

## Novel C–C Bond Cleavage under Mild, Neutral Conditions: Conversion of Electron-Deficient Aryl Alkyl Ketones to Aryl Carboxylic Esters

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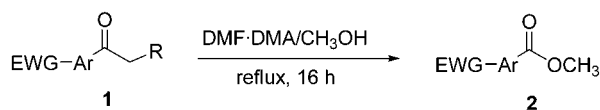
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Received September 24, 2001

**Abstract:** A novel, unique way to cleave the carbon–carbon bond in aryl alkyl ketones under mild, neutral conditions is described. Treatment of aryl alkyl ketones in a refluxing mixture of *N,N*-dimethylformamide dimethyl acetal and methanol for 16 h provided aryl carboxylic esters. The scope and limitations of the reaction are discussed. Useful yields of the reaction can be obtained with electron-deficient aryl groups, and the yields are higher when the alkyl group is larger than a methyl group. Studies toward elucidation of the reaction mechanism led to a proposed mechanism that is consistent with all the observations.

Carbon–carbon bond cleavage of ketones is widely utilized to prepare carboxylic acids and derivatives. The most commonly used method is the Baeyer–Villiger oxidation,<sup>2</sup> which involves treatment of ketones with peracids, hydrogen peroxides, or other peroxy compounds. Other methods, such as the haloform reaction<sup>3</sup> used mostly for the cleavage of methyl ketones and the Haller–Bauer reaction<sup>4</sup> for the cleavage of nonenolizable ketones, are more limited in the scope of substrates. A general method for the cleavage of aryl methyl or aryl ethyl ketones to form aromatic carboxylic acids was recently reported using an excess of KOH in DMF at an elevated temperature.<sup>5</sup> These cleavage methods have a common feature in that they invariably require a strong oxidative agent and/or a strong base. Here we report a novel carbon–carbon bond cleavage reaction of aryl alkyl ketones to aryl carboxylic esters in a refluxing mixture of *N,N*-dimethylformamide dimethyl acetal (DMF·DMA) and methanol. Although useful yields of the reaction are limited to electron-deficient aryl groups, the method represents a novel, unique way to cleave a carbon–carbon bond under mild, neutral conditions.



(1) 2001 Wyeth-Ayerst Chemical Sciences Summer Intern from Fordham University, Bronx, NY 10458.

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**Table 1.** Conversion of Aryl Alkyl Ketones **1** to Aryl Esters

Entry	Substrate	Yield (%) <sup>a</sup>	Entry	Substrate	Yield (%) <sup>a</sup>
a		87	h		26
b		84	i		42
c		95	j		8
d		40	k		4
e		71	l		11
f		40	m		9
g		50	n		0

<sup>a</sup> Isolated yield except entries l and m, where the product was obtained as a nonseparable mixture with the starting material.

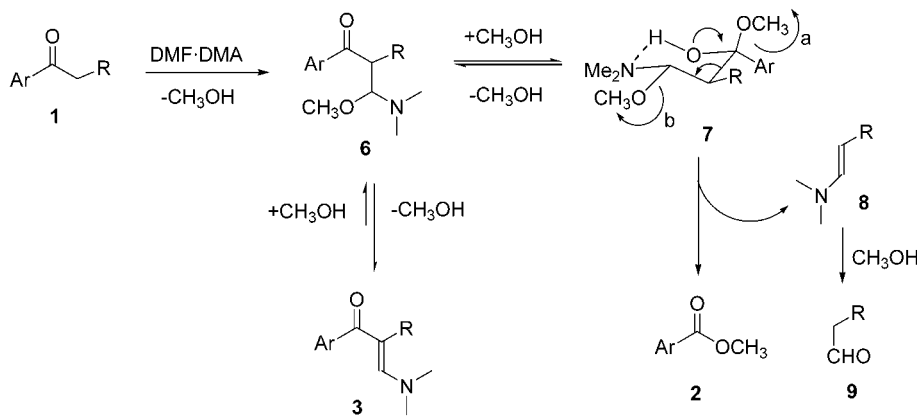
Treatment of 3'-nitropropiophenone (**1a**, Table 1) with DMF·DMA under reflux for 16 h yielded methyl 3-nitrobenzoate (**2a**) in 67% yield. Prolonged reaction time (to 40 h) did little to improve the yield. An increase in the reaction yield (to 87%) was achieved by addition of methanol as a cosolvent, in agreement with our proposed reaction mechanism (discussed below). We explored the scope and limitations of this reaction by treating a variety of aryl alkyl ketones in a refluxing mixture of DMF·DMA and methanol for 16 h. The results are summarized in Table 1.

The reaction yield is sensitive to the electron density of the carbonyl group as well as the size of the R group. As shown in Table 1, with the same alkyl group, the yields are higher when the carbonyl group is more electron deficient. Thus, a 4-nitrophenyl gives better yields than a 3-nitrophenyl (entries c vs a and g vs f), and a 4-pyridyl gives better yields than a 3-pyridyl (entries e vs d and i vs h). Useful yields can be obtained only when the aromatic ring is highly electron-deficient. In the absence of such electron-deficient aromatic groups, the reaction yields are very low (entries j–m),<sup>6</sup> while the reaction gives no desired product in the presence of an electron-donating group (entry n). Another trend of this reaction is that with the same aromatic ring the yields are higher when R is bigger than a hydrogen (entries a and b vs f, c vs g, d vs h, and e vs i).

