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Preparation and Reactions of Acylzinc Species

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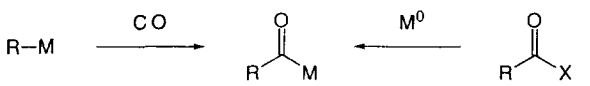
Abstract : The reduction of acyl chlorides by zerovalent zinc dust is described. The reaction gives enol esters of (Z) configuration in high yields. The initial product is presumed to be an acyl zinc species, which gives the enol ester in a stereospecific manner by a 1,2-hydrogen shift on the carbene intermediate. © 1997 Elsevier Science Ltd.

Acylmetals of the general formula RC(O)-M have been widely studied over the past twenty years. When M is a transition metal, these acylmetals are well-known and used in organic chemistry and have found wide application in industrial processes and in catalysis. When M is a main group metal (M = Li, Mg, Cd, Zn, Al...), these acylmetals have been shown to be highly reactive and to present a limited stability. Two methods of preparation can be mainly found in the literature (eq.1): the carbonylation of organometallics (path A) and the reduction of acyl derivatives such as acyl halides (Path B):



(Eq.1)

Path A Path B

The carbonylation of main-group organometallic compounds has been reviewed[1] and has found recent development, especially in the case of acyllithiums[2-5]. The reduction of acyl halides is known for a long time[6], but because of the numerous products often obtained, few methods have been developed. In fact, the reduction of acyl halides by metals generally gives mixtures of products of a one-electron (α-diketone) or two-electron reaction (acyloin), as resumed on the following scheme (Scheme 1). The acyloin can be produced by further reduction of the α-dione or by dimerization of the intermediate carbene, and can also be transformed to enolate diester by further acylation.

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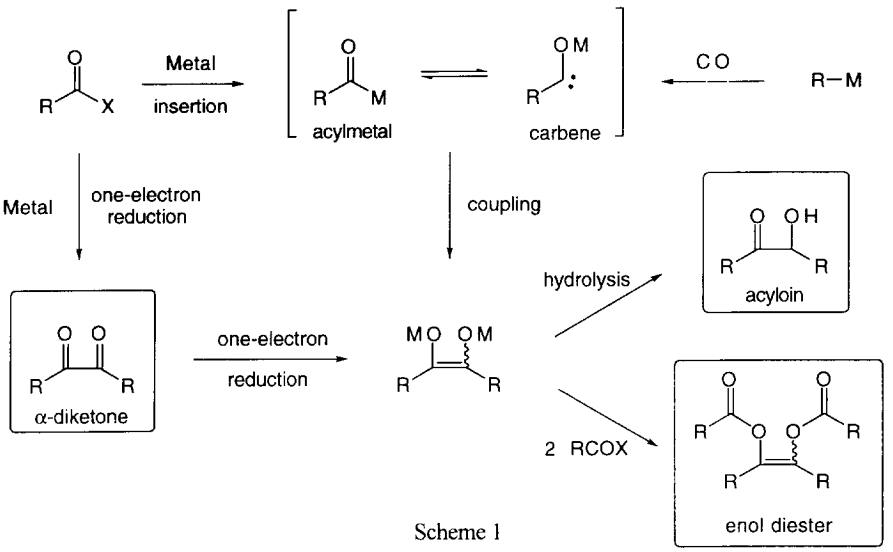
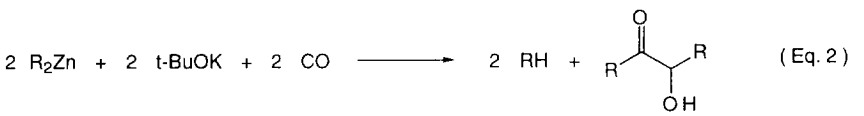


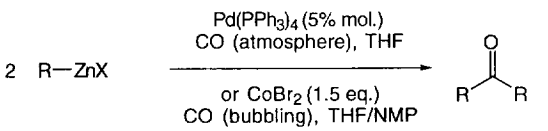
Scheme 1

The carbonylation of organozinc species was also studied. No reaction was observed with carbon monoxide either for organozinc halides $RZnX$[7] or for diorganozinc R_2Zn[8]. However, absorption of CO occurred in diglyme in the presence of potassium *tert*-butoxide[8] to give acyloins in fair yields. The stoichiometry seemed to be in agreement with the following equation (eq. 2):



