Tetrahedron Letters, Vol. 34, No. 15, pp. 2483-2486, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Trifluoromethyl Substitution Affects the Regiochemistry of Cyclising Condensation in 1,4 Substitution Processes

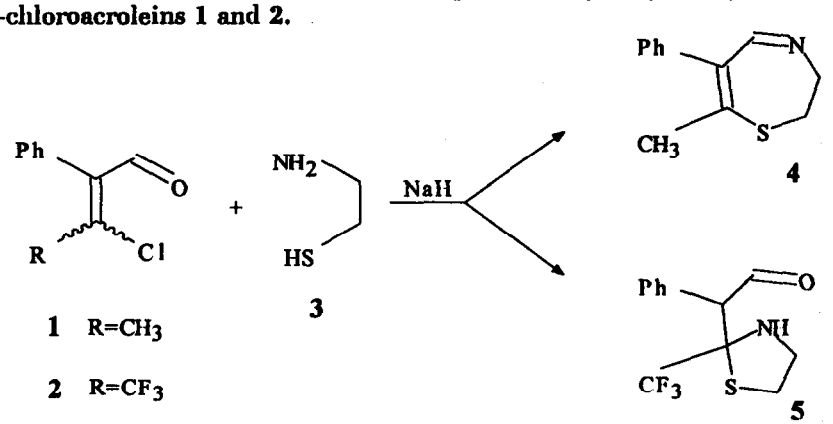
Gérard M. Alvernhe, André J. Laurent, Isabelle M. Le Dréan and Abdelaziz Selmi

Université Claude Bernard-Lyon I, Laboratoire de Chimie Organique 3, associé au CNRS,
43, Bd du 11 Novembre 1918, 69622 Villeurbanne (France)

Key words : Trifluoromethyl ; Michael reaction ; regiochemistry ; thiazolidine ; thiazepine

Abstract : β-Trifluoromethyl β-chloroacrolein **2** reacts with 2-mercaptoethylamine **3** to produce thiazolidine **5** instead of the expected thiazepine **8**. The reason of this behaviour is the formation of the tetrahedral intermediate **6** because of stabilisation by the trifluoromethyl group ; an intramolecular substitution takes place faster than a 1,4 addition-elimination process.

Recently, we reported that 3-chloro-2-phenylacroleins **1**, **2**, react with 2-mercaptoethylamine **3**, in basic medium, to deliver two different heterocyclic compounds (1) : the 3-methylacrolein **1** gives the thiazepine **4** in a quantitative yield, whereas the 3-trifluoromethyl compound **2** only produces the thiazolidine **5** (yield 94 %). In this paper, we report the reason of the difference, in the regiochemistry of cyclising condensation, of these two β-chloroacroleins **1** and **2**.



1 R=CH_3

2 R=CF_3

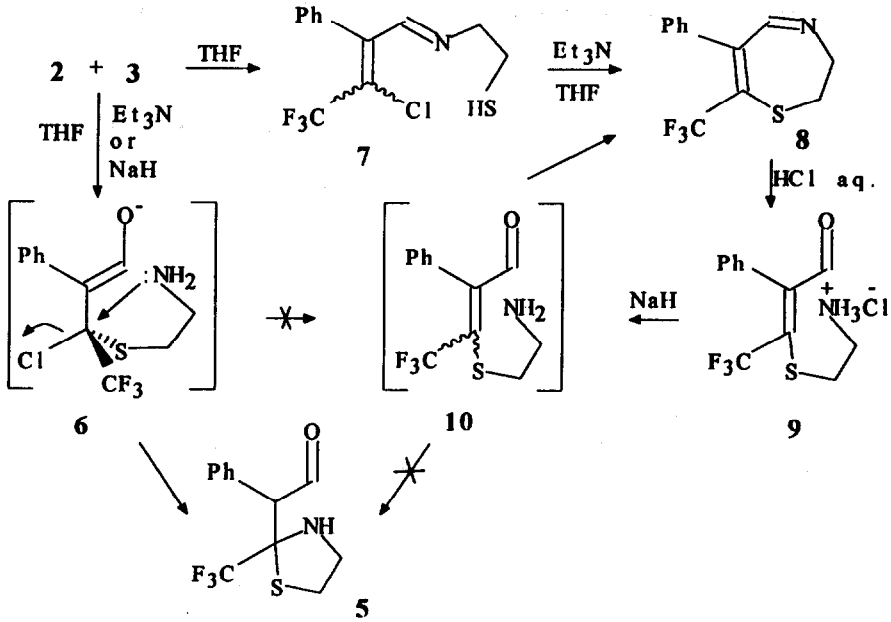
3

4

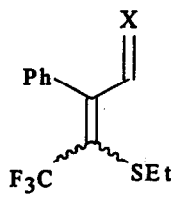
5

It is well known that 1,4 thiazepine derivatives are obtained by reaction of 2-mercaptoethylamine **3** with α,β unsaturated carbonyl compounds (2). Besides, the 1,4 addition-elimination of the 3-chloroacroleins and 3-chloro 2-alken-1-ones is well documented in the literature : it was shown (3) that the rate determining step is the second order addition reaction of nucleophile on the starting material and that the following elimination of the leaving group is the fast one. So from this classical mechanism, β-chloroacrolein **2** must give the β-vinylsulfure **10** from the intermediate **6**.

