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COMMUNICATION

# An organometallic route for the preparation of ring-substituted 2-aryl-propanoic and -butanoic acids

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**This communication presents a simple and efficient way to synthesize 2-arylalkanoic acids via chromium carbonyl complexation.**

**Keywords: 2-Arylalkanoic acids, analgesics, anti-inflammatories, chromium carbonyl complex, benzylic activation, carbanion, alkylation**

## INTRODUCTION

The significance of compounds of the 2-arylalkanoic acids series in pharmacology, with respect to their anti-inflammatory and analgesic properties,[1] has stimulated considerable investigation of synthetic strategies towards their preparation.[2] These routes include the exploitation of the (1,2)-aryl migration of alkyl aryl ketones and their derivatives in the presence of an oxidant, usually a thallium salt.[3–6] Other oxidation routes to these compounds utilize diacetoxyiodobenzene, silver iodonitrate,[7] and the treatment of enamines with diphenylphosphorylazide.[8] Alternatively, the 2-arylalkanoic acids may be prepared from 2-halogenoketones and their acetals, in the presence of silver salts,[9,10] or Lewis acids such as zinc bromide ($ZnBr_2$), tin dichloride ($SnCl_2$) and cobalt dichloride ($CoCl_2$).[11] A similar reaction was performed under thermal conditions, using the corresponding tosylates in the presence of calcium carbonate.[12,13] Recently, a new synthetic approach has been proposed, involving the reaction of thallium salts with 1-halogenoaryl alkyl ketones.[14]

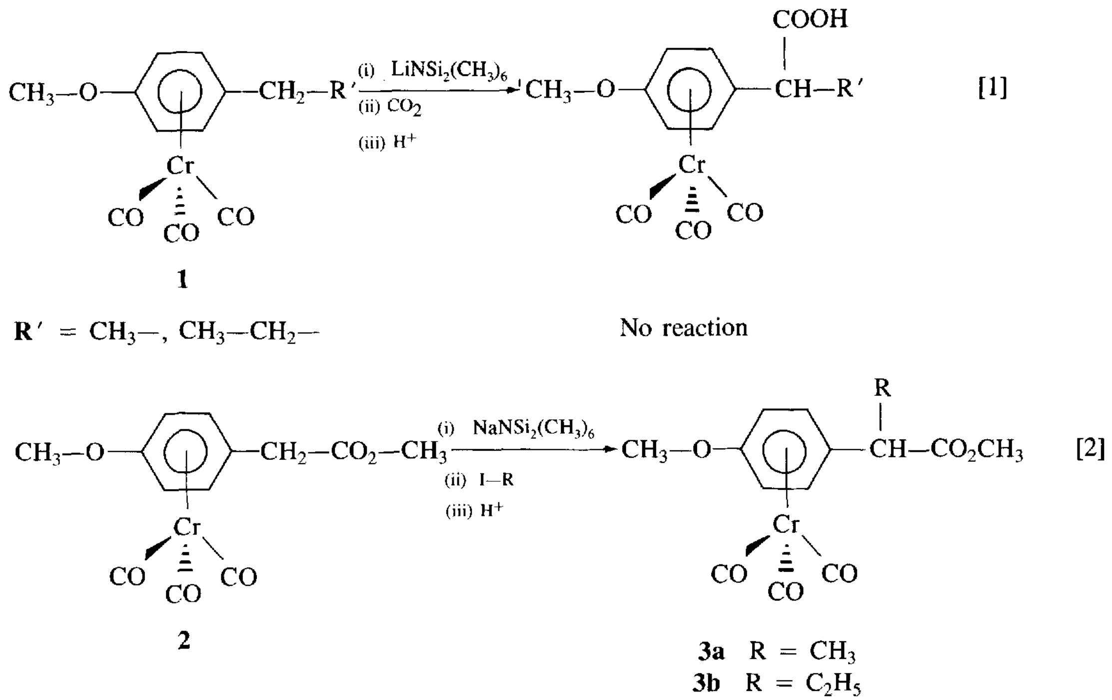
Notably, these preparations all depend upon a (1,2)-migratory step. In contrast, we would like to propose an organometallic route, for the direct functionalization of the arylacids. This approach proceeds via the temporary complexation of the aromatic ring to a chromium carbonyl [$Cr(CO)_3$] moiety, which renders the benzylic protons more acidic. Subsequent stabilization of the benzylic anion facilitates electrophilic attack. This methodology is well precedented in organometallic chemistry,[15] where the facility of substitution is largely dependent upon the nature and position of the arene substituents.

*A priori*, there are two possible routes, mediated by the transition metal complex, for the preparation of 2-aryl-propanoic and -butanoic acids, incorporating 4-methoxy substitution. They are depicted in Eqns [1] and [2] in Scheme 1.