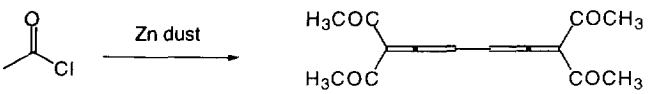
(Eq. 2)

On the other hand, carbonylations of organozinc species were observed under palladium[9] or cobalt[10] catalysis (eq.3):



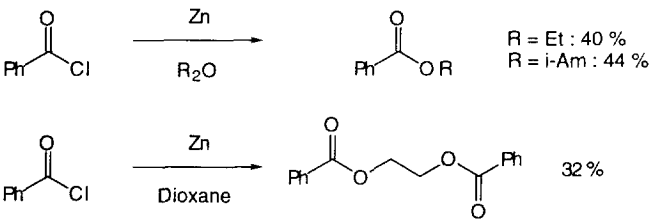
(Eq. 3)

The other route to acylzincs, namely the reduction of acyl halides by zinc, was little studied in the literature. Reduction of acetyl chloride with zinc dust is described, leading to 1,1,6,6-tetraacetyl-3,4-dimethyl-1,2,4,5-hexatetraene (eq. 4), probably formed from the enol of biacetyl[11]:



(Eq. 4)

Reaction of benzoyl chloride with zinc dust was also studied[12]. No reaction was observed in benzene, carbon disulfide or carbon tetrachloride. In etheral solvents, reaction of benzoyl chloride with the solvent was observed, leading to the corresponding ester (Scheme 2):

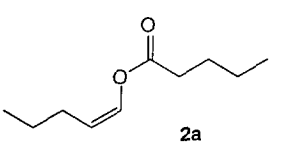


Scheme 2

This reaction was recently studied and extended to other ethers by Ranu[13].

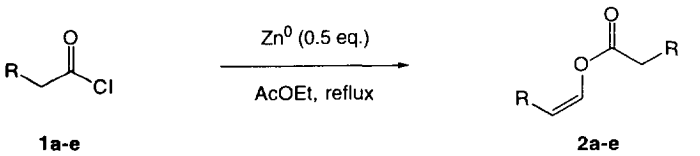
We thought that to obtain acylzinc species, it was necessary to avoid any ethereal solvent. By mixing valeroyl chloride **1a** with zinc dust in pentane, no reaction was observed. Without any solvent, a violent reaction occurred when the temperature was raised to 50°C. However, no identified product could be isolated. In DMF or DMSO, a quick reaction occurs, giving valeric anhydride in very good yield. This reaction is quite general and further details will be reported soon [14].

In refluxing ethyl acetate, a new product was obtained, which was identified as an enol ester **2a**:



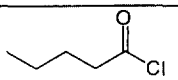
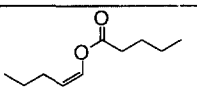
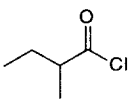
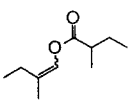
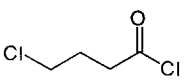
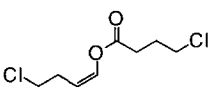
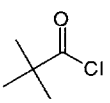
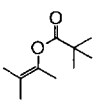
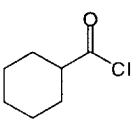
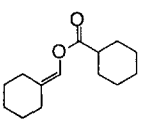
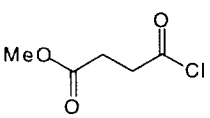
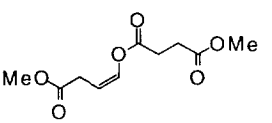
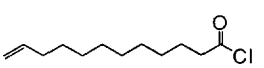
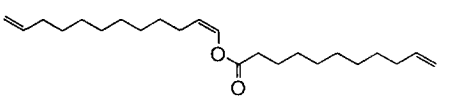
2a

The same reaction was observed with other acyl chlorides. Only half an equivalent of zinc was consumed. *The enol esters prepared from primary acyl chlorides were obtained in more than 95% of the (Z)-isomer*, from ^{1}H NMR analysis (eq.5); the results for some representative acyl chlorides are reported in the Table 1.