To study the reactivity of a β-trifluoromethyl β-sulfuracrolein with a primary amine, we realised first the reaction of the propylamine on **11**. No 1,4 addition was observed ; only the imine **12** is formed in a quantitative yield (4). This result is at variance with the formation of **10** as intermediate in the synthesis of the thiazolidine **5**.

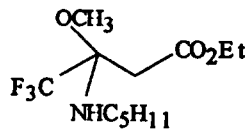


To confirm this hypothesis, we decided to try to prepare **10** and the thiazepine **8**. When **2** and **3** react together at 0°C during 15 min., without any base, the imine **7** is formed (5). Addition of triethylamine to a solution of the imine **7** produces its cyclisation into the thiazepine **8** (yield 80 %) (6). The thiazepine **8** was hydrolysed in acidic medium into the aminochlorhydrate **9** (7). In basic medium **9** gives only the thiazepine **8** (**9** → **10** → **8**). No formation of the thiazolidine **5** was observed by NMR of the crude. The β-trifluoromethyl β-sulfur **10** is not an intermediate in the formation of the thiazolidine **5**.



11 X=O

12 X=N-Pr

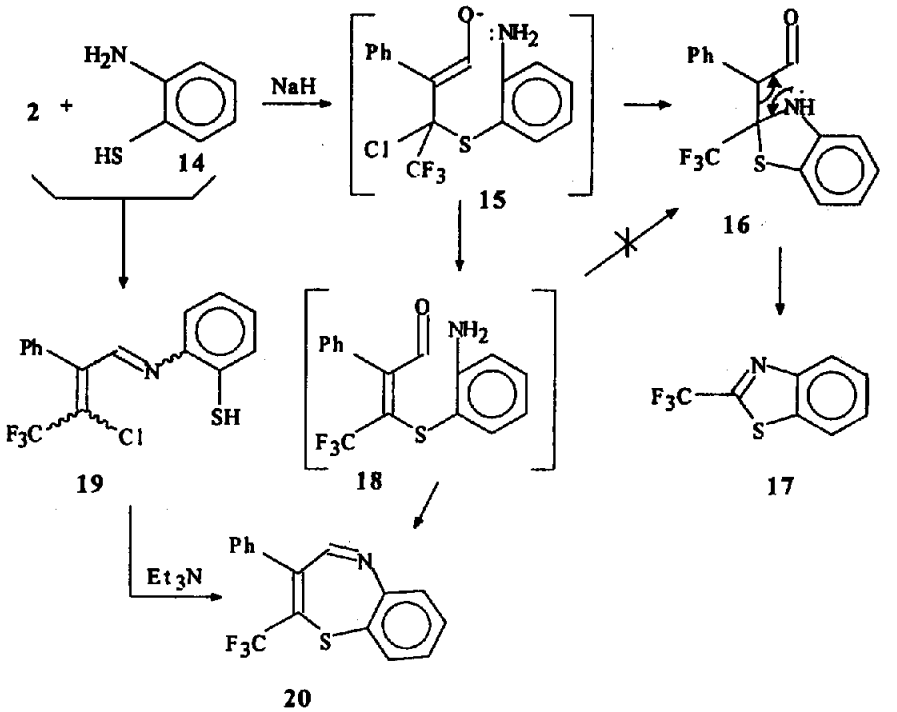


13

It is well known (8) that a trifluoromethyl group stabilises a tetrahedral intermediate : Joullié (9) has isolated at 0°C the ethyl 3-methoxy-3-(1-n-pentylamino)-4,4,4-trifluorobutyrate **13**. The well known stability of such trifluoromethyl adducts can explain the for-

mation of the thiazolidine **5**. The trifluoromethyl group stabilises the tetrahedral intermediate **6** and the intramolecular cyclisation of **6** to **5** takes place faster than the elimination of the chloride anion to form the 1,4 substitution product **10**.

The competition between the rate of the intramolecular cyclisation of the tetrahedral intermediate (**6** → **5**) and the elimination of the chloride anion (**6** → **10**) depends on the nucleophilicity of the amino group. Therefore we realised the same study on **2** with 2-thioaminophenol **14**.



In basic medium the tetrahedral intermediate **15** is probably formed. Owing to the poor nucleophilicity of the amino group of **15**, there is a competition between the intramolecular cyclisation (**15** → **16** → **17** yield 33 %) and the elimination of the chloride anion (**15** → **18** → **20** yield 30 %). The benzothiazepine **20** was also obtained by cyclisation of the iminothiol **19** (10).

