ELSEVIER

Journal of Fluorine Chemistry 81 (1997) 169–172

JOURNAL OF FLUORINE CHEMISTRY

Regioselective synthesis of (trifluoromethyl)-β-chloroenones

Gérard Alvernhe [a], Abdelkader Bensadat [b], Abdelkader Ghobsi [b], André Laurent [a], Eliane Laurent [a]

[a] *UCB-Lyon I, Laboratoire de Chimie Organique 3, associé au CNRS, 43, Boulevard du 11 Novembre 1918, 69622 Villeurbanne Cedex, France*
[b] *Université d'Oran Es-Sénia, Laboratoire de Chimie et d'Electrochimie Organique, Oran, Algeria*

Received 23 March 1996; accepted 23 July 1996

Abstract

The regioselectivity of the conversion of 1,3-diketones into β-chloroenones can be changed by the appropriate choice of the reagent: reaction with "Vilsmeier's reagent" prepared from $POCl_3$ and dimethylformamide or treatment of the diketone with the oxalyl chloride in the presence of dimethylformamide.

Keywords: Vilsmeier's and related reactions; Regioselectivity; Unsymmetrical diketones; β-Chloro-(trifluoromethyl)enones

1. Introduction

"Vilsmeier's reagent" or equivalent ones are useful reagents for the conversion of 1,3-diketones into β-chloro-α,β-unsaturated ketones by exchange of the hydroxyl group in the enolic form with a chlorine atom [1–3]. Oxalyl chloride, alone or in the presence of dimethylformamide (DMF) [4,5], was also used advantageously for the same purpose. However these reaction are mainly utilized with symmetrical diketones (Scheme 1).

In this paper we show with unsymmetrical diketones, how the regioselectivity depends on either substituent (Ar and CH_3 or Ar and CF_3, Scheme 2) or reagent: addition of the diketone [3] to the "Vilsmeier's reagent" previously prepared ($POCl_3$, DMF) or "Vilsmeier's reagent" generated in the presence of the diketone [5]. The results are summarized in Table 1.

For **1a** ($R^1 = CH_3$), although the literature reports clearly that at equilibrium the two enol forms [6] **2a** and **3a** are present in almost equivalent amounts (**2a**/**3a** = 56/44), entries 1, 2, 3 show that the chlorination reaction is strongly regioselective (more than 80% of **5a**). It is possible to obtain **5a** with an expected correct yield. Moreover observed regioselectivity does not depend on the experimental condition used.

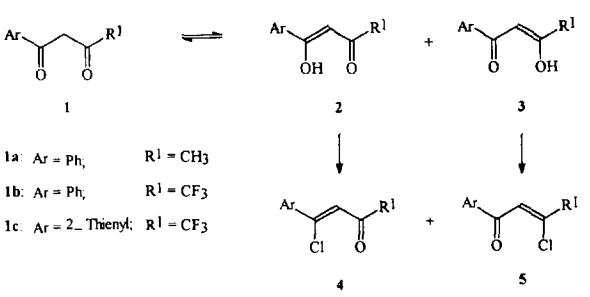
Scheme 1.

In the case of the diketones **1b** and **1c** ($R^1 = CF_3$) (entries 4 to 7) it clearly appears that the reagent used deeply influences the regioselectivity of the reaction. With a preformed "Vilsmeier's reagent" ($POCl_3$/DMF experiments, entries 4 and 6), the chloroenones **4** are the major compounds.

Using oxalyl chloride and DMF (entries 5 and 7), the yield of **5** increased: **5c** even became the major one (≈78% relative) when starting from **1c**.

If we consider the generally depicted mechanism of the Vilsmeier's reaction (Scheme 3 [1]) or equivalent ones (Scheme 4 [5]), the final step is the same in the two reactions (**7** + **8** → **4** + **5**). Therefore the difference in regioselectivity is determined in early step. For the Vilsmeier's reaction summarized in Scheme 3 the regioselectivity must reflect the relative nucleophilicity of the enols **2** and **3**.

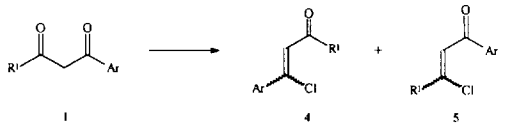
When $R^1 = CH_3$, we can reasonably assume that the enol **3a** is more nucleophilic than the enol **2a** (Ph–CO– group being less electron withdrawing group than CH_3–CO–) and, therefore, **5a** is the major product of the reaction. When



Scheme 2.

