Pergamon

Tetrahedron Letters, Vol. 36, No. 13, pp. 2247-2250, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00262-6

Transformation of Acid Chlorides into Aldehydes by Reduction of *In-situ* Formed Acyltributylphosphonium Ions with Zinc-Copper Couple or Zinc

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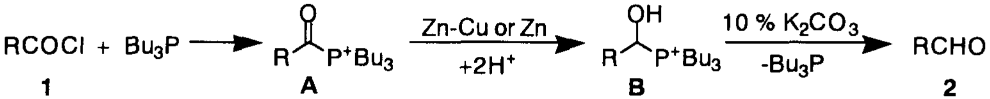
Abstract: Transformation of acid chlorides into the corresponding aldehydes without over-reduction to alcohols was effectively achieved by the reduction of acyltributylphosphonium ions, formed *in-situ* from the chlorides and tributylphosphine in CH_3CN, with Zn-Cu couple or Zn in the presence of CH_3SO_3H under an N_2 atmosphere.

Partial reduction of acid chlorides into the corresponding aldehydes is one of the most important transformations in organic synthesis. In order to achieve the selective conversion without over-reduction to alcohols, various hydride reagents have been developed.[1] However, the reduction with these reagents often require the severe control of their amounts and the reaction temperature as well as rather tedious preparation of the reagents themselves. Recently, we have found that carboxylic acids are reduced to the corresponding aldehydes by constant current electrolysis in the presence of Ph_3P or Bu_3P in an undivided cell.[2] A mechanistic study of the transformation has revealed two featuring points: (1) anodic formation of acylphosphonium ions enables the apparent cathodic reduction of the acids to aldehydes; (2) the cathodic reduction products of the phosphonium ions, α-hydroxyalkylphosphonium ions such as **B** in Scheme 1 remain intact during the reaction, which is the reason why the electrolysis effects the partial reduction of the acids in a highly selective manner.[2b,c] Furthermore, it has been demonstrated that 6-phenyl-5-hexenoic acids and δ-keto carboxylic acids are transformed into 2-benzyl- and 2-hydroxy-cyclopentanones, respectively, by the electrolysis in the presence of Bu_3P in an undivided cell, suggesting that the species generated by one- and two-electron reduction of acyltributylphosphonium ions will function as acyl radical and acyl anion equivalents, respectively.[3] These findings have prompted us to investigate a chemical reduction of acyltributylphosphonium ions formed not electrochemically but chemically from acid chlorides and Bu_3P,[4] because such a study will prove the synthetic utility of acylphosphonium ions. Herein we describe another novel method of transformation of acid chlorides to aldehydes without any formation of alcohols, based on the process shown in Scheme 1, where the *in-situ* formed phosphonium ions **A** are reduced with Zn-Cu couple or Zn.



Scheme 1

As a model compound, octanoyl chloride (**1a**) was chosen. When **1a** was added to a solution of Bu_3P in CH_2Cl_2 under an N_2 atmosphere, octanoyl tributylphosphonium chloride was immediately formed, which was confirmed by ^{31}P-NMR spectroscopy on the mixture diluted by $CDCl_3$ using H_3PO_4 (5 % in D_2O) as an external standard: a peak at -30.73 ppm due to the phosphine disappeared and a new peak corresponding to the adduct was observed at +27.92 ppm located in the region for an alkylphosphonium ion.[5] To the solution, Zn-Cu couple[6] was added at 0°C in the presence of CH_3SO_3H as a proton source. After stirring for 1 h at room temperature, aqueous work-up with 10 % HCl and 10 % K_2CO_3 gave the aldehyde **2a** in a 40 % yield (run 1 in Table 1). Solvent effects were important on the partial reduction of **1a** *via* the acylphosphonium ion. Thus, the reaction in DME resulted in the formation of **2a** in a 76 % yield, and utilizing CH_3CN improved the yield dramatically, leading into the quantitative conversion of **1a** into **2a** (runs 2 and 3). Regarding to a reducing metal, Zn-Cu couple was superior to Zn for the present transformation (runs 3 and 5). In the absence of Bu_3P, that is, without *in-situ* formation of the

Table 1. Preparation of Aldehydes (**2**) from Acid Chlorides (**1**) by Reduction of *In-situ* Formed Acyl Tributylphosphonium Ions with Zn-Cu Couple or Zn

