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A FACILE TRANSFORMATION OF ALKYL ARYL KETONES TO METHYL α-ARYLALKANOATES BY ANODIC OXIDATION IN THE PRESENCE OF IODINE OR IODO COMPOUNDS[1]

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Summary: Anodic oxidation of easily accessible alkyl aryl ketones 1 in trimethyl orthoformate containing a small amount of iodine or organo-iodo compounds gave methyl α-arylalkanoates 2 in high yields.

As new development of our continuing studies on anodic oxidation using halogen ions as mediators,[2] we report herein a new reaction system which makes a convenient transformation of alkyl aryl ketones 1 to methyl α-arylalkanoates 2 possible. Although the antiinflammatory and analgesic activities shown by some of the compounds having the structure of α-arylalkanoic acid 3[3] have stimulated the exploitation of a variety of methods of synthesis of 2,[4] a synthetic route of 2 from 1 involving oxidative 1,2-aryl migration (eq. 1) as a key step has never been considered to be one of the most convenient methods since those reported[5a-d] so far need more than one equivalent of highly toxic oxidizing agents such as thallium (III)[5b] or lead (IV)[5c] salts.

On the other hand, this method represented by eq. 1 seems to be worthwhile due to the high accessibility of starting compounds and the short reaction pathway. Although iodine has recently been shown to be an effective oxidizing agent for this type of 1,2-aryl migration,[5d] excess amount of iodine was necessary and it was not effective for the 1,2-migration of aryl groups having electron-withdrawing substituents.

1a-f

2a-f; R'=Me
3a-f; R=H

(1)

a; X=H, R=Me
b; X=iso-Bu, R=Me
c; X=tert-Bu-CO_2, R=Me
d; X=Cl, R=Me
e; X=Br, R=Me
f; X=H, R=H

The electrooxidative method shown in this report, however, is effective to alkyl aryl ketones such as 1a-f with using 0.1-0.7 equiv. of iodine, iodomethane, or other organo-iodo compounds as the sources of mediators.

A typical experiment is as follows: Into an undivided electrolysis cell equipped with two platinum electrodes (1 cm x 1 cm) and a magnetic stirring bar was put a solution of trimethyl orthoformate (TMOF) (3 ml) containing 1 (4 mmol), iodine (1 mmol) and $LiClO_4 \cdot 3H_2O$ (300 mg).[6] Anodic oxidation was carried out under the conditions of constant current (0.05 A/cm^2) at room temperature.

Table 1. Anodic Oxidation of Alkyl Aryl Ketones 1 to Yield Methyl α-Arylalkanoates 2 in TMOF Containing Iodine or Organo-Iodo Compounds

Run	Reaction System[a]		Electricity, *F*/mol	Products	Yield, %[b]
1	1a	I_2 (0.1)	30	2a	85
2	1a	I_2 (0.25)	8	2a	88
3[c]	1a	I_2 (0.25)	25	2a	83
4[d]	1a	I_2 (0.25)	8	2a	80
5	1c	I_2 (0.25)	24	2c	60
6	1d	I_2 (0.25)	15	2d	88
7	1e	I_2 (0.25)	10	2e	88
8	1f	I_2 (0.25)	8	2f	83
9	1a	MeI (0.7)	8	2a	100
10	1b	MeI (0.7)	9	2b	80[e]
11	1c	MeI (0.7)	17	2c	93
12	1e	MeI (0.7)	8	2e	100
13	1f	MeI (0.7)	8	2f	100
14	1a	iso-PrI (0.5)	8	2a	76[f]
15	1a	PhI (0.5)	8	2a	27[f,g]
16	1a	CHI_3 (0.17)	8	2a	90[f]
17	1a	TMSI[h] (0.5)	8	2a	84[f]

[a] The value shown in the parenthesis was the ratio of iodine or iodo-compounds to 1.

[b] Isolated yields. [c] Solvent was a 1:1 (volume) mixture of TMOF and MeOH.

[d] Solvent was a 1:1 (volume) mixture of TMOF and AcOMe.