References and notes

^{1}H NMR spectra were taken at 300.1 MHz ; ^{13}C spectra at 75.3 MHz and ^{19}F spectra at 57.8 MHz. Chemical shifts are given in ppm (δ H,C ; ϕ F) relative to TMS and $CFCl_3$ respectively. Coupling constants are in Hz.

1 a) Alvernhe G.; Langlois B.; Laurent A.; Le Dréan I. and Selmi A., *Tetrahedron Lett.*, **1991**, *32*, 643.
b) Laurent A.; Le Dréan I. and Selmi A., *Tetrahedron Lett.*, **1991**, *32*, 3071.

2 a) "*Comprehensive Organic Chemistry*", D.H.R. Barton ed., Volume 4, p. 1161, Pergamon Press Ltd., Oxford, 1979.
b) "*Comprehensive Heterocyclic Chemistry*", A.R. Katritsky ed., Volume 7, p. 631, Pergamon Press Ltd., Oxford, 1984.

3 Kashima C.; Tajima T.; Higuchi C. and Omote Y., *J. Heterocycl. Chem.*, **1984**, *2*, 345.

4 **11** is treated with 1 equivalent of n-propylamine in THF at r.t. (15 h) to give **12** (92 %). IR : 1620, $\nu_{C=N}$. ^1H NMR : δ=0.86 (t, J=7.3, 3H), 1.09 and 1.34 (2t, J=7.3, 3H E/Z), 1.60 (sex., J=7.3, 2H), 2.46 and 2.84 (2q, J=7.3, 2H E/Z), 3.55 (t, J=7.3, 2H), 7.0 to 7.4 (m, 5H), 8.45 (q, J_{HF}=3.35) and 8.89 (s, 1H E/Z). ^{19}F NMR : E/Z isomers, ϕ=-55.4 (27 %), -55.7 (73 %). ^{13}C NMR : δ=11.74 and 14.59 (E/Z $\underline{C}H_3$), 23.78 ($\underline{C}H_2$), 30.85 ($\underline{C}H_2$), 64.19 ($\underline{C}H_2$), 123.25 (J=275.5, $\underline{C}F_3$), 159.12 (J=1.76) and 162.32 (s) : E/Z isomers.

5 **7** : IR : 1630, $\nu_{C=N}$. ^1H NMR : δ=2.75 (q, J=8, 2H), 3.20 (q, J=8, 2H), 5.9 (s, 1H), 7.1 to 7.6 (m, 6H). ^{19}F NMR : ϕ=-61.2. ^{13}C NMR : δ=34.8 ($\underline{C}H_2$), 62.1 ($\underline{C}H_2$), 119.8 ($\underline{C}F_3$), 162.1 (H$\underline{C}$=N).

6 **2** is treated with one equivalent of **3** at 0°C for 15 min. in THF, one equivalent of Et_3N is added and the reaction is stirred at r.t. for 5 h and chromatographied over SiO_2. **5** (10 %) (1) is first eluted. **8** is eluted with Et_2O. IR : 1640, $\nu_{C=N}$. ^1H NMR : δ=2.86 (m, 2H), 3.62 (m, 2H), 7.0 to 7.8 (m, 6H). ^{19}F NMR : ϕ=-71.1. ^{13}C NMR : δ=38.42 ($\underline{C}H_2$), 48.20 (CH_2), 117.5 (J=257, $\underline{C}F_3$), 160.27 (H$\underline{C}$=N). MS m/z : 27, 28, 86 (100 %), 172, 188, 257 ($M^{\cdot+}$).

7 **8** is treated with 50/50 mixture of THF and 2.5N aqueous HCl. Water and THF are removed under vacuum. **9** : ^1H NMR : δ=3.0 (m, 2H), 3.67 (m, 2H), 7.0 to 7.7 (5H), 8.44 (m, NH_3^+), 10.72 (s, CHO). ^{19}F NMR : ϕ=-72.5.

8 a) Husted D.R. and Ahlbrecht D.L., *J. Amer. Chem. Soc.*, **1952**, *74*, 5422.
b) Salvador R.L. and Saucier M., *Tetrahedron*, **1971**, *27*, 1221.
c) Massyn C. and Cambon A., *J. Fluorine. Chem.*, **1975**, *5*, 67.
d) Gelb M.H.; Svaren J.P. and Abeles R.H., *Biochemistry*, **1985**, *24*, 1813.

9 Slusarczuk G.M.J. and Joullié M.M., *J. Org. Chem.*, **1971**, *36*, 37.

10 1 equivalent of **14** is added to **2** in THF. The reaction mixture is stirred at r.t. for 3 h. **19** : IR : 1640, $\nu_{C=N}$. ^1H NMR : δ=4.42 (1H), 7.25 to 8.10 (10H). ^{19}F NMR : E/Z isomers, ϕ=-58.98 (65 %), -61.62 (35 %). MS m/z : 69, 304 (100 %), 341 ($M^{\cdot+}$). **20** (1).

(Received in France 14 January 1993; accepted 15 February 1993)