A New Synthesis of 2-Aryloxypropionic Acids Derivatives via
Selective Mono-C-Methylation of Methyl Aryloxyacetates
and Aryloxyacetonitriles with Dimethyl Carbonate

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Abstract A one-pot procedure for the mono-C-methylation of methyl aryloxyacetates and aryloxyacetonitriles by dimethyl carbonate (DMC) is reported. The reaction is carried out in an autoclave at high temperatures (180-200 °C) and in the presence of a base (K$_2$CO$_3$ or t-BuOK). Although DMC is used either as the alkylating agent or as the solvent (30 molar excess with respect to the substrates), the selectivity towards the mono-methylated products (methyl 2-arylxypropionates and 2-aryloxypropio nitriles, respectively) is typically up to 99%, at complete conversion, no dialkylated by-products form. The reasons of such an unusual behaviour is explained by a mechanism involving an initial carboxymethylation followed by a methylation reaction.

INTRODUCTION

The 2-aryloxypropionic acid derivatives [ArOCH(Me)X, X = COOMe (1), X = CN (2)] constitute a class of compounds widely used as precursors for both biologically active derivatives 1-5 and plant growth regulators. 6-12 For instance, several 2-aryloxypropionic acids are in the herbicides market with common names such as dichlorprop, mecoprop and silvex [2-(2,4-dichlorophenoxy)-, 2-(4-chloro-o-tolyloxy- and 2-(2,4,5-trichlorophenoxy) propionic acids, respectively], and are used as very selective weeds killers in the presence of cereal crops. 13

By far, the most common synthesis of compounds (1) and (2) is accomplished by the Williamson reaction through the nucleophilic displacement of an aroxide ion on methyl α-halo-propionates, 4-5, 8 and α-halo- or α-tosyloxy-propionitriles. 1-3, 7, 12, 14-15 respectively (Eq. 1).

\[
\text{base} \\
\text{ArOH} \cdot Y\text{CH(Me)X} \quad \text{----------------} \quad \text{ArOCH(Me)X} \\
\begin{align*}
Y &= \text{Br, Cl, } p-\text{CH}_3-C_6\text{H}_4\text{-SO}_3, \quad X = \text{COOMe (1), CN (2)}
\end{align*}
\]

Occasionally, nucleophilic substitutions of aroxide anions on α-halo-acetates have been reported under phase-transfer catalysis (PTC) conditions. 16,17 Other methods such as the homolytic chloroformylation of alkyl aryl ethers has also been devised for the preparation of aryloxypropanoic acid derivatives. 18
An alternative straightforward synthesis of compounds (1) and (2) could be the direct mono-methylation of the corresponding aryloxyacetic acid derivatives [ArOCH$_2$X; X = COOMe (3); X = CN (4)], these products being cheaper and often readily available commercially. However, this is not the procedure of choice if conventional alkylating agents (alkyl halides and dialkylsulfates) are used, because sizable amounts of dialkylated by-products form, especially when the methylation reaction is concerned.\(^{19}\)

Noteworthy, the use of non-toxic dimethyl carbonate (DMC) as a methylating agent may be considered.\(^{20}\) In fact, we have recently reported that operating at high temperatures (\(\geq 180 \, ^\circ\text{C}\)), in the presence of weak bases (alkaline carbonates), dialkyl carbonates [dimethyl (DMC), diethyl (DEC) and dibenzyl (DBzIC) carbonate] allow very selective batchwise and continuous-flow mono-alkylation of both arylacetonitriles and alkyl arylacetates.\(^{21}\) For instance, in the presence of K$_2$CO$_3$, the reaction of phenylacetonitrile with DMC at 180 °C, gives phenyl propionitrile with \(>\text{99}\%\) selectivity at complete conversion.

We have explained this singular selectivity towards the mono-alkylation reaction through a mechanism involving two consecutive reactions, both very selective. That is, \(i\) an initial attack of an ArCH$^\sim$X (X = COOR, CN) anion on the acyl carbon of the dialkylcarbonate (BAc2 mechanism) giving a carboxyalkylated intermediate, ArCH(COOR)X, followed by \(ii\) the attack of the corresponding anion, ArC$^\sim$(COOR)X, on the alkyl carbon of the dialkylcarbonate (BAc2 mechanism) which yields an alkylated intermediate, ArC(R)(COOR)X. Then, an equilibrium decarboxyalkylation reaction affords the final product, ArCH(R)X. Both intermediates ArCH(COOR)X and ArC(R)(COOR)X, have been observed during the overall reaction.