[e] After 9 *F*/mol of electricity was passed, the reaction mixture was stirred for 24 hrs at room temperature. When great excess of electricity (32 *F*/mol) was passed, the yield of 2b decreased to 17% due to further oxidation of 2b. [f] GLC yield.

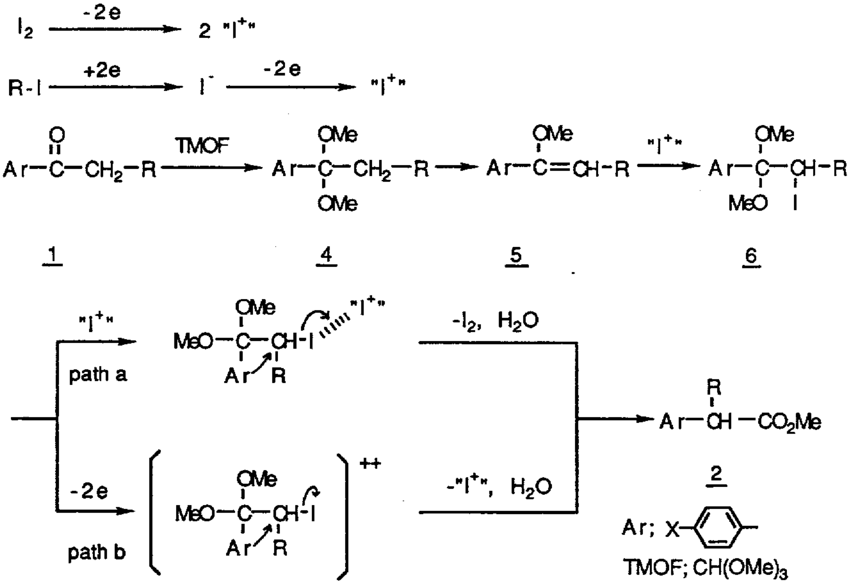
[g] Propiophenone dimethyl ketal was the main product (69%). [h] Trimethylsilyl iodide.

Since TMOF has a low electric conductivity[7] and the surface of the cathode was gradually covered with nonconducting materials, it was necessary to alternate anode and cathode with suitable interval (7 seconds for example) in order to keep the constant current conditions. After 8 *F*/mol of electricity was passed, the reaction mixture was poured into an aqueous sodium thiosulfate containing sodium bicarbonate, and then the organic portion was extracted with methylene chloride (3 x 50 ml). The combined organic solution was dried, evaporated, and then subjected to column chromatography to give 2. This 1,2-aryl migration was also promoted by the anodic oxidation using a variety of iodo compounds instead of iodine. The yields and reaction conditions are summarized in Table 1.

The use of TMOF as the solvent of electrolysis was crucially important for the 1,2-aryl migration, since the electrolysis of 1a in methanol containing iodine (0.5 equiv.) and lithium perchlorate resulted in the recovery of 1a with a formation of a trace of dimethyl ketal of 1a, whereas a mixed solvent of TMOF and methanol or methyl acetate gave satisfactory results (runs 3 and 4).[8] The presence of iodine or organo-iodo compounds was also essencial, since the anodic oxidation of 1a in the absence of iodine or organo-iodo compounds in TMOF gave methyl benzoate as a main product which might be formed by direct oxidation of 1a.

The catalytic nature of iodine in this anodic reaction system was typically shown in the experiment where 0.1 equivalent of iodine was used (run 1), while treatment of 1a with 0.1 equivalent of iodine in TMOF without passing electricity resulted in the recovery of most of 1a.

A reaction mechanism involving a mediatory system may be suggested for the conversion of 1 to 2 on the basis of these results (Scheme 1).