PII S0022-1139(96)03523-3

Table 1
Addition of "Vilsmeier's reagents" to β-diketones **1**



Entry	Diketone **1**	Reagent (molar equivalents)	Time (h)	T (°C)	Yield (%) [a], Z, E ratio		**4/5** ratio
					4	**5**	
1	**1a** Ar = Ph $R^1 = CH_3$	$POCl_3$ (3) DMF	3	25	2.7[b]	40 E/Z (92/8)	6/94
2		$(COCl)_2$ (1,2) DMF/CH_2Cl_2	15	25	12 Z/E (80/20)	54 E/Z (82/18)	18/82
3		$(COCl)_2$ (2) $CHCl_3$	0.33	62	traces	(86)	0/100
4	**1b** Ar = Ph $R^1 = CF_3$	$POCl_3$ (5) DMF	3.5	50	(44.8)	(5.2)	83/17
5		$(COCl)_2$ (1,2) DMF/CH_2Cl_2	15	25	43	46	48/52
6	**1c** Ar = 2-Thienyl $R^1 = CF_3$	$POCl_3$ (3) DMF	3	25	33 Z/E (84/16)	26 Z/E (75/25)	56/44
7		$(COCl)_2$ (1,2) DMF/CH_2Cl_2	4.5	25	(10) Z/E (90/10)	(36) Z/E (100/0)	22/78

[a] Isolated yields; GPC yield is shown in parentheses (see experimental part).
[b] Converted in **6**:

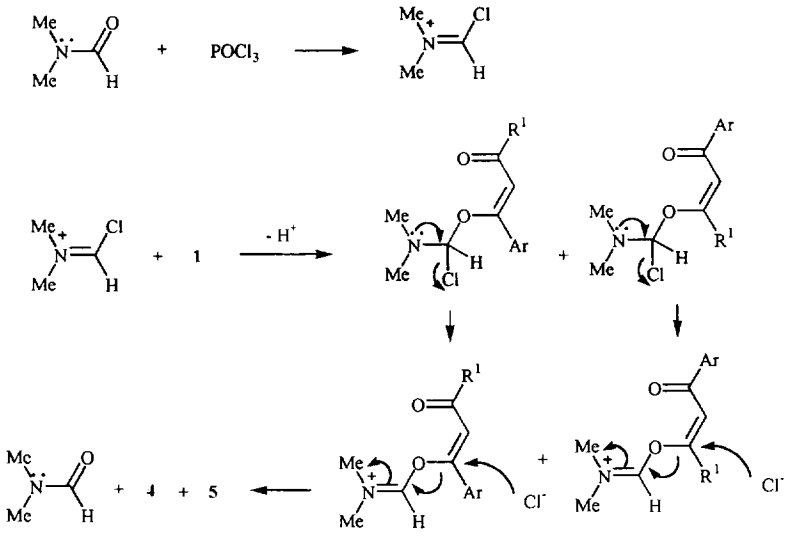
$R^1 = CF_3$ the important inductive effect of the trifluoromethyl group decreases the nucleophilicity of **3** and consequently compounds **4** become the major products of the reaction.

The observed change of regioselectivity with trifluoromethyl diketones with the reagents (especially in the case of diketone **1c**) clearly indicates that the reaction using oxalyl chloride/DMF does not simply provide "Vilsmeier's reagent" nor direct reaction with oxalyl chloride (we have checked the absence of any reaction between **1b** and oxalyl chloride without DMF). It should be noticed that it was reported in the literature that the addition of DMF to oxalyl chloride greatly improved the yield of the reaction [7].

Formation of O-acylated intermediate from tertiary amides and acyl halides is well known in the literature [8]. For the reaction of carboxylic acid chlorides with nucleophiles in the presence of DMF some authors [9] have proposed a general acid catalysis mechanism (Scheme 4) in which the reaction occurs via a transition state like **A**.