RESULTS AND DISCUSSION

In order to extend the use of the DMC as a safe methylating agent to other alkylation reactions and explore whether the same mechanism could be followed by other CH$_2$-acidic compounds, we investigated the reaction of methyl aryloxyacetates and aryloxyacetonitriles with DMC. In particular, this paper reports that these compounds [(3) and (4)] are selectively mono-methylated by DMC to produce the corresponding methyl 2-aryloxypropionates and aryloxypropionitiles (Eq. 2).

\[
\text{ArOCH}_2\text{X} + \text{CH}_3\text{OCCOOCH}_3 \xrightarrow{\text{base}} \text{ArOCH(CH}_3\text{)X} + \text{CH}_3\text{OH} + \text{CO}_2 \tag{2}
\]

All reactions were performed at 180-200 °C, under batch conditions, by loading an autoclave with a mixture of substrate [(3) or (4)], DMC and a base (K$_2$CO$_3$ or t-BuOK) in a 1 : 30 : 2 molar ratio, respectively. DMC was used in a large excess acting both as the alkylating agent and the reaction solvent.

Table 1 reports the results of the methylation of different methyl aryloxyacetates (3) and aryloxyacetonitriles (4). In general, the reaction occurs faster on nitriles than on esters: compounds (3) require higher temperatures and longer reaction times than compounds (4) for the conversion to be completed (compare entries 1 and 5, 2 and 6, 3 and 7, 4 and 8, respectively). This behaviour well parallels the trend already observed in both the methylation and the benzylzation reactions of arylacetanisoles and alkyl arylacetates by DMC and DBzIC, respectively; esters always being less reactive than nitriles.\(^{21}\) However, the aryloxypropionitiles are obtained in lower yields than the methyl 2-aryloxypropionates. In fact, during the reaction (2), both compounds (3) and (4) also produce the corresponding anisoles but for nitriles, these by-products form to a greater extent (ArOMe: 22, 33, 41 and 13 % by GC for 4a-d, respectively, and ≤ 5% by
GC for compounds (3), at complete substrate conversion).

Under the reported basic conditions, an explanation for the higher reactivity of the nitriles is that the formation of the corresponding carbamions ArOCH_{2}CN is easier. While, the presence of anisoles as side products may be justified through a nucleophilic displacement on the ArOCH_{2}CN by a nucleophile present in the reaction mixture (CH_{3}O-, CO_{3}^{2-}, etc.). The so formed phenolate leaving group (ArO−) rapidly reacts with DMC to give the corresponding anisole through a B_{A2} mechanism. Thus, the higher reactivity and the greater anisoles formation in the reaction of nitriles (4) [with respect to esters (3)] may be due to a poor electron-availability of the methylenic carbon of these compounds, which render them both more acidic and electrophilic in character.

Under the conditions of Table 1, the reaction of phenylthioacetonitrile with DMC has also been investigated. In this case, the substrate conversion is complete after 6 hours at 180 °C but thioanisole is the major product (70% by GC). This result well agree to the above suggested pathway for the anisole formation. In fact, it is well known that the thiophenolate (ArS−) is a better leaving group than the phenolate ion.

However, in the case of both esters (3) and nitriles (4), the selectivity in the methylation reaction (2) is always very high towards the mono-alkyl derivatives since dialkylated by-products are observed in only trace amounts (≤1% by GC). Thus, the mono-methylated compounds (1) and (2) are separated from the reaction mixture with very high purity (>99% by GC) by a simple distillation.

Table 1 also reports the reaction of phenoxycetic acid with DMC (entry 9). Under the reported conditions, the acid is at first esterified by DMC, then, the methylation reaction occurs to give the corresponding methyl 2-phenoxypropionate. The selectivity in the mono-methyl derivative is still very high (>99%), but a stronger base (t-BuOK) and a higher temperature (200 °C) are needed.

The unusually high selectivity observed in the mono-methylation of methyl aryloxy acetates and aryloxyacetonitriles may be explicable through the mechanism previously described for the reaction of DMC and DBzIC with methyl arylacetates and arylacetonitriles where ArCH(COOR)X and ArC(R)(COOR)X are the key intermediates. In fact, also in this case, the reaction proceeds through the formation of methyl-carboxymethyl intermediates ArOC(Me)(COOMe)X, being these derivatives detected (by the GC/MS analysis) during the course of the reaction (2). Accordingly, Scheme 1 shows the proposed overall sequence of reactions.

