Generation of Acyl Anion Equivalents by *In Situ* Cathodic Reduction of Acyl Tributylphosphonium Ions Anodically Generated from Tributylphosphine and Carboxylic Acids: Preparation of α-Hydroxy Cycloalkanones from Keto Acids

Hatsuo Maeda, Toshihide Maki, Haruka Ashie and Hidenobu Ohmori*

Faculty of Pharmaceutical Sciences, Osaka University, 1–6 Yamadaoka Suita, Osaka 565, Japan

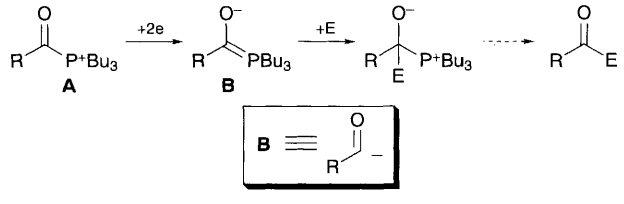
The preparation of α-hydroxy cycloalkanones from keto acids was effectively achieved by constant current electrolysis in the presence of Bu_3P in an undivided cell under an N_2 atmosphere, where the α-oxy ylides generated by the *in situ* cathodic reduction of acyl tributylphosphonium ions, formed anodically from tributylphosphine and carboxylic acids, seems to function as a novel acyl anion equivalent.

Although various acyl anion equivalents have been developed and well recognized to be useful synthons for the direct introduction of a carbonyl moiety,[1] the C–C bond formation utilizing them is limited to intermolecular reactions since it is difficult to generate an acyl anion equivalent when an electrophilic site such as a carbonyl group exists in the same molecule. Thus, it is important for organic synthesis to develop a novel methodology to generate acyl anion equivalents applicable to intramolecular reactions, although Shono *et al.* have reported[2,3] that the preparation of cyclic α-ketols, the products when acyl anion equivalents are allowed to react with internal ketones, can be achieved alternatively by electroreductively promoted couplings of ketones with internal nitriles.

Recently, we found that the partial reduction of carboxylic acids to the corresponding aldehydes can be achieved by constant current electrolysis of the acids in the presence of Ph_3P[4,5] or Bu_3P[6] in an undivided cell. Based on the proposed mechanism[5,6] and the finding that an α-hydroxymethyl phosphonium moiety is equivalent to a carbonyl group, it was expected that the α-oxy ylide **B** generated by the two-electron reduction of the acyl phosphonium ion **A** produced at the anode would function as a novel acyl anion equivalent (Scheme 1). In this paper, we describe the use of acyl phosphonium ions **A** as precursors of novel acyl anion equivalents available for C–C bond formation through addition to an internal carbonyl group.

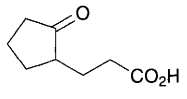
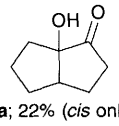
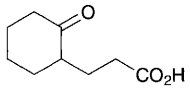
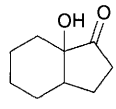
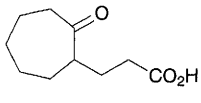
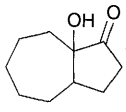
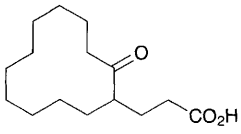
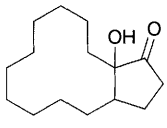
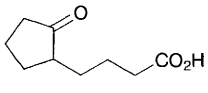
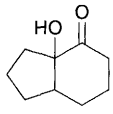
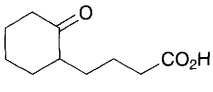
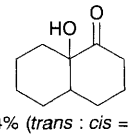
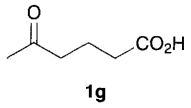
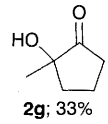
The electrolysis was carried out as follows. A solution of a keto acid **1** (3 mmol), Bu_3P (9 mmol), $MeSO_3H$ (6 mmol) and $PhCH_2(Et)_3NCl$† (3 mmol) in CH_2Cl_2 (30 ml) was placed in an undivided cell equipped with two graphite plates (each 12.5 cm^2) as the anode and cathode, the separation of which was kept at *ca.* 1 cm. A constant electric current (20 mA) was applied to the solution with stirring under an N_2 atmosphere at 0 °C.‡ After 3.0 F mol^{-1} of electricity, compound **1** had been consumed, work-up with 10% aq. K_2CO_3 followed by column chromatography on SiO_2 (hexane–ethyl acetate or CH_2Cl_2–acetone) gave the products, which were fully characterised by spectroscopy and by comparison with literature data.[3]

The results obtained for several keto acids are shown in Table 1. By electrolysis, cyclic δ- and ε-keto acids such as **1b–1d** and **1f** were transformed into bicyclic α-hydroxy ketones in good to fair yields (runs 2–4 and 6). *trans*-Fused products predominated in the electrochemical five-membered ring formation while **2f** (six-membered ring) was afforded as an almost 1 : 1 mixture of *trans*- and *cis*-isomers. It is noteworthy that the stereoselectivity in the present transformations for **1b–1d** is the opposite to that observed in Shono's reactions.[2,3] The intramolecular cyclization onto cyclopentanone moiety was not successful. Thus, the electrolyses of **1a** and **1e** gave the bicyclic products in poor yields with large amounts of the corresponding aldehydes being isolated, although a good *cis*-selectivity in each cyclized product was observed (runs 1 and 5). This procedure was also applied to the transformation of acyclic keto acid **1g** into α-hydroxy cyclopentanone **2g** (run 7).