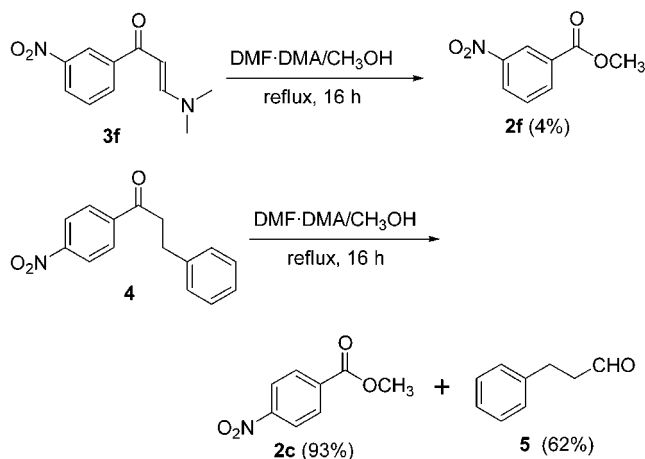
To elucidate the mechanism of this novel transformation, we prepared a possible intermediate, 3-(dimethylamino)-1-(3-nitrophenyl)-2-propen-1-one (**3f**),<sup>7</sup> from 3-nitroacetophenone (**1f**). The resultant **3f** was then subjected

(6) Reaction of 2'-(trifluoromethyl)propiophenone gave an inseparable mixture containing a small quantity of methyl 2-(trifluoromethyl)benzoate as evidenced by <sup>1</sup>H NMR analysis.

## Scheme 1. Proposed Reaction Mechanism



to the standard reaction conditions, refluxing in a mixture of DMF·DMA and methanol for 16 h. Methyl 3-nitrobenzoate (**2f**) was obtained in 4% yield, suggesting that **3f** is not an obligatory intermediate, but can be converted to the intermediate in low yield. Further evidence of the reaction mechanism is provided by the reaction of 1-(4-nitrophenyl)-3-phenylpropan-1-one (**4**),<sup>8</sup> which has a large alkyl group that enables us to follow up on the alkyl portion of the molecule. A mixture of methyl 4-nitrobenzoate (**2c**, 93% yield) and 3-phenylpropanal (**5**, 62% yield) was obtained from the reaction.



Based on these results, we propose the reaction mechanism shown in Scheme 1. Reaction of the aryl alkyl ketone **1** (via its enol) with DMF·DMA generates the first intermediate **6**, which can either eliminate 1 equiv of methanol to form the dimethylaminoenone **3** or undergo an addition reaction with methanol to another intermediate **7**. Intermediate **7**, which can adopt the cyclic conformation as shown in Scheme 1, can either eliminate methanol (pathway a) to regenerate **6** or eliminate enamine **8** (pathway b) to generate ester **2**. This mechanism is consistent with our observed results. We found that the yields of the ester **2** were higher when methanol was used as a cosolvent. This is because excess methanol helps formation of **7** (vs formation of **3**) from **6** in the two competing pathways. Addition of methanol to the carbo-

nyl group in **6** is also more favored (over formation of **3**) when the carbonyl group is more electrophilic. As a result, higher yields of ester **2** were obtained when the Ar group was more electron deficient. Formation of **6** is also facilitated by the electron-deficient Ar groups, since when the Ar groups are electron-rich, starting materials were recovered. Larger R groups disfavor elimination of **6** to **3** owing to their unfavorable steric interaction with the dimethylamino group in the planar enone **3**. Additionally, larger R groups may also facilitate pathway b from the intermediate **7** owing to relief of the steric congestion.

In conclusion, we have demonstrated a novel, unique way to cleave the carbon-carbon bond in aryl alkyl ketones to furnish esters under mild, neutral conditions. Useful yields of the reaction are limited to electron-deficient aryl groups, and the yields are higher when the alkyl group (CH<sub>2</sub>R) is larger than a methyl group. The reaction is under further investigation with more elaborate alkyl groups.

## Experimental Section

All reactions were conducted under nitrogen atmosphere with magnetic stirring. All reagents and solvents were commercial grade. Column chromatography was performed on Baker silica gel (40 μm). Starting materials (Table 1, entries a, b, and e-l) were purchased from Aldrich and Lancaster and used without purification. The starting materials of Table 1, entries c (compound **1c**)<sup>9</sup> and d (compound **1d**)<sup>10</sup> were prepared according to the literature procedure.

**General Procedure of the Reaction.** A mixture of the aryl alkyl ketone **1** (5 mmol) in a mixture of *N,N*-dimethylformamide dimethyl acetal (DMF·DMA) (10 mL) and anhydrous methanol (2 mL) was refluxed under nitrogen for 16 h. The reaction time was not optimized. The solvents were removed, and the product was then purified using flash column chromatography over silica gel eluting typically with hexanes-ethyl acetate, providing the ester **2**. Yields are given in Table 1. Structural confirmation of the esters **2** was accomplished by comparison to the authentic commercially available material.

**Acknowledgment.** We thank Dr. Semiramis Ayril-Kaloustian for the support of the Summer Intern Program and helpful discussions on this work. We are very grateful to Professor Michael Jung (UCLA) for helpful discussions and suggestions.

JO016145L

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