimydoyl chloride ; Linderman (5) described also a regioselective synthesis of trifluoromethylquinolines from trifluoroacetylacetylenes. We wish to describe the synthesis of β-chloro(trifluoromethyl)acroleins and the specific reactivity of one of these towards two aminothiols.

We recently reported that the Vilsmeier's reaction applied on **1a** (6a) delivers a mixture of the **2a** Z,E diastereoisomers (80 % yield) (7). We investigated this synthesis more deeply and widened it to other substrates. Under the same experimental conditions, ethyl(trifluoro-acetyl)acetate **1b** gives only tars. Thus **1b** must be treated under much milder conditions (8). Compounds **4** [E/Z = 1 (9)], regio-isomers of **2a** were also prepared from **3**, obtained according to Hojo's method (10).

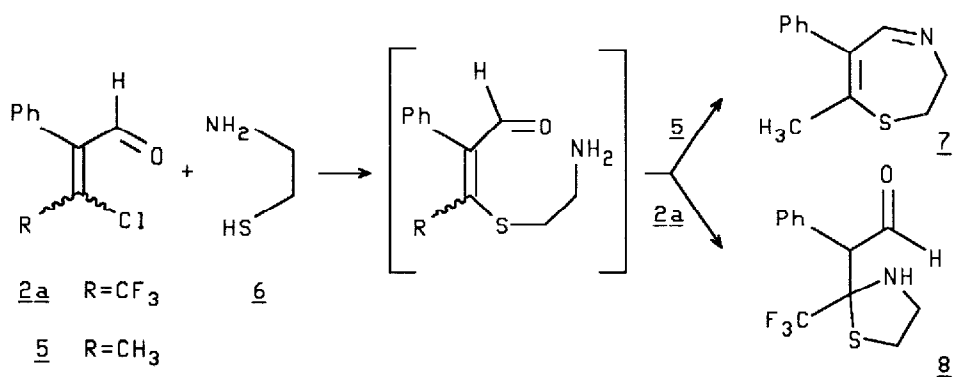


1 a R=Ph, b R=CO2Et — 2 Z/E — 3 — 4 Z/E

E,Z diastereoisomers from 2a,b were separated by column chromatography [2a · E/Z = 40/60 and 2b : E/Z = 72/28]. The attribution of the E or Z configuration was established by using Lloyd's results (8) concerning the differentiation of *trans* and *cis* chlorovinylaldehydes (11). A confirmation was obtained from the coupling constant between fluorine nuclei and aldehydic proton (12).

In order to prove the influence of the trifluoromethyl group, the reactivity of 2a was compared to that of the methylated analog 5E,Z obtained from the Vilsmeier's reagent and phenylacetone. 2a and 5 were reacted in T.H.F. with two α,β-aminothiols, in the presence of sodium hydride. The results are reported in schemes 1 and 2. Under these conditions, the methylated acrolein 5 reacted with α,β-aminoethanethiol 6 to deliver the thiazepine 7 exclusively (13) whereas the trifluoromethylated compound 2a produced the thiazolidine 8 only (14).

The first step of these reactions involves the known 1,4 addition of sulfur atom on the acrolein (scheme 1), in the same way as previously described with sodium sulfide (6). When the substituent is a methyl group, a further classical **1,2-addition of the nitrogen atom** on the aldehyde takes place to form the thiazepine 7. On the contrary, the strong electrowithdrawing effect of the trifluoromethyl group reverses the reactivity of the conjugated aldehyde : **1,4-addition of the nitrogen atom** occurs only, to form the thioazolidine 8.

