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CONVENIENT ELECTROCHEMICAL METHOD FOR THE SYNTHESIS OF α-BROMO ALKYL ARYL KETONES

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An electrochemical procedure for the effective α-bromination of alkyl aryl ketones in excellent yield has been reported. The simple experimental procedure, catalyst-free conversion, and excellent yield of monobrominated products are the advantages of this method.

Keywords: Alkyl aryl ketone; α-bromination; carbonyl compounds; constant-current electrolysis; electrochemical bromination; electrosynthesis

The α-bromination of carbonyl compounds is an important transformation in synthetic organic chemistry because the resulting products are very useful as intermediates in the synthesis of biologically active compounds.[1,2] For example, in the preparation of Naproxen (a nonsteroidal anti-inflammatory agent), α-bromination of alkyl aryl ketone is an important step in the 1,2-migration of the aryl group to get the product in very good yield.[3] A number of methods have been described for the bromination of ketones, employing compounds such as acetyl cupric bromide,[4] ammonium bromide,[5] dioxane dibromide,[6] and tetrabutyl ammonium tribromide.[7] Recently, Podgorsek and coworkers have described a green method for the bromination of ketones in an aqueous H_2O_2-HBr system.[8] α-Bromination of carbonyl compounds in the presence of ionic liquids have been investigated also.[9] All these methods require high temperature and suitable catalysts[6] or free radical initiators[10] for the reaction to proceed. In continuation of our interest in organohalogen chemistry,[11,12] herein we report the α-bromination of carbonyl compounds without any catalyst by an electrochemical method at a temperature of $10 \pm 2\,^{\circ}C$ using 20% HBr in acetonitrile (Scheme 1); 20% HBr is used as a bromine source as well as for conductivity.

The method has been applied to a series of aromatic ketones. The present method furnished only the monobrominated products. However, the α,α-dibromo acetophenone can be obtained in 92% yield when a charge of 12 F was passed. This

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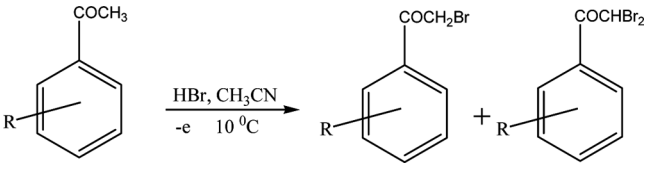


Scheme 1. Electrochemical bromination of carbonyl compounds.

method is associated with only the alkyl group of ketones, but the nuclear bromination in the aromatic ring did not occur.

Electrochemical α-bromination of alkyl aryl ketones occurred smoothly to give the corresponding α-brominated products in excellent yields. The results of these studies are summarized in Table 1. At optimum operating conditions, acetophenone gave 83% of monobromo acetophenone and 10% of dibromo acetophenone. With an increase of reaction temperature from 10 to 25 °C, the rate of conversion of acetophenone increased 1.5 times but selectivity for monobromination decreased (31% dibrominated product was formed). Optimization of the reaction conditions for the electrochemical α-bromination of the carbonyl compounds was investigated using acetophenone as the model substrate and acetonitrile as an efficient reaction medium. Though 4-methyl acetophenone (entry 11) has methyl as well as acetyl groups, the acetyl group is brominated rather than the methyl group because of the electron-withdrawing nature of the carbonyl function.

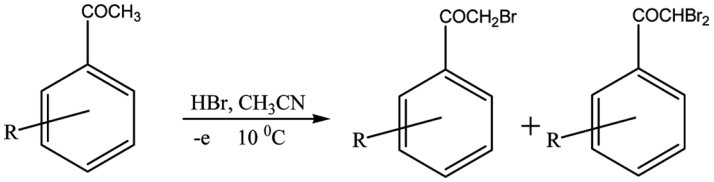
The effect of different solvents on the α-bromination of acetophenone was studied, and the results are summarized in Table 2. Among the different solvents used for the α-bromination of ketones, acetonitrile was found to be the most suitable. The reaction was fast without any catalyst, with 93% conversion, and a selectivity of 90% monobromo acetophenone was observed in acetonitrile solvent. The conversion of acetophenone in different solvents was in the following order: 1,4-dioxane > dimethylformamide (DMF) > CH_3CN > tetrahydrofuran (THF) > CH_2Cl_2 > dimethylsulfoxide (DMSO), whereas the selectivity toward α-bromo acetophenone was in the following order: CH_3CN > DMSO > DMF > CH_2Cl_2 > 1,4-dioxane > THF.