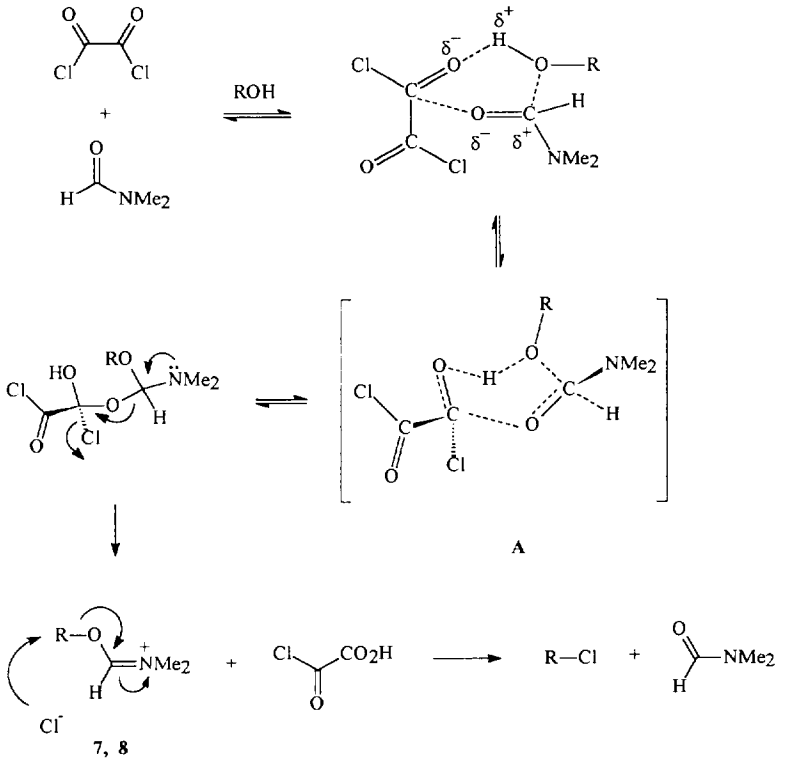
Comparison of ethanol acidity ($pK_a = 15.9$) [10] and with trifluoroethanol ($pK_a = 12.4$) [11] shows that the enols **3b** or **3c** must be more acidic and thus better catalysts than the enol **2b** or **2c** respectively. According to Scheme 4, we propose that the selectivity of the reaction must be controlled by the relative acidity of the enols **2** and **3**.The greatly acidic enol **2b** leads to more exchange of the hydroxyl group.

In conclusion, the results reported here underline the non equivalence of the "Vilsmeier's reagent" prepared by $POCl_3$ and DMF and of the reaction of oxalyl chloride/DMF, in the



7 **8**

Scheme 3.



Scheme 4.

exchange of hydroxyl group by chlorine atom. Therefore the regioselectivity of the chlorination of unsymmetrical diketone can be changed by the appropriate choice of the reagent.

2. Experimental

^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker AC 200 (200.133 MHz) spectrometer. ^{13}C NMR spectra were recorded on Bruker AC 200 (50.32 MHz) spectrometer and are reported in ppm relative to TMS (0.00 ppm). ^{19}F NMR spectra were recorded on Bruker AC 200 (188.31 MHz) and Varian EM 360 (56.4 MHz) spectrometers in $CDCl_3$ as solvent and are in δ units upfield from internal $CFCl_3$. The mass spectra were recorded on a Nermag R10-105 Spectrograph (electron impact at 70 eV) after mass chromatography coupling. Column chromatography was performed on Merck silicagel (40–60 Mesh) with light petroleum ether or light petroleum/diethyl ether mixture. Samples were examined by gas chromatography on a Varian 3300 apparatus with pentadecane as internal standard or by ^{19}F NMR analysis with $PhCF_3$ or $PhOCF_3$ as internal standard.

Starting diketones are commercially available from Aldrich. Dimethylformamide (SDS company, anhydrous analytical grade) was kept on 4 Å molecular sieves before use.

3. General procedure for Vilsmeier's reactions

3.1. With phosphorus oxychloride/DMF

Dimethylformamide (25 ml) was added slowly over 2 h to phosphorus oxychloride while keeping the temperature below 30 °C. Then the diketo compound was added in small portions. The reaction mixture was stirred for variable times and at variable temperature and then hydrolyzed with a saturated solution of NaOAc. After classical workup the etheral layers were washed with a solution of $NaHCO_3$ until basic, dried over $MgSO_4$ and concentrated. The crude product of reaction was purified by column chromatography or analysed by GPC.