DMC acts both as a carboxymethylating and as a methylating agent of ArOCH_{2}X derivatives. In particular, selectivity comes from the fact that the first generated ArOCH_{2}X anion attacks only the acyl carbon of the DMC (B_{A2} mechanism) and not the methyl one. Then, methylation occurs on the ArOC(O)(COOMe)X anion through its reaction to the alkyl carbon of DMC (B_{A2} mechanism). In this case, the attack to the acyl carbon producing the possible intermediate PhC(COOME)_{2}X does not effect the selectivity, this reaction being an equilibrium one.

However, as the selectivity is concerned, an intriguing question still remains open; that is, why the reaction occurs through the carboxymethyl intermediates and no direct methylation takes place.

**CONCLUSIONS**

In conclusion, the reported reaction represents an alternative method for the synthesis of methyl 2-aryloxypropionates and aryloxypropionitriles which are both intermediates for the preparation of 2-aryloxypropionic acids, these compounds being of commercial interest particularly in the herbicidal market.
Especially in the case of nitriles, the methylation by DMC avoids the use of costly acylating agents (2-halo-propionitriles).

Besides the high selectivity which allows the preparation of high-purity mono-methyl derivatives, the reaction produces no inorganic wastes and needs no solvent; these benign features further encourage the use of DMC in organic synthesis.

\[ \text{ArOCH}_2X + \text{DMC} \xrightarrow{\text{base}} \text{DMC} \xrightarrow{\text{base}} \text{ArOCH}_2X + \text{CH}_3\text{OH} \]

\[ \text{DMC} + \text{ArOCH}_2X \xrightarrow{\text{CH}_3\text{OH}} \text{ArOCX} + \text{CH}_3\text{OH} - \text{CO}_2 \]

\[ \text{ArOCH}_2X \xrightarrow{\text{base}} \text{ArOCX} \xrightarrow{\text{CH}_3\text{OH}} \text{CH}_3 \]

Scheme 1

**EXPERIMENTAL.**

All the compounds used were ACS grade and were employed without further purification. $^1$H NMR spectra were recorded on a Varian Unity 400 (400 MHz) spectrometer using CDCl$_3$ with tetramethylsilane as the internal standard. GC analyses were performed on a Varian GC 3300 using a 30 m, DB5 capillary column. GC/MS analyses were performed on an HP 5971 mass detector at 70 eV coupled to an HP 5890-Series II gas chromatograph fitted with a 30 m, DB5 capillary column.

Methyl 2-phenoxy-, methyl 2-(4-methylphenoxy)-, and methyl 2-(4-chlorophenoxy)-acetates were prepared by the esterification of the corresponding acids with MeOH in the presence of a catalytic amount of p-toluenesulfonic acid at 20 °C, according to established procedures. 23

2-Phenoxycarbonyl, 2-(4-methylphenoxycarbonyl), 2-(3-chlorophenoxy)carbonyl, and 2-(4-chlorophenoxy)carbonyl acetonitriles were prepared by reacting the corresponding substituted phenols, chloroacetonitrile, and anhyd. K$_2$CO$_3$ in refluxing
Table 1 - Reactions of Aryloxyacetic Esters and Aryloxyacetonitriles with Dimethyl Carbonate

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Temp (°C)</th>
<th>Reaction time (h)</th>
<th>Conv'n (%)</th>
<th>Product (°a)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a: PhOCH₂COOMe</td>
<td>190</td>
<td>40</td>
<td>90%</td>
<td>1a: PhOCH(Me)COOMe (94)</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>3b: p-MeC₆H₄OCH₂COOMe</td>
<td>190</td>
<td>70</td>
<td>100</td>
<td>1b: p-MeC₆H₄OCH(Me)COOMe (92)</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>3c: p-ClC₆H₄OCH₂COOMe</td>
<td>190</td>
<td>48</td>
<td>100</td>
<td>1c: p-ClC₆H₄OCH(Me)COOMe (92)</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>3d: m-ClC₆H₄OCH₂COOMe</td>
<td>190</td>
<td>26</td>
<td>100</td>
<td>1d: m-ClC₆H₄OCH(Me)COOMe (91)</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>4a: PhOCH₂CN</td>
<td>190</td>
<td>32</td>
<td>100</td>
<td>2a: PhOCH(Me)CN (69)</td>
<td>62</td>
</tr>
<tr>
<td>6</td>
<td>4b: p-MeC₆H₄OCH₂CN</td>
<td>180</td>
<td>40</td>
<td>100</td>
<td>2b: p-MeC₆H₄OCH(Me)CN (51)</td>
<td>46</td>
</tr>
<tr>
<td>7</td>
<td>4c: p-ClC₆H₄OCH₂CN</td>
<td>180</td>
<td>41</td>
<td>100</td>
<td>2c: p-ClC₆H₄OCH(Me)CN (59)</td>
<td>52</td>
</tr>
<tr>
<td>8</td>
<td>4d: m-ClC₆H₄OCH₂CN</td>
<td>180</td>
<td>24</td>
<td>100</td>
<td>2d: m-ClC₆H₄OCH(Me)CN (79)</td>
<td>71</td>
</tr>
<tr>
<td>9</td>
<td>PhOCH₂COOH</td>
<td>200</td>
<td>48</td>
<td>100</td>
<td>1a: PhOCH(Me)COOMe (96)</td>
<td>81</td>
</tr>
</tbody>
</table>