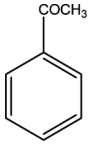
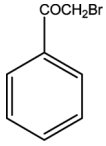
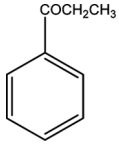
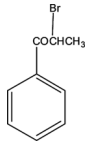
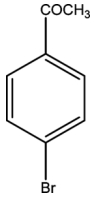
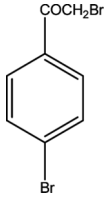
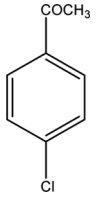
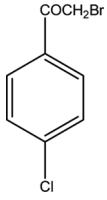
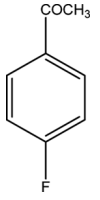
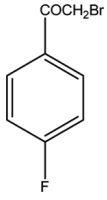
In the cases of 1,4-dioxane and DMF as solvents, the rate of conversion of acetophenone was ~1.5 times greater than acetonitrile, with an increase of α,α-dibrominated acetrophenone formation. When graphite was used as an anode instead of platinum, monobromo acetophenenone was obtained in 80% yield.

Some authors believe that the bromination of alkyl aryl ketone follows a free radical mechanism.[12] The electrochemical oxidation of bromide ion leads to controlled formation of a bromine radical that reacts with the substrate molecules at a steady rate, thereby increasing the conversion of the substrate to the formation of monobromo ketones and eliminating side product formation.

In conclusion, we have demonstrated an electrochemical procedure for the effective α-bromination of alkyl aryl ketones in excellent yields. The simple experimental procedure, catalyst-free conversion, and good yield of monobrominated products are the advantages of the present method. This method is expected to be of great synthetic utility because of its high selectivity for the α-monobrominated products.

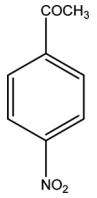
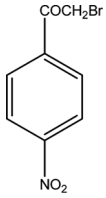
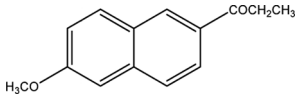
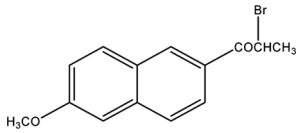
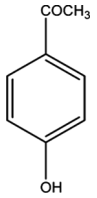
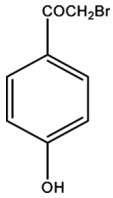
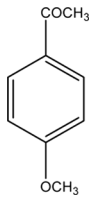
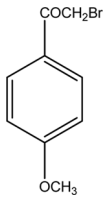
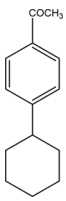
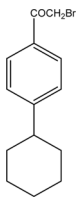
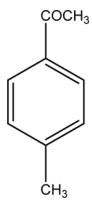
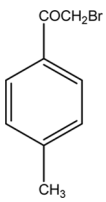
Table 1. Electrochemical α-bromination of alkyl aryl ketones with HBr in acetonitrile



Entry	Substrate	Product	Charge passed (F)	Yield (%)	Current efficiency (%)
1			4.5	83	36
2			3.8	91	50
3			4.0	85	40
4			4.2	89	39
5			5.0	81	32

(*Continued*)

Table 1. Continued

Entry	Substrate	Product	Charge passed (F)	Yield (%)	Current efficiency (%)
6			5.0	85	31
7			2.0	92	83
8			4.7	82	35
9			6.0	74	25
10			5.5	84	28
11			3.9	81	38

Note. Alkyl aryl ketone (10 mmol), acetonitrile (25 ml), and hydrobromic acid (10 ml of 47% solution) were electrolyzed at $10 \pm 2\,^{\circ}C$.