1a-e **2a-e** Eq. 5

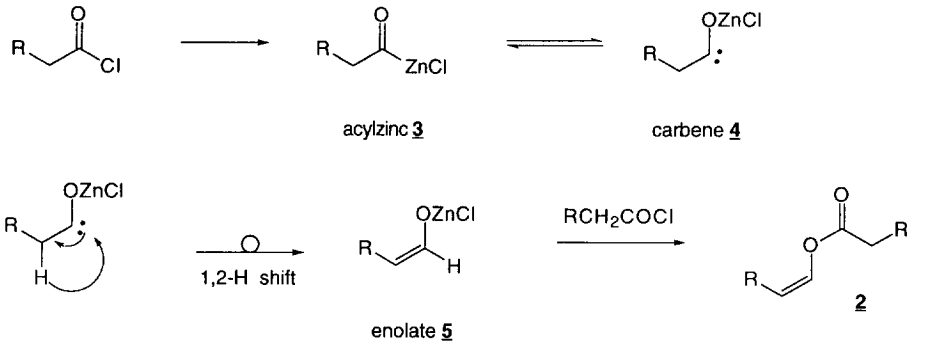
Table 1 : Preparation of Enol Esters from Acyl Chlorides

Entry	Acyl chloride		Enol ester		Yield (%)
1		**1a**		**2a**	88
2		**1b**		**2b**	84 (*)
3		**1c**		**2c**	66
4		**1d**		**2d**	65
5		**1e**		**2e**	92
6		**1f**		**2f**	48
7		**1g**		**2g**	72

(*) The compound **2b** was obtained as a 2:1 mixture of diastereoisomers.

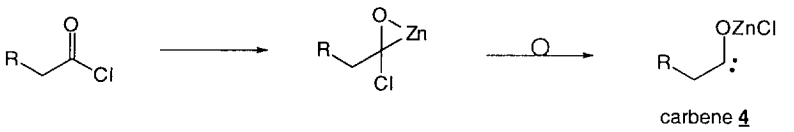
The reaction is quite general and stereoselective. The smooth reaction conditions are compatible with the presence of functionality such as a carbon-chlorine bond (entry 3), an ester moiety (entry 6) or a double bond (entry 7). The reaction from secondary acyl chlorides proceeds also with good yield (entries 2 and 5), albeit with lower selectivity (entry 2). The reaction from a tertiary acyl chloride gives the product resulting from methyl migration (entry 4), excluding apparently any radical mechanism.

We envisioned the mechanism described in Scheme 3: insertion of Zn^0 into the carbon-chlorine bond of the acyl chloride should give the corresponding acylzinc species **3** which undergoes a metallotropic tautomerism from carbon to oxygen leading to the alcoholate-carbene **4**.



Scheme 3

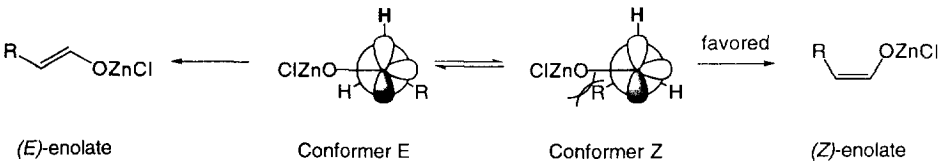
Alternatively this carbene **4** could also be produced by direct reduction of the carbon-oxygen double bond, as in the Clemmensen reduction of ketones[15], and decomposition of the carbenoid intermediate to carbene, as represented in Scheme 4[16].



Scheme 4

This resulting carbene should then effect a 1,2-hydrogen shift[17] to give the corresponding zinc enolate **5** which then reacts with another acyl chloride to give the observed enol ester **2**. This type of 1,2-hydrogen shift was already observed in carbenes[18] α to oxygen.