a All reactions were carried out in an autoclave using the substrate, DMC and base (K₂CO₃: entries 1 and 3-8; t-BuOK: entries 2 and 9) in a 1:30:2 molar ratio, respectively. b By GC analyses. c Yields based on distilled products. Starting from 4.0 g of reagent: entries 2, 4, 6-9; starting from 5.0 g of reagent: entries 1, 3, 5.
The same procedure was used to prepare the methyl 2-(3-chloro phenoxy)-acetate by reacting 3-chlorophenol with methyl chloroacetate.

Reactions carried out in autoclave. General procedure. (Table 1). All methylation reactions by DMC were carried out in a stainless-steel (AISI 316) autoclave (internal volume 250 cm³), equipped with a purging valve, through which, at room temperature, air was removed before each reaction by purging with N₂ stream. A magnetically stirred mixture of the alkylating agent, the aryloxyacetonitrile or aryloxyacetic ester and the base in the reported molar ratio (see Table 1) was heated in the autoclave, itself heated in an electrical oven, at high temperatures (180-200 °C). A thermocouple and a needle valve were fixed onto the autoclave head, the former dipping into the reaction mixture and the latter connected to a 1/8 inch stainless-steel suction pipe which, in turn, was immersed into the reaction mixture. In this way it was possible to extract samples (analysed by GC) during the course of the reactions.

All the mono-methylated derivatives were purified by distillation in a micro-Claissen distillation apparatus with a fused-on Liebig condenser. All compounds were colourless liquids and their purity was >99% (by GC).

Methyl 2-phenoxycaproate 1a. Starting from methyl phenoxyacetate 3a (5.0 g), after distillation, 1a (4.3 g, 80%) was obtained. b.p. 75-76 °C/0.60 mmHg (lit.,¹⁰ b.p. 75-76 °C/0.65 mmHg); m/z 180 (M⁺, 36%), 121 (100), 94 (38), 93 (14), 77 (47), 65 (11), 59 (10) and 51 (15); ¹H-NMR (400 Mhz, CDCl₃), δ, ppm: 1.62 (d, 3H, J = 7, CH₃), 3.76 (s, 3H, OCH₃), 4.77 (q, 1H, J = 6.7, CH₂), 6.87-6.99 and 7.26-7.30 (m, 5H, Ph).

Methyl 2-(4-methylphenoxy)-propionate 1b. Starting from methyl 2-(4-methylphenoxy)-acetate 3b (4.0 g). After distillation, 1b (3.6 g, 83%) was obtained. b.p. 80-81 °C/0.25 mmHg; m/z 194 (M⁺, 9%), 135 (54), 108 (51), 107 (56), 91 (86), 77 (65), 65 (100), 59 (73) and 51 (65); ¹H-NMR (400 Mhz, CDCl₃), δ, ppm: 1.61 (d, 3H, J = 7.0, CH₃), 2.28 (s, 3H, CH₃), 3.75 (s, 3H, OCH₃), 4.73 (q, 1H, J = 7.0, CH₂), 6.77-6.79 and 7.06-7.08 (m, 4H, Ph).

Methyl 2-(4-chlorophenoxy)-propionate 1c. Starting from methyl 2-(4-chlorophenoxy)-acetate 3c (5.0 g). After distillation, 1c (4.5 g, 84%) was obtained. b.p. 80-81 °C/0.50 mmHg (lit.,¹⁰ b.p. 100-101 °C/1.50 mmHg), m/z 214 (M⁺, 40%), 157 (33), 155 (100), 130 (22), 128 (68), 111 (20), 91 (19), 75 (24) and 59 (26); ¹H-NMR (400 Mhz, CDCl₃), δ, ppm: 1.61 (d, 3H, J = 6.8, CH₃), 3.75 (s, 3H, OCH₃), 4.72 (q, 1H, J = 6.8, CH₂), 6.79-6.81 and 7.21-7.23 (m, 4H, Ph).