Table 2. Effect of solvent on the electrochemical bromination of acetophenone

Entry	Solvent	Conversion (%)	Selectivity (%)	
			Monobromo	Dibromo
1	CH_3CN	68	90	10
2	DMSO	50	85	15
3	DMF	76	83	17
4	CH_2Cl_2	61	82	18
5	1,4-Dioxane	95	59	41
6	THF	65	53	47

Note. Acetophenone (10 mmol), acetonitrile (25 ml), and hydrobromic acid (10 ml of 47% solution) were electrolyzed at $10 \pm 2\,^{\circ}C$, and the analysis was conducted after passing a charge of 2 F.

EXPERIMENTAL

Representative Procedure for Electrochemical Bromination

Hydrobromic acid (10 ml of 47% solution) was added to a solution of ketone (10 mmol) in acetonitrile (25 ml), and the resulting solution was taken in an undivided electrolytic cell. Platinum electrodes (each of 6 cm^2 area) were used as electrodes. The reaction mixture was cooled to $10\,^{\circ}C$ with constant stirring, and the current was passed galvanostatically as mentioned in Table 1 with a current density of 50 mA cm^{-2}. The reaction was monitored by high-performance liquid chromatography (HPLC; Shimadzu) using methanol and water (80:20) as eluent. After completion of electrolysis, the reaction mixture was diluted with cold water (50 ml), and the product was extracted with dichloromethane (3×20 ml). The extract was washed with water (20 ml) and dried over anhydrous sodium sulfate. The product α-bromo acetophenone was obtained after evaporation of the solvent at reduced pressure and crystallized from a mixture of methanol and hexane. The product was analyzed by ^1H NMR, ^{13}C NMR, and Fourier transform–infrared (FT-IR) spectra.

Spectral Data

2-Bromo acetophenone. ^1H NMR (400 MHz, $CDCl_3$): δ 7.9–7.6 (5H, m), 4.4 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.07, 1324.23, 133.73, 133.64, 129.40, 128.65, 128.61, 30.82; FT-IR (KBr): ν 3072, 2981, 2890, 1692, 1634, 1445, 1279, 1197, 683, 620, 550 cm^{-1}.

2-Bromo, 4′-bromo acetophenone. ^1H NMR (400 MHz, $CDCl_3$): δ 7.8–7.6 (4H, m), 4.4 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.17, 132.32, 131.96, 130.16, 129.05, 30.14; FT-IR (KBr): ν 3084, 2998, 2953, 1696, 1583, 1481, 716, 650, 547 cm^{-1}.

2-Bromo propiophenone. ^1H NMR (400 MHz, $CDCl_3$): δ 8.0–7.2 (5H, m), 5.3 (1H, q), 1.9 (3H, d, $J = 7$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.09, 133.72, 133.42, 128.64, 128.48, 41.21 19.85; FT-IR (KBr): ν 3062, 2979, 2938, 1687, 1593, 1452, 1220, 692, 635, 567 cm^{-1}.

2-Bromo, 4′-methoxy acetophenone. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (2H, d, $J = 9$ Hz), 6.98 (2H, d, $J = 9$ Hz), 4.42 (2H, s), 3.90 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.73, 163.86, 131.97, 131.09, 126.60, 113.94, 113.79, 55.31, 30.50; FT-IR (KBr): ν 3072, 2964, 1669, 1603, 1461, 1252, 1175, 630, 582 cm^{-1}.

2-Bromo-(6′-methoxy 2′-naphthyl)propiophenone. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.5–7.2 (6H, m), 5.4 (1H, q), 4.0 (3H, s), 1.9 (3H, d, $J = 7$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.52, 155.79, 135.40, 130.73, 130.69, 129.45, 128.26, 126.60, 125.94, 113.80, 99.69, 56.67, 41.26, 19.89; FT-IR (KBr): ν 3076, 3015, 2944, 1680, 1597, 1478, 1278, 1197, 702, 664, 596 cm^{-1}.

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