Scheme 1

Thus, enol ethers 5 were yielded from the ketals 4 which were formed by ketalization of ketones 1 with TMOF. The attack of "I^+",[9] which was anodically generated from iodine[10] or I^- [11] formed by cathodic reduction of iodo compounds, on 5 afforded 6. Generally, the 1,2-migration of aryl groups possessing electron-withdrawing substituents hardly occurs in this type of rearrangement, whereas it smoothly proceeded under the conditions of anodic oxidation in TMOF containing iodine (runs 5, 6 and 7).[12] Hence, the heterolytic cleavage between iodo atom and β-carbon of 6 might be assisted with "I^+" at the step from 6 to 2 (path a) or direct anodic oxidation of 6 (path b)[13,14] might promote the migration of aryl groups. Consequently, 1 was electrooxidatively transformed to 2 in the presence of a small amount of iodine or iodo compounds.

Although the details of the mechanism are still not always clear, and further mechanistic studies will be desirable, the results obtainted in this study are very worthwhile from a synthetic viewpoint.

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References and Notes

1. Electroorganic Chemistry. 114.
2. Shono,T.; Matsumura,Y.; Inoue,K. *J. Am. Chem. Soc.* 1984, *106*, 6075. Shono,T.; Matsumura,Y.; Inoue,K.; Iwasaki,F. *J. Chem. Soc., Perkin Trans. 1* 1986, 73, and references cited therein.
3. Ferreira,S.H.; Vane,J.R., "Antiinflammatory Drugs," Springer, Berlin, 1979, p.321.
4. Hiyama,T.; Saito,K.; Sato,K.; Wakasa,N.; Inoue,M. *Chem. Lett.* 1986, 1471. Sugai,S; Kodama,T.; Akaboshi,S.; Ikegami,S. *Chem. Pharm. Bull.* 1984, *32*, 99. Giordano,C.; Castaldi,G.; Uggeri,F. *Angew. Chem., Int. Ed. Engl.* 1984, *23*, 413, and references cited therein. Mandai,T.; Hara,K.; Nakajima,T.; Kawada,M.; Otera,J. *Tetrahedron Lett.* 1983, *24*, 4993. Tsuchihashi,G.; Kitajima,K.; Mitamura,S. *Ibid.* 1981, *22*, 4305.
5. a) Castaldi,G.; Cavicchioli,S.; Giordano,C.; Uggeri,F. *J. Org. Chem.* 1987, *52*, 3018, and references cited therein. b) Fujii,K.; Nakao,K.; Yamauchi,T. *Synthesis* 1983, 444. Higgins,S.D.; Thomas,C.B. *J. Chem. Soc., Perkin Trans. 1* 1983, 1483, and references cited therein. c) Yamauchi,T.; Nakao,K.; Fujii,K. *Ibid.* 1987, 1433. Myrboh,B.; Ila,H.; Junjappa,H. *Synthesis* 1981, 126. d) Citterio,A.; Tinucci,L.; Filippini,L.; Belli,A. Eur. Pat. Appl. EP 171,840 (1986); *Chem. Abstr.* 1986, *105*, 6321p. Yamauchi,T.; Hattori,K.; Nakao,K.; Tamaki,K. *J. Org. Chem.* 1988, *53*, 4858.
6. When anhydrous $LiClO_4$ was used, the electric current immediately decreased to zero.
7. Foos,J.S.; McVeigh,J. *J. Electrochem. Soc.* 1983, *130*, 628.
8. The alternation of anode and cathode was not necessary in these cases.
9. "I^+" denotes the positive halogen species generated by anodic oxidation of I_2 or I^-.
10. Dryhurst,G.; Eiving,P.J. *Anal. Chem.* 1967, *39*, 606.
11. Iwamoto,R.T. *Anal. Chem.* 1959, *31*, 955.
12. Treatment of 6e (Ar=p-Br-Ph, R=Me) with I_2/TMOF or with I_2/TMOF/H_2SO_4 overnight resulted in the recovery of 6e.
13. Alkyl iodides are electrochemically oxidizable; Miller,L.L.; Hoffman,A.K. *J. Am. Chem. Soc.* 1967, *89*, 593.
14. α-Haloalkyl aryl ketone dimethylacetals are converted into esters of 2-arylalkanoic acids by reaction with peroxides; Higgins,S.D.; Thomas,C.B. *J. Chem. Soc., Perkin Trans. 1* 1983, 1483.

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