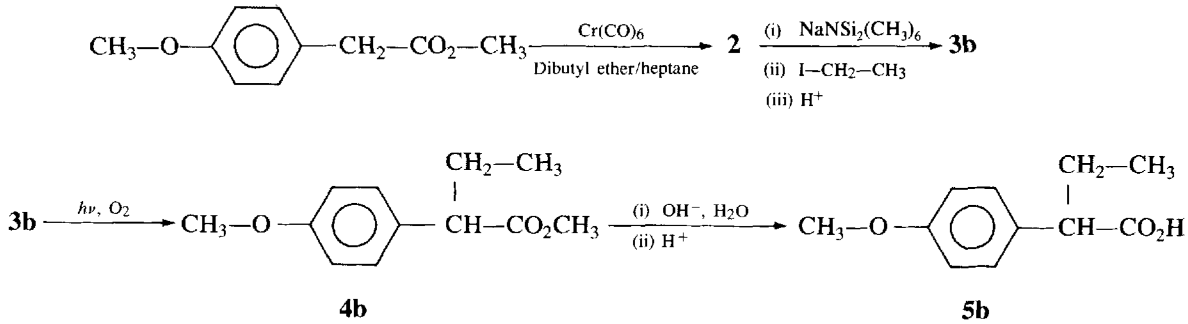
Attempts to prepare 2-arylalkanoic acids following the first method (Eqn [1], Scheme 1)[1] were unsuccessful. The anionic intermediate was not observed, even in the presence of tetrahydrofuran (THF) or hexamethylenephosphotriamine (HMPT); these results are in agreement with previous reports.[16]

This behaviour may be attributable to the inductive effect of the 4-methoxy group, which would disfavour the formation of the benzylic anion and counteract the activating influence of $Cr(CO)_3$ complexation.

Inhibition of benzylic substitution is overcome in the second pathway (Eqn [2], Scheme 1), however, which leads to the target molecules in high yield. In this case, deactivation by the 4-methoxy group is largely compensated by the electron-withdrawing character of the ester group, in cooperation with activation by the $Cr(CO)_3$ group. This type of selectivity has not been previously reported.[17] A wide range of alkyl groups may be introduced via this methodology, in sharp contrast to the above approaches.[2] However, the



Scheme 1



Scheme 2

product distribution is dependent upon the nature of the incoming group.

For example, we note a difference in the reactivity of iodomethane (MeI) and iodoethane (EtI). In both cases, the yields of products functionalized at the benzylic position was over 80%. However, with MeI, both the mono- and bis-alkylated products were isolated in approximately 50%:50% proportion. Reaction with EtI yielded only the monoalkylated species. This reactivity difference may be explained by consideration of the presence of an equilibrium between the base and the complexed benzylic anion. The irreversible reaction of the anion with the alkyl halide (RX), in the case of MeI, proceeds further by abstraction of the remaining benzylic proton and anion formation. The second step is not observed for R = Et, which is probably due to the better donor properties and increased steric demands of the ethyl moiety relative to those of the methyl group.

The complete synthetic scheme is represented in Scheme 2. The yield for the synthesis of **5b** from **2** is 77%; the compound is obtained from the ester in about 45% yield for each run and the untreated material is recycled.

## EXPERIMENTAL

### Complexation of the methyl ester of 2-(4-methoxyphenyl)butanoic acid

The complexation reaction was performed by refluxing a mixture of dibutyl ether and heptane (1:1) containing 5 g of the ester ($2.77 \times 10^{-2}$ mol) and 4.4 g ($2.0 \times 10^{-2}$ mol) of chromium hexacarbonyl, for a period of 12 h. After cooling, the reaction mixture was filtered over silica gel to yield, after evaporation of the solvent, a microcrystalline product. Crystallization from ether/pentane (1:1) afforded 2.9 g of yellow crystals of **2** (46%). The unreacted starting materials were recovered at the end of the reaction and then set up for another run.

### Spectroscopic details for 2

$^1$H NMR, 250 MHz ($CDCl_3$), $\delta$(ppm): 5.57 (1H, d, 7.5 Hz); 5.13 (1H, d, 7.5 Hz); 3.74 (3H, s); 3.70 (3H, s); 3.26 (2H, s).

### 2-(4-methoxyphenyl)butanoic acid

Compound **2** (3.16 g; $10^{-2}$ mol) in 50 cm$^3$ of dried THF was added dropwise to a solution containing 2 g ($1.1 \times 10^{-2}$ mol) of $NaN[Si(CH_3)_3]_2$ in 25 cm$^3$ of THF at −30°C. After the addition was over, 2 g ($7.8 \times 10^{-3}$ mol) of EtI in 10 cm$^3$ of dried THF was added and the solution was stirred for an additional period of 1.5 h. The reaction mixture was taken to dryness, and separation by flash chromatography over silica gel yielded 3.3 g of a yellow solid ether–pentane complex to afford 2.9 g (84%) of yellow crystals of **3b**. This compound was decomplexed in 100 cm$^3$ of chloroform in the presence of sunlight. Complete decomplexation was observed after 18 h. The chromium oxide was then separated by filtration on silica and 1.7 g (97%) of the ester **4b** was recovered. The ester **4b** was saponified by addition of 50 cm$^3$ of a solution of 8 mol dm$^{-3}$ aqueous sodium hydroxide (NaOH) over 5 h under reflux. Normal work-up procedure yielded 1.5 g (94%) of a crystalline product **5b**.

### Spectroscopic details for 5b

IR ($CCl_4$): 1706 cm$^{-1}$ (v CO). MS: $M^{\cdot +}$ 194. $^1$H NMR ($CDCl_3$) $\delta$(ppm): 7.23 (1H, d, 6.5 Hz); 6.86 (1H, d, 6.5 Hz); 3.79 (3H, s); 3.40(1H, t, 7.7 Hz); 2.05 (1H, m); 1.77 (1H, m); 0.89 (3H, t, 7.5 Hz).

### Elemental analysis

Calculated for **5b**: C, 68.02; H 7.27. Found: C, 67.91; H 7.39%.

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