Methyl 2-(3-chlorophenoxy)-propionate 1d. Starting from methyl 2-(3-chlorophenoxy)-acetate 3d (4.0 g). After distillation, 1d (3.5 g, 82%) was obtained. b.p. 84-85 °C/0.45 mmHg (lit.,¹⁰ b.p. 89-90 °C/0.65 mmHg); m/z 214 (M⁺, 23%), 157 (31), 155 (100), 130 (10), 128 (28), 111 (20), 91 (22), 75 (25) and 59 (24); ¹H-NMR (400 Mhz, CDCl₃), δ, ppm: 1.61 (d, 3H, J = 6.9, CH₃), 3.76 (s, 3H, OCH₃), 4.74 (q, 1H, J = 6.9, CH₂), 6.74-6.76, 6.87-6.88, 6.94-6.96 and 7.16-7.20 (m, 4H, Ph).

2-Phenoxyacronitrile 2a. Starting from phenoxyacetanilide 4a (5.0 g), after distillation, 2a (3.4 g, 62%) was obtained. b.p. 88-90 °C/1.00 mmHg (lit.,¹¹ b.p. 98-102 °C/2.00 mmHg); m/z 147 (M⁺, 53%), 95 (7), 94 (100), 93 (24), 77 (6), 66 (13), 65 (35), and 51 (6); ¹H-NMR (400 Mhz, CDCl₃), δ, ppm: 1.79 (d, 3H, J = 6.7, CH₃), 4.89 (q, 1H, J = 6.7, CH₂), 7.00-7.1 and 7.33-7.37 (m, 5H, Ph).

2-(4-methylphenoxy)acetonitrile 2b. Starting from 4-(4-methylphenoxy)-acetanilide 4b (4.0 g), after distillation, 2b (2.0 g, 46%) was obtained. b.p. 87-88 °C/0.50 mmHg; m/z 161 (M⁺, 34%), 108 (18), 107 (100), 91 (4), 79 (46), 77 (53), 65 (6), 53 (10) and 51 (15); ¹H-NMR (400 Mhz, CDCl₃), δ, ppm: 1.77 (d, 3H, J = 6.7, CH₃), 2.31 (s, 3H, CH₃), 4.84 (q, 1H, J = 6.7, CH₂), 6.91 and 7.13 (two d, 4H, J = 8.6, Ph).
2-Aryloxypropionic acid derivatives

2-(4-Chlorophenoxy)-propionitrile 2c. Starting from 2-(4-chlorophenoxy)-acetonitrile 4c (4.0 g), after distillation, 2c (2.3 g, 53%) was obtained. b.p. 95-96 °C/0.70 mmHg (lit., b.p. 75-80 °C/0.15 mmHg); m/z 181 (M+, 59%), 146 (29), 128 (68), 127 (97), 101 (33), 99 (100), 75 (18), 73 (25) and 63 (27); 1H-NMR (400 MHz, CDCl₃). δ, ppm: 1.78 (d, 3H, J = 6.8, CH₃), 4.84 (q, 1H, J = 6.8, CH), 6.93-6.95 and 7.29-7.31 (m, 4H, Ph).

2-(3-Chlorophenoxy)-propionitrile 2d. Starting from 2-(3-chlorophenoxy)-acetonitrile 4d (4.0 g), after distillation, 2d (3.1 g, 71%) was obtained. b.p. 88-89 °C/0.30 mmHg (lit., b.p. 83-88 °C/0.10 mmHg); m/z 181 (M+, 6%), 130 (30). 128 (100), 111 (7), 101 (13), 99 (34), 75 (15) and 63 (27); 1H-NMR (400 MHz, CDCl₃). δ, ppm: 1.79 (d, 3H, J = 7.0, CH₃), 4.87 (q, 1H, J = 7.0, CH), 6.89-7.09 and 7.27-7.29 (m, 4H, Ph).

Methyl 2-phenoxypropionate 1a. Starting from phenoxycetic acid (4.0 g), after distillation. 1a (3.8 g, 81%) was obtained. b.p. 75-76 °C/0.60 mmHg (lit., b.p. 75-76 °C/0.65 mmHg).

Acknowledgements: This work was supported by MURST (Ministero Universitaria e Ricerca Scientifica Tecnologica: fondo 40%). Dr. Jacopo Zanon is also gratefully acknowledged for his support on NMR spectra.

REFERENCES AND NOTES


22. The selectivity is here calculated according to the following relation:

\[
\text{Selectivity (\%)} = \frac{[\text{ArOCH(Me)X}]}{[\text{ArOCH(Me)X}] + [\text{ArOC(Me)2X}]} \times 100
\]


(Received in UK 2 August 1995; revised 31 August 1995; accepted 1 September 1995)