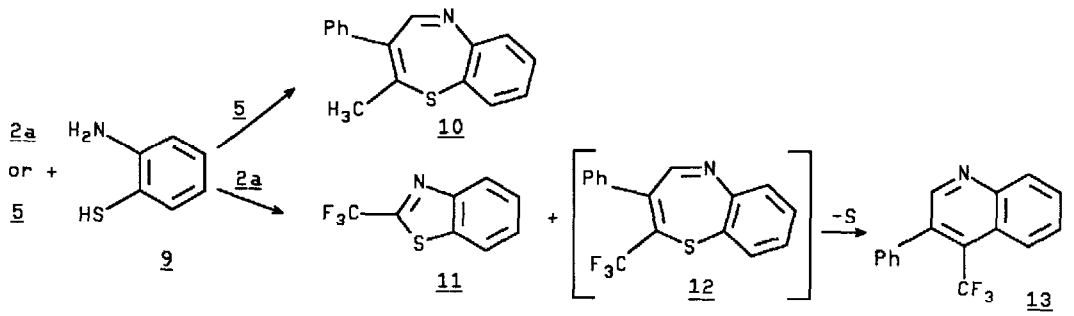


2a R=CF3 6

5 R=CH3

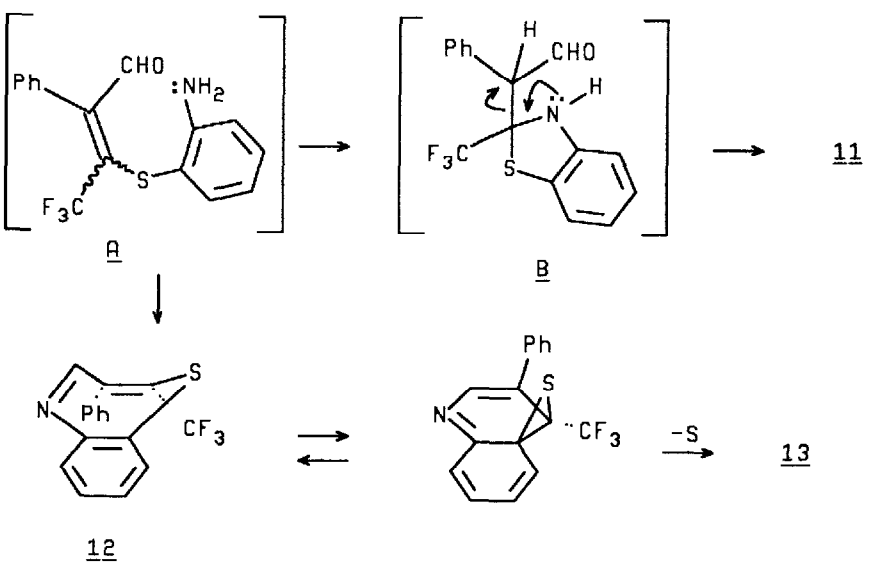
Scheme 1

In order to try to force the 1,2-addition of the nitrogen atom on the aldehyde 2a, we reacted the trifluoromethylated compound with 2-aminothiophenol 9, the structure of which should favoured 1,2-addition (scheme 2). Whereas methylated acrolein 5 gave quantitatively the benzothiazepine 10 (15), the trifluoromethylated compound 2a delivered a mixture of the benzothiazole 11 (33 %) (16) and the unstable benzothiazepine 12 which is evolved into the quinoline 13 (30 %) at room temperature (17).



Scheme 2

The first step of the reaction (scheme 3) involves probably the formation of the A intermediate. Benzothiazole 11 further results from a 1,4 intramolecular addition of the nitrogen atom, followed by a retroaldolisation, favoured by an extension of the aromaticity. The 1,2-intramolecular addition of the nitrogen atom takes place also from A and leads to the benzothiazepine 12 (caracterized by its N.M R. spectra). The elimination of a sulfur atom from heterocyclic systems has been previously reported (18).



Scheme 3

A thiirane intermediate is postulated in all cases. The rearrangement of **12** to **13**, which occurs at room temperature is favoured by the trifluoromethyl group since the methylated thiazepine **10** is stable. The instability of the trifluoromethylated benzothiazepine versus the methylated thiazepine should agree with a mechanism in which the rate determining step should be an electrocyclic isomerization on a boat like conformation, which must be favoured by the interaction between sulfur and the electronegative trifluoromethyl group (scheme 3).

Notes and references

Chemical shifts are given in ppm (δ H,C ; ϕ F) relative to the T.M.S. and $CFCl_3$. Coupling constants for J_{ab} are in Hz.

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b) R. Hoffmann, D. Greif, M. Pulst, M. Weissenfels and A. Laurent, Z Chem , 1990, **30**, 247.

7 - **2a** experimental procedure · $POCl_3$ (309 mmol), DMF (110 mmol), **1a** (110 mmol) stirring 3 h at 65°C ; work up with water and AcONa.

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9 - **4** (50 %) **E/Z**=1 ; ϕ=-70.5 and -73 7 ; δ_{CHO}=10.40 and 10.22

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11 - **2aZ** : δ_{CHO}=10.5, ϕ=-62, $J_{F,CHO}$=0 ; **2aE** : δ_{CHO}=10.2, ϕ=-58.3, $J_{F,CHO}$=2.2 ; **2bZ** : δ_{CHO}=9 98 ; ϕ=-60 7, $J_{F,CHO}$=1.41 ; **2bE** : δ_{CHO}=10 1, ϕ=-67.7, $J_{F,CHO}$=0

12 - a) F.B. Mallory, C.W. Mallory and M.B. Baker, J. Am Chem Soc., 1990, **112**, 2577.
b) C. Beguin (U.J.F., Grenoble), private communication.

13 - **7** is obtained by addition of **6** chlorhydrate at -70°, using 2 NaH RT 30 mn and work up (quantitative yield) ; mp=75-76°C (EtOH) ; δ_{CH_3}=1.96, δ_{CH_2S}=3.63, δ_{CH_2N}=2.90 (t, $J_{CH_2-CH_2}$=7), δ_{CHN}=9.10. δ_{CH_3}=17.05, δ_{CH_2S}=42.2, δ_{CH_2N}=37.9. MS m/z 203 ($M^{+\cdot}$), 188, 174, 115, 57, 29, 27 (100 %).

14 - **8** (94 %) (two diastereoisomers) : δ_{PhCH}=4 26 and 3 88, δ_{CHO}=9 9 and 9.85, ϕ=-74.3 and -74.6. IR : 1720 cm^{-1} ($\nu_{C=O}$).

15 - **10** : mp=132-133°C (EtOH). IR · 1640-1650 cm^{-1} ($\nu_{C=C}$ and $\nu_{C=N}$). δ_{CH_3}=2.82, δ_{CHN}=9 09. MS m/z 149 and 150 (100 %), 117, 108 and 109, 82, 69.

16 - **11** (33 %) : ϕ=-62.2. MS m/z 203 ($M^{+\cdot}$).
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17 - NMR spectrum shows a mixture of **12** and **13**. **12** is slowly transformed into **13** at room temperature. **12** : δ_{CHN}=8.6, ϕ=-60.3 **13** : δ_{CHN}=8.93, ϕ=-53.0. MS m/z 273 (M^{+}).

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