Run	**1**	Reducing Metal	Solvent	Yield (%) of $\mathbf{2}^{a,b)}$
1	$CH_3(CH_2)_6COCl$ (**1a**)	Zn-Cu	CH_2Cl_2	40
2	"	"	DME	76
3	"	"	CH_3CN	100
$4^{c)}$	"	"	"	0
5	"	Zn	"	62
6	$PhCH_2CH_2COCl$ (**1b**)	Zn-Cu	"	100
7	$(CH_3)_2CHCOCl$ (**1c**)	"	"	(96)
8	$(CH_3)_3CCOCl$ (**1d**)	"	"	(66)
9	$EtOCOCH_2CH_2COCl$ (**1e**)	"	"	(77)
10	PhCOCl (**1f**)	"	"	100
11	"	Zn	"	100
12	*p*-Cl-C_6H_4COCl (**1g**)	Zn-Cu	"	100
13	"	Zn	"	100
14	*p*-CH_3-C_6H_4COCl (**1h**)	Zn-Cu	"	100
15	"	Zn	"	100
16	*p*-CH_3O-C_6H_4COCl (**1i**)	Zn-Cu	"	100
17	"	Zn	"	86

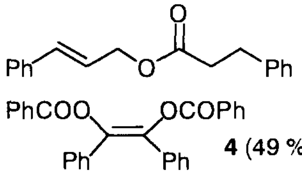
a) Determined by GLC. b) The numbers in the parentheses show isolated yields as 2,4-dinitrophenylhydrazones.

c) The reaction was carried out in the absence of Bu_3P.

acylphosphonium ion, **2a** was not obtained at all and **1a** was recovered (run 4), demonstrating that the derivatization of **1a** into the acylphosphonium ion is essential for the preparation of **2a** with the reducing metal; otherwise **1a** can not enter the electron transfer reaction under the conditions. The result is in consistent with the voltammetric observation that acyltributylphosphonium ions exhibit their cathodic reduction peaks at potentials over 600 mV more positive than those of the corresponding acid chlorides.[2c]

The partial reduction was applied to various acid chlorides employing the conditions in run 3. The reaction was carried out as follows: to a solution of Bu_3P (1.2 mmol) in CH_3CN (10 ml) deoxygenated by bubbling an N_2 gas,[7] an acid chloride (1 mmol) was added at 0°C under an N_2 atmosphere. After the mixture was stirred for a few minutes, CH_3SO_3H (2 mmol) and Zn-Cu couple (2 mmol) was added successively. The mixture was allowed to warm to room temperature, stirred for 1 h, poured into aq. 10 % HCl (50 ml), and extracted with CH_2Cl_2 (50 ml X 3). The combined organic layer was washed with aq. 10 % K_2CO_3 (100 ml) and dried over Na_2SO_4, and analyzed by GLC or treated with 78 % aq. EtOH (40 ml) containing 2,4-dinitrophenylhydrazine (1.3 g) and conc. H_2SO_4 (6.7 ml) in order to isolate the product as its hydrazone derivative.

As apparent from the results summarized in Table 1, the present method is remarkably general since it can be applied to the preparation of various aliphatic and aromatic aldehydes. The branching situations at α-carbon in aliphatic acid chlorides and the substitutions on aromatic ones cause no trouble in the transformation at all. Even from pivaloyl chloride (**1d**), the corresponding aldehyde was isolated as its hydrazone derivative in a good yield (run 8), although partial reduction with mild hydride reagents tends to be affected by steric factor, resulting in poor yields of the aldehyde especially in the case of tertiary acid chlorides.[1a,d] Furthermore, ester group is tolerated under the reaction conditions and the selective reduction of acid chloride moiety of **1e** was realized (run 9), which will be difficult for hydride reagents to achieve. In the case of benzoyl chlorides (**1f**~**1i**), Zn was also proved to be effective as a reducing metal in contrast to the reaction for **1a** (runs 5 and 11, 13, 15, 17), which is well in line with the observation that benzoyltributylphosphonium ions are cathodically reduced at less negative potentials than alkanoylphosphonium ions.[2c] It should be mentioned here that no formation of the corresponding alcohols was observed in any case. The reactions for **1b** and **1f** in the absence of CH_3SO_3H resulted in the formation of the corresponding aldehydes in less than 20 % yields, and as major products **3** and **4** (Chart 1) were obtained, respectively,[8] demonstrating that the addition of the acid is crucial for the preparation of aldehydes by the present method.



