Synthesis of 2-Arylalkanoic Acids: Zinc Bromide-Assisted Methanolysis of α-Bromoalkyl Aryl Ketones

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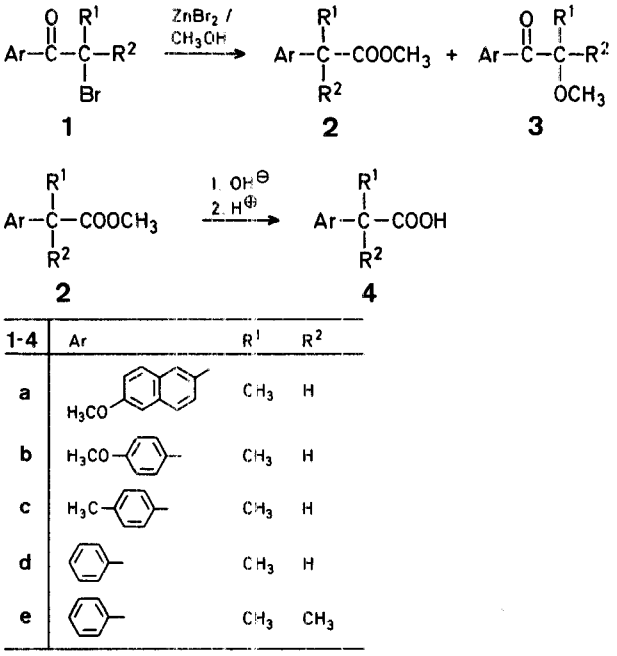
It is well documented that, among the nonsteroidal antiinflammatory agents, 2-arylalkanoic acids have acquired great importance[1]. For many years the synthetic approach to this class of compounds was restricted to the Willgerodt[2] and Darzens[3] reactions. More recently, several methods have been developed which are based on the 1,2-aryl shift in acetals of α-halo[4,5,6], α-thallio-[7], α-tosyl-[8], and α-diazoalkyl aryl ketones[9,10].

Moreover, α-haloalkyl aryl ketones can be converted, in a one-pot reaction, into methyl esters of 2-arylalkanoic acids when treated in trimethyl orthoformate with thallium(III) nitrate[11] or in methanol with silver salts[12]. Both methods suffer from limitations for the preparation of 2-arylalkanoic acids on a multigram scale; the first one because of the well-known toxicity of thallium salts, while the latter method requires at least a stoichiometric amount of expensive silver salts.

We now report that the above-mentioned disadvantages can be overcome by replacing silver salts by another metal catalyst. We have found that zinc bromide promotes the conversion of α-bromoalkyl aryl ketones **1** into methyl esters of 2-arylalkanoic acids **2** and α-methoxyalkyl aryl ketones **3**.

The method consists of heating a mixture of concentrated solutions of an α-bromoalkyl aryl ketone **1** and anhydrous zinc bromide in methanol at 50–115 °C. After careful hydrolysis[13] of the crude reaction mixture, the free acids **4** are isolated. Secondary and tertiary α-bromoalkyl aryl ketones **1** provide products **4** in moderate to good yields (Table), while primary α-bromoalkyl aryl ketones give rise mainly to the substitution products **3** ($R^1 = R^2 = H$), rearrangement products **2** ($R^1 = R^2 = H$) being present as by-products.



1-4	Ar	R^1	R^2
a	H_3CO	CH_3	H
b	H_3CO	CH_3	H
c	H_3C	CH_3	H
d		CH_3	H
e		CH_3	CH_3

Table. 2-Arylpropanoic Acids **4a–e** prepared[a]

Product	Reaction Time	Yield[b] [%]	m.p. [°C] found (solvent)	m.p. [°C] reported
4a	5 h	86	154–155° (acetone/hexane)	154–155°[4]
4b	3 h	80	57° (hexane)	57°[4]
4c	4 h	58	38–40° (hexane)	36–37°[11]
4d	6 h	48	16° (hexane)	16°[12]
4e	4 h	69	79–80° (ethanol)	80–81°[16]

[a] Not optimized reaction conditions: Ketone **1** (50 mmol), zinc bromide (500 mmol), and methanol (880 mmol) at 115 °C following the typical procedure given.

[b] Yield of **4** isolated, based on **1** introduced. Purities of products ≧ 96% [17] as determined by G.L.C. analysis of the corresponding trimethylsilyl esters.

The present procedure, avoiding the masking of the carbonyl group of **1** as an acetal[10], represents a direct route for converting **1** ($R^1 = H, CH_3$; $R^2 = CH_3$) into **2** ($R^1 = H, CH_3$; $R^2 = CH_3$). As from competitive experiments[14], the selectivity towards the formation of **2**, and the reaction rate are enhanced when the aryl moiety in **1** bears electron-donating substituents. Generally, the reaction has to be carried out in the presence of a high concentration of the zinc salt because the selectivity towards **2** decreases on lowering the zinc bromide concentration. It is worth noting that, on replacing part of the zinc bromide by a Lewis acid such as boron trifluoride, the reaction selectivity is unchanged and that boron trifluoride itself does not promote the rearrangement.

From the above findings, it is clear that zinc bromide is needed to achieve the rearrangement, while a high selectivity towards ester formation is obtained only at high acid concentration. The formation of **3** is the result of zinc bromide-

assisted methanolysis of **1**. As far as **2** is concerned, the catalyst has a two-fold effect: to set up the equilibrium between the α-bromoketone **1** and methanol, thus producing a hemiacetal- or an acetal-like form, and to assist the heterolysis of the carbon-bromine bond in these latter species.

The method provides an additional and significant example of the possibility of using zinc salts instead of silver salts in the heterolysis of the carbon-halogen bond in protic solvents[15].

The α-bromoalkyl aryl ketones **1a–e** are known compounds and were prepared as previously described[18]. All the products **4** prepared were characterized by m.p. (Kofler method), I.R. and ^{1}H-N.M.R. spectra [taken at 60 MHz ($CDCl_3$/TMS)] and by comparison with authentic samples.

2-(4-Methylphenyl)-propanoic Acid (4c); Typical Procedure:
Anhydrous zinc bromide (112.6 g, 500 mmol) is added at room temperature under nitrogen and with stirring to methanol (28.2 g, 880 mmol). The temperature of the solution increases spontaneously to 60–70°C. The solution is heated at 115°C and 2-bromo-1-(4-methylphenyl)-propan-1-one (**1c**; 11.4 g, 50 mmol) is added. The mixture is kept under nitrogen and with stirring at 115°C for 4 h. It is cooled to room temperature, poured into water (250 ml), and extracted with dichloromethane (2 × 75 ml). The combined organic extracts are washed with water (2 × 40 ml) and dried with sodium sulfate. Evaporation of the solvent under reduced pressure gives a residue (8.7 g), which is dissolved in water (30 ml) and methanol (70 ml). The solution is heated at reflux, flushed with nitrogen, then cooled to room temperature. Sodium hydroxide (1.4 g, 35 mmol) is added to the solution and the mixture is stirred under nitrogen at room temperature for 7 h. It is then poured into water (100 ml) and extracted with dichloromethane (3 × 50 ml). The aqueous phase is acidified with concentrated hydrochloric acid and extracted with dichloromethane (3 × 50 ml). The combined organic extracts are washed with water (3 × 50 ml) and dried with sodium sulfate. Evaporation of the solvent under reduced pressure gives **4c**; yield: 4.7 g (58%); m.p. 35–36°C. Crystallization from *n*-hexane gives an analytically pure product; m.p. 38–40°C (Lit.[11], m.p. 36–37°C).

Received: October 22, 1984

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