The reason[19] of the *Z*-exclusive stereodirection of this 1,2-hydrogen shift can be attributed to stereoelectronic effects. It has already been shown that 1,2-hydrogen shift is due to singlet carbenes[17]. Thus, two conformers can be envisioned, each leading to a precise stereochemistry for the rearrangement, as shown in Scheme 5. The shifting H is highlighted in bold character.



Scheme 5

As discussed earlier[17], a 1,2-hydrogen shift requires the C-**H** bond to be parallel to the vacant p orbital of the singlet carbene, as in conformers E and Z. Conformer E is favoured over conformer Z on the basis of steric repulsion between R and the zinc alkoxide groups, whereas conformer Z is favoured over conformer E considering the hyperconjugation of the carbene lone pair and the low-lying C-R σ^* orbital[17,20]. This last effect seems to be predominant here since the 1,2-shift only yields the *(Z)*-enolate. The presence of an alkoxide substituent on the carbene obviously reinforces the hyperconjugation.

Unfortunately, we were unable to quench this enolate with electrophiles other than the acyl chloride already present in the reaction medium. Even when the reaction was conducted in the presence of twenty-fold excess chlorotrimethylsilane we obtained only the enolester.

In conclusion, we have disclosed a new method for the synthesis of *(Z)*-enol esters in good to excellent yields. Enol esters are useful reagents for carbon-carbon and carbon-heteroatom bond formation through the generation of enolates or acylation reactions[21]. However, few methods are known for their stereoselective formation. Mercury(II)-assisted carboxylation of alkynes[22,23] leads preferentially to *(E)*-enol esters, as well as *in situ* reduction and quenching of ynolates[24]. Stereoselective ring-opening of α,β-epoxysilanes by acetic acid gives *(E)* or *(Z)*-enol acetates but stereodefined *syn* or *anti* epoxides are needed[25]. From the best of our knowledge, stereoselective synthesis of *(Z)*-enol esters can be achieved only *via* the thermal reaction of chromium (acyloxy)carbene complexes[26] or by ruthenium-catalyzed addition of carboxylic acids to terminal alkynes[27].

EXPERIMENTAL

NMR spectra have been recorded on either a BRUKER ARX 400 or BRUKER AC 200 in $CDCl_3$. Chemical shifts are reported in part per million (ppm) relative to tetramethylsilane (TMS) as an internal standard (0.1 %) in ^1H NMR spectra.. In ^{13}C NMR spectra, $CDCl_3$ (δ=77.2 ppm) has been used as a reference. The following abbreviations are used : s: singlet, d: doublet, t: triplet, q: quadruplet, m: multiplet. IR spectra were

recorded on a Perkin Elmer 1420 and expressed in cm^{-1}. Zinc dust was purchased from Aldrich as a 325 mesh powder. Ethyl acetate was distilled over CaH_2 before use.

General procedure for the reduction of acyl halides. Zn dust (1.63g, 25mmol) is suspended in ethyl acetate (60mL) and activated following the Knochel's procedure[28]. Acyl halide (50mmol) is added and the mixture heated to reflux four hours. After cooling the resulting solution is poured into a saturated aqueous $NaHCO_3$ solution (150mL), extracted twice with ethyl acetate (70mL each), washed with a saturated aqueous $NaHCO_3$ solution (100mL), brine (100mL), and dried over sodium carbonate. After filtration the solvents are removed under vacuum to yield the enol ester which can be purified, if necessary, by distillation or chromatography over SiO_2.

Pentanoic acid pent-1-enyl ester (2a). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.83 (t, *J*=7Hz, 3H), 0.85 (t, *J*=7Hz, 3H), 1.10-1.45 (m, 4H), 1.45-1.70 (m, 2H), 2.03 (dq, *J*=7Hz, *J'*=1Hz, 2H), 2.31 (t, *J*=7H, 2H), 4.77 (dt, *J*=7Hz, *J'*=6Hz, 1H), 6.95 (d, *J*=6Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.5, 22.1, 22.3, 26.4, 26.7, 33.7, 113.6, 134.0, 170.7. IR(film) 3000-2800, 1740, 1660, 1455, 1150 cm^{-1}; MS (NH_3) m/z 171(MH^+), 188(MNH_4^+); Microanalysis : calculated for $C_{10}H_{18}O_2$: C : 70.55 H : 10.66; found : C : 70.72; H :10.21.