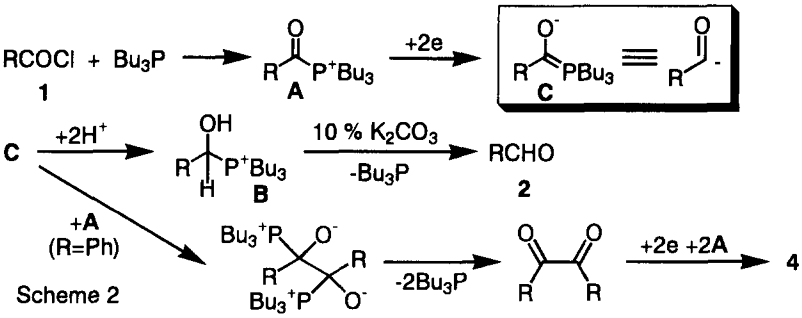
3 (31 %)

4 (49 %)

Chart 1

The mechanism for the present transformation can be proposed as shown in Scheme 2. Two-electron reduction of the *in-situ* formed acyltributylphosphonium ions generates α-oxyylides **C**, which can be regarded as an acyl anion equivalent. Their protonation gives α-hydroxyalkylphosphonium ions **B** as final reaction products, which decompose the corresponding aldehydes and Bu_3P upon weakly basic aqueous work-up. In the absence of a proton source, the ylide **C** (R=Ph) derived from benzoylphosphonium ion seems to react with another phosphonium ion **A** to give **4** probably *via* the reaction course as depicted in Scheme 2. At present, the mechanism for the formation of **3** is not clear.

In summary, the *in-situ* derivatization of acid chlorides into acyltributylphosphonium ions has shown to be useful not only in activation of the chloride as an electron-acceptor but also in temporary protection of the


Scheme 2

products (**B** in Scheme 2). The present method is believed to offer a general tool for the transformation of acid chlorides into the corresponding aldehydes without over-reduction to alcohols.[9]

References and Notes

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5. Denny, D. B. *The Chemistry of Phosphorus*, John Emsley and Dennis Hall: London, 1976; pp. 77-109.
6. The intermetallic couple was examined first for the present reaction since it is well known to be more effective than Zn alone in zinc-mediated processes such as Reformatsky and Simmons-Smith reactions as well as other reductive transformation, and was prepared from Zn and $CuSO_4$. Cf. a) Cinas, P. *Activated Metals in Organic Synthesis*, CRC Press, Inc.: London, 1993. b) Simmons, H. E.; Cairns, T. L.; Vladuchick, S. A.; Hoiness, C. M. *Org. React.*, **1973**, *20*, 1-131.
7. Deoxygenation of the solvent has proved to be essential in order to obtain the good results in Table 1. At present, the reason is not clear, but one-electron reduced species of acyl phosphonium ions seems to react with molecular oxygen or function as an electron carrier to it, which will decrease the yields of the products.
8. Physical data for **3**: ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.41-7.19 (m, 10H), 6.73 (1H, dt, J=15.7 and 1.3 Hz), 6.25 (1H, dt, J=15.7 and 6.4 Hz), 4.73 (2H, dd, J=6.4 and 1.3 Hz), 2.98 (2H, t, J=7.8 Hz), 2.68 (2H, t, J=7.8 Hz); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 172. 52 (s), 140. 38 (s), 136.12 (s), 134.09 (d), 128.53 (d), 128.44 (d), 128.26 (d), 128.01 (d), 126.58 (d), 126.15 (d), 123.09 (d), 64.98 (t), 35.81 (t), 30.89 (t); IR (KBr) 1735, 1604 cm^{-1}; MS m/e 266 (M$^+$). Selected physical data for **4** obtained as a mixture of *E*- and *Z*-isomers: ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 164.49 (s), 164.19 (s), 139.87 (s), 138.87 (s); IR (KBr) 1740, 1601 cm^{-1}; MS m/e 420 (M$^+$), 105 (base peak).
9. This work was supported in part by a Grant-in-Aid for Scientific Research (06226246) on Priority Areas (No. 236) from the Ministry of Education, Science, and Culture, Japan.

(*Received in Japan* 25 *October* 1994; *revised* 24 *December* 1994; *accepted* 1 *February* 1995)