3.2. With oxalyl chloride/DMF

To a solution of dimethylformamide and diketone in CH_2Cl_2, oxalyl chloride was added dropwise at 0 °C. After stirring at room temperature for a variable time, the mixture was poured into ether (100 ml) and cool water (40 ml) was added. The organic layer was separated, dried over magnesium sulfate and concentrated. The crude product was purified by column chromatography.

3.3. With oxalyl chloride/$CHCl_3$

Oxalyl chloride was added dropwise at 0 °C to a solution of the diketone in $CHCl_3$. After stirring at room temperature the reaction mixture was treated as in procedure b).

Entry 1: $POCl_3$ (8.6 ml, 94 mmol), DMF (14 ml), **1a** (5 g, 30.8 mmL), 3 h at room temperature. Purification of the crude product (4.56 g) gave **5a** *E*/*Z* (93/7) 1.82 g (10.1 mmol, 32,8%), **6** 0.193 g (mixture of stereoisomers 0.84 mmol, 2.7%), **5a** *E*/*Z* (13/87), 0.391 g (2.2 mmol, 7.1%).

6: ^1H NMR: Major isomer: δ 6.65 (s, 1H), 6.87 (d, 1H, 6.7 Hz), 7.3–7.85 (m, 5H), 10.3 (d, 1H, 6.5 Hz), MS *m*/*z* (rel. intensity) 228 (M^+, $^{35}Cl^{37}Cl$, 14), 227 (7), 226 (M^+, $^{35}Cl^{35}Cl$, 14), 225 (8), 193 (12), 191 (37), 162 (21), 163 (53), 164 (12), 165 (18), 126 (27), 127 (100), 128 (84), 129 (9), 77 (35), 63 (22), 51 (29).

5a *E* and *Z* have been already described [12].

Entry 2: CH_2Cl_2 (46 ml), DMF (1.5 ml, 19.7 mmol), $(COCl)_2$ (1.6 ml, 17.2 mmol), **1a** (2.5 g, 15.4 mmol), 15 h at room temperature. Purification of the crude product (2.53 g) gave **5a** *E*/*Z* (88/12) 1.31 g (7.3 mmol, 42.4%), **5a** *E*/*Z* (28/72) 0.32 g (1.77 mmol, 11,5%), **4a** *E*/*Z* (27/73) 0.33 g (1.83 mmol, 11.9%). **4a** *E* and *Z* have been already described [13].

Entry 3: $CHCl_3$ (5 ml), $(COCl)_2$ (2.7 ml, 30.4 mmol), **1a** (2.5 g, 15.4 mmol), 20 min reflux, gave 3.21 g of crude product analysed by gas chromatography as **5a** E 2.39 g (13.2 mmol, 86%).

Entry 4: $POCl_3$ (11 ml, 115 mmol), DMF (16 ml, 211 mmol), **1b** (5 g, 23.1 mmol), 2 h 30 min at room temperature and 30 min at 55°C, gave 4.97 g of the crude product analysed by gas chromatography, as a mixture of **4b** and **5b**, 2.93 g (12.5 mmol 54%, **4b/5b**: 83/17).

Entry 5: **1b** (61.6 mmol), CH_2Cl_2 (200 ml), DMF (80.1 mmol), $(COCl)_2$ (73.9 mmol), 15 h at room temperature. Purification by flash chromatography (petroleum ether/CH_2Cl_2: 8/2) of the crude product (15.1 g) yields **4b** 6.67 g (28.46 mmol, 46%) and **5b** 6.23 g (26.57 mmol, 43%). ^1H and ^{19}F identical with that previously reported [15,14].

Entry 6: $POCl_3$ (3.7 ml, 40.5 mmol), DMF (7.5 ml), **1c** (3 g, 13.5 mmol), 3 h at room temperature. Purification of the crude product (2.85 g) gave 0.354 g (1.47 mmol) **4c** (*Z*/*E*: 81/9), 0.761 g (3.17 mmol) **5c** (*Z*/*E*: 75/25) and 0.775 g as a mixture of **4c** (0.722 g, *Z*/*E*: 86/14) and **5c** (0.053 g, *Z*/*E*: 100/0). Yields were **4c** (33%, *Z*/*E*: 84/16), **5c** (26%, *Z*/*E*: 77/23).