2-Methylbutanoic acid 2-methylbut-1-enyl ester (2b). Obtained as an unseparated mixture of two diastereoisomers, in the ratio 2:1.

Major isomer : ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.91 (sextet., *J*=1.3Hz, 1H), 2.46 (sextet, *J*=7Hz, 2H), 2.01 (q, *J*=8Hz, 1H), 1.68 (d, *J*=1.5Hz, 3H), 0.8-1.35 (m, 11H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 11.6, 12.5, 16.5, 22.7, 26.7, 41.0, 123.5, 129.7, 174.0.

Minor isomer : ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.83 (bs, 1H), 2.14 (q, *J*=8Hz, 2H), 2.01 (q, *J*=8Hz, 1H), 1.64 (d, *J*=1.6Hz, 3H), 0.8-1.35 (m, 11H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 12.0, 13.5, 17.0, 26.2, 27.1, 123.6, 129.3, 174.0.

4-Chlorobutanoic acid 4-chloro-but-1-enyl ester (2c). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.00-2.2 (m, 2H), 2.6-2.8 (m, 2H), 3.55 (t, *J*=7Hz, 2H), 3.63 (t, *J*=7Hz, 2H), 4.98 (q, *J*=7Hz, 1H), 7.15 (dt, *J*=7Hz, *J'*=1Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 27.3, 27.9, 30.9, 43.6, 43.9, 109.6, 135.8, 169.6. Microanalysis : calculated for $C_8H_{12}Cl_2O_2$: C : 45.52 H : 5.73; found : C : 45.67; H :5.68.

2,2-Dimethylpropanoic acid 1,2-dimethylpropenyl ester (2d). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.15 (s, 9H), 1.41 (s, 3H), 1.62 (s, 3H), 1.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.7, 17.1, 18.8, 27.1, 38.9, 117.9, 138.9, 176.7. IR (film) : 2970-2800, 1740, 1480, 1390, 1360, 1280, 1120 cm^{-1}; Microanalysis : calculated for $C_{10}H_{18}O_2$: C : 70.55 H : 10.66; found : C : 70.74; H : 10.58.

Cyclohexanecarboxylic acid cyclohexylidenemethyl ester (2e). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25-1.35 (m, 4H), 1.40-1.60 (m, 8H), 1.70-1.85 (m, 2H), 1.97 (bd, *J*=12Hz, 2H), 2.05 (bs, 2H), 2.25 (bs, 2H), 2.38 (m, 1H), 6.87 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.78, 27.13, 27.51, 27.93, 28.20, 29.30, 30.27, 31.96, 44.41, 126.54, 128.58, 174.50. IR (film) 2920, 2860, 1740, 1450, 1160, 1130 cm^{-1}; MS (NH_3) m/z 223(MH^+), 240(MNH_4^+), 205, 145, 128; Microanalysis : calculated for $C_{14}H_{22}O_2$: C : 75.63 H : 9.97; found : C : 75.38; H : 10.24.

Butanedioic acid 1-(3-methoxycarbonyl-propenyl)-ester 4-methyl ester (2f). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.30-2.70 (m, 4H), 3.05 (d, J=7.5Hz, 2H), 3.5 (s, 6H), 4.95 (q, J=7.5Hz, 1H), 7.00 (d, J=7.5Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.17, 28.44, 30.10, 105.50, 135.77, 167.94, 168.97.

Undec-10-enoic acid undeca-1,10-dienyl ester (2g). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.0-1.4 (m, 20H), 1.4-1.7 (m, 2H), 1.8-2.2 (m, 6H), 2.2-2.4 (m, 2H), 4.7-5.0 (m, 5H), 5.6-5.8 (m, 2H), 7.95 (d, *J*=7Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.72, 25.20, 29.24, 29.41, 29.56, 29.61, 34.14, 34.35, 114.21, 114.51, 134.36, 139.29, 170.99.IR (film) 2900, 1750, 1670, 1630, 1450, 1150, 900 cm^{-1}.

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