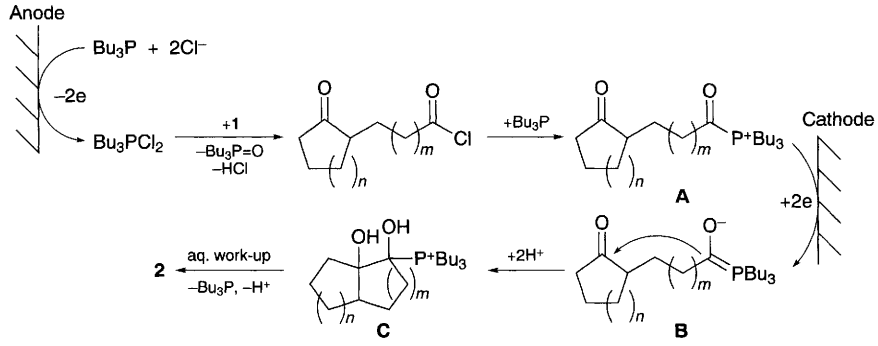


Scheme 1. E = electrophile

Table 1 Electrochemical preparation of α-hydroxy cycloalkanones from keto acids

Run	Substrate	Product[b]
1[a]	 **1a**	 **2a**; 22% (*cis* only)
2	 **1b**	 **2b**; 63% (*trans* : *cis* = 81 : 19)
3	 **1c**	 **2c**; 56% (*trans* : *cis* = 69 : 31)
4	 **1d**	 **2d**; 53% (*trans* : *cis* = 84 : 16)
5[a]	 **1e**	 **2e**; 19% (*trans* : *cis* = 15 : 85)
6	 **1f**	 **2f**; 44% (*trans* : *cis* = 52 : 48)
7	 **1g**	 **2g**; 33%

[a] The corresponding aldehyde was obtained (40–50%). [b] The ratio between *trans*- and *cis*-isomers was determined by GLC analysis of the crude products.



Scheme 2

The proposed mechanism for this reaction is shown in Scheme 2. The anodic process is considered to be the formation of an acyl tributylphosphonium ion **A** probably initiated by anodic oxidation of chloride anion leading into the formation of Bu_3PCl_2, as described for the preparation of aldehydes from carboxylic acids by electrolysis in the presence of Bu_3P.[6] An α-oxy ylide **B** generated by *in situ* cathodic reduction of **A** attacks the internal carbonyl carbon, giving an α,β-dihydroxy phosphonium ion **C**, which decomposes into the cyclized product **2** and Bu_3P upon weakly basic aqueous work-up. The indispensability of the cathodic process in the cyclization was confirmed by the fact that anodic oxidation of the mixture containing **1b** by constant current electrolysis in a divided cell resulted in no formation of **2b**. An alternative cyclization mode initiated by cathodic reduction of the ketone moiety in **A** can be ruled out by the fact that the keto acids **1** showed no cathodic peak even in the presence of $MeSO_3H$ before the discharge of the solvent, and by the observation that the acyl phosphonium ions are reduced at less negative potentials than the corresponding acid chlorides.[6] The role of $MeSO_3H$ in the electrolysis seems to be to prevent the anion formed by the cyclization of **B** from being acylated by **A**, based on the results that the electrolysis for **1b** in the absence of the acid gave only a trace amount of **2b** with larger amounts of unidentified more polar products, probably phosphonium ions.

The results described so far confirm our initial hypothesis that acyl tributylphosphonium ions are potential precursors of acyl anion equivalents when subjected to electrochemcial reduction. This methodology is beleived to find further synthetic applications, provided that an acid chloride from a keto acid is available, since the phosphonium ions **A** can also be generated chemically from acid chlorides and Bu_3P by a simple procedure.[7,§]

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, 17th January 1995; Comm. 5/00293A

Footnotes

† As supporting electrolytes, Bu_4NBr and $PhCH_2NEt_3Br$ could also be utilized for the preparation of the cyclized products, and as yet unidentified by-products were formed in larger amounts than in the case of $PhCH_2NEt_3Cl$.

‡ Without passing the electric current, no change in the reaction mixture was detected. The electrolysis for **1b** at room temp. also gave the cyclized product although the yield of **2b** was not satisfactory (21%).

§ At present we have been unsuccessful in attempts to prepare an acid chloride from a keto acid by common methods due to the problem reported in ref. 8.

References

1 For reviews, O. W. Lever Jr., *Tetrahedron*, 1976, **32**, 1943; B. T. Grobel and D. Seebach, *Synthesis*, 1977, 357; S. F. Martin, *Synthesis*, 1976, 633.
2 T. Shono and N. Kise, *Tetrahedron Lett.*, 1990, **31**, 1303.
3 T. Shono, N. Kise, T. Fujimoto, N. Tominaga and H. Morita, *J. Org. Chem.*, 1992, **57**, 7175.
4 H. Maeda, T. Maki and H. Ohmori, *Tetrahedron Lett.*, 1992, **33**, 1347.
5 H. Maeda, T. Maki and H. Ohmori, *Chem. Pharm. Bull.*, 1994, **42**, 1041.
6 H. Maeda, T. Maki and H. Ohmori, *Denki Kagaku*, 1994, **62**, 1109.
7 E. Vedejs and S. T. Diver, *J. Am. Chem. Soc.*, 1993, **115**, 3358, and references therein.
8 S. Kafka, J. Kytner, A. Šilhánková and M. Ferles, *Collect. Czech. Chem. Commun.*, 1987, **52**, 2035.