4cZ: ^1H NMR: δ 7.10 (s, 1H), 7.20 (dd, 1H, ^3J=5.1, ^3J=3,9), 7.62 (dd, 1H, ^4J=1.2, ^3J=5.1), 7.77 (dd, 1H, ^4J=1.2, ^3J=3.9), ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 116.0 (q, $^1J_{CF}$=291.6), 109.9, 132.6, 132.4, 129.1, 140.7, 146.6, 176.7 (q, $^2J_{CF}$=35.5), MS *m*/*z* (rel. intensity) 240 (M^+, 23), 205 (73), 171 (100), 143 (26), 108 (84), ^{19}F NMR: δ −79.2 (s, 3F).

4cE: MS *m*/*z* (rel. intensity) 240 (M^+, 23), 205 (75), 171 (100), 143 (23), 108 (81), ^{19}F NMR: δ −78.2 (s, 3F).

5cZ: ^1H NMR: δ 7.20 (dd, 1H, ^3J=4.9, ^3J=3.9), 7.46 (dd, 1H, $^4J_{HF}$=1.7), 7.75 (dd, 1H, ^3J=3.9, ^4J=1.1), 7.80 (dd, 1H, ^3J=4.9, ^4J=1.1), δ ^{13}C 119.9 (q, $^1J_{CF}$=273.8), 126.3 (q, $^3J_{CF}$=3.6), 130.1, (q, $^2J_{CF}$=38.6), 136.4, 134.5, 128.8, 143.4, 179.7, MS *m*/*z* (rel. intensity) 240 (M^+, 43), 212 (23), 157 (7), 129 (4), 111 (100), 83 (13), ^{19}F NMR: δ −70.5 (s, 3F).

5cE: MS *m*/*z* (rel. intensity) 240 (M^+, 27), 212 (16), 111 (100), ^{19}F NMR: δ −65.3 (s, 3F).

Entry 7: **1c** (3.4 g, 15.4 mmol), CH_2Cl_2 (50 ml), DMF (1.5 ml), $(COCl)_2$ (1.6 ml, 18.2 mmol), 4 h 30 min at room temperature. The crude product (3.6 g) was analysed by gas chromatography as a mixture of **4c** (0.370 g, 10%, *Z*/*E*: 90/10) and **5c** (1.333 g, 36%, *Z*/*E*: 100/0) in a ratio **4c/5c**: 22/78. *Z* and *E* are identified by comparison with NMR spectra of the furanic analogous [15].[15]

References

[1] C.M. Marson and P.R. Giles, *Synthesis using Vilsmeir's Reagents*, C.R.C. Press, Boca Raton, FL, 1994, and references cited therein.
[2] A.R. Katritzky and C.M. Marson, *Tetrahedron Lett., 26* (1985) 4715.
[3] M. Weissenfeld, M. Pulst, M. Haase, U. Pawlowski and H.F. Uhlig, *Z. Chem., 17* (1977) 56.
[4] R.D. Clark and C.H. Heathcock, *Synthesis* (1974) 47.
[5] R.E. Mewshaw, *Tetrahedron Lett., 30* (1989) 3753.
[6] M. Gorodetsky, Z. Luz and Y. Mazur, *J. Am. Chem. Soc., 89* (1967) 1183.
[7] R.D. Clark and C.H. Heathcock, *J. Org. Chem., 41* (1976) 636.
[8] B.C. Challis and J. Challis, in J. Zabicky (ed), *The Chemistry of Amides*, Interscience, London, 1970.
[9] G. Asensio, E. Gonzales-Nunez and T. Varea, paper presented at *Seventh IUPAC Conf. on Organic Chemistry, Nancy, France, July 4–7, 1988*, communication 7-R38.
[10] J. Murto, *Acta Chem. Scand., 18* (1964) 1043.
[11] P. Ballinger and F.A. Long, *J. Am. Chem. Soc., 81* (1959) 1050.
[12] H. Martens, G. Hoornaert and S. Toppet, *Tetrahedron, 29* (1973) 4241.
[13] D. Manoiu, M. Manoiu, I.G. Dinulescu and M. Avram, *Rev. Roumaine Chim., 29* (1984) 193.
[14] G. Alvernhe, D. Greif, B. Langlois, A. Laurent, I. Le Drean, M. Pulst, A. Selmi and M. Weissenfels, *Bull. Soc. Chim. France, 131* (1994) 167.
[15] T. Okano, T. Uekawa and S. Eguchi, *Bull. Chem. Soc. Japan., 62* (1989) 2575.