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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 aryloxyaceto nitriles 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_2CO_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-aryloxypropionates 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*-tolyl)oxy- 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).

$$\text{ArOH} + \text{YCH(Me)X} \xrightarrow{\text{base}} \text{ArOCH(Me)X} \qquad (1)$$

$$\text{Y} = \text{Br, Cl, } p\text{-}CH_3\text{-}C_6H_4\text{-}SO_3\text{, X} = \text{COOMe } (\mathbf{1})\text{, CN } (\mathbf{2})$$

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 [$ArOCH_2X$; 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 (≥ 180 °C), in the presence of weak bases (alkaline carbonates), dialkyl carbonates [dimethyl (DMC), diethyl (DEC) and dibenzyl (DBzlc) carbonate] allow very selective batchwise and continuous-flow mono-alkylation of both arylacetonitriles and alkyl arylacetates. [21] For instance, in the presence of K_2CO_3, the reaction of phenylacetonitrile with DMC at 180 °C, gives phenyl propionitrile with >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 $ArCH^{(-)}X$ (X = COOR, CN) anion on the acyl carbon of the dialkylcarbonate ($B_{Ac}2$ mechanism) giving a carboxyalkylated intermediate, ArCH(COOR)X, followed by *ii)* the attack of the corresponding anion, $ArC^{(-)}(COOR)X$, on the alkyl carbon of the dialkylcarbonate ($B_{Al}2$ 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 aryloxypropionitriles (Eq. 2).

$$ArOCH_2X + CH_3OCOOCH_3 \xrightarrow{\text{base}} ArOCH(CH_3)X + CH_3OH + CO_2 \quad (2)$$

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_2CO_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 benzylation reactions of arylacetonitriles and alkyl arylacetates by DMC and DBzlC, respectively; esters always being less reactive than nitriles. [21] However, the aryloxypropionitriles are obtained in lower yields than the methyl 2-aryloxy propionates. 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 carbanions $ArOCH^{(-)}CN$ is easier. While, the presence of anisoles as side products may be justified through a nucleophilic displacement on the $ArOCH_2CN$ by a nucleophile present in the reaction mixture (CH_3O^-, CO_3^{2-}, etc.). The so formed phenolate leaving group (ArO^-) rapidly reacts with DMC to give the corresponding anisole through a $B_{Al}2$ mechanism.[21] 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 ($\leq$1% by GC).[22] 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 phenoxyacetic acid with DMC (entry 9). Under the reported conditions, the acid is at first esterified by DMC;[21] 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 DBzlC with methyl arylacetates and arylacetonitriles where ArCH(COOR)X and ArC(R)(COOR)X are the key intermediates.[21] 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 $ArOCH_2X$ derivatives. In particular, selectivity comes from the fact that the first generated $ArOCH^{(-)}X$ anion attacks only the acyl carbon of the DMC ($B_{Ac}2$ mechanism) and not the methyl one. Then, methylation occurs on the $ArOC^{(-)}(COOMe)X$ anion through its reaction to the alkyl carbon of DMC ($B_{Al}2$ mechanism). In this case, the attack to the acyl carbon producing the possible intermediate $PhC(COOMe)_2X$ does not effect the selectivity, this reaction being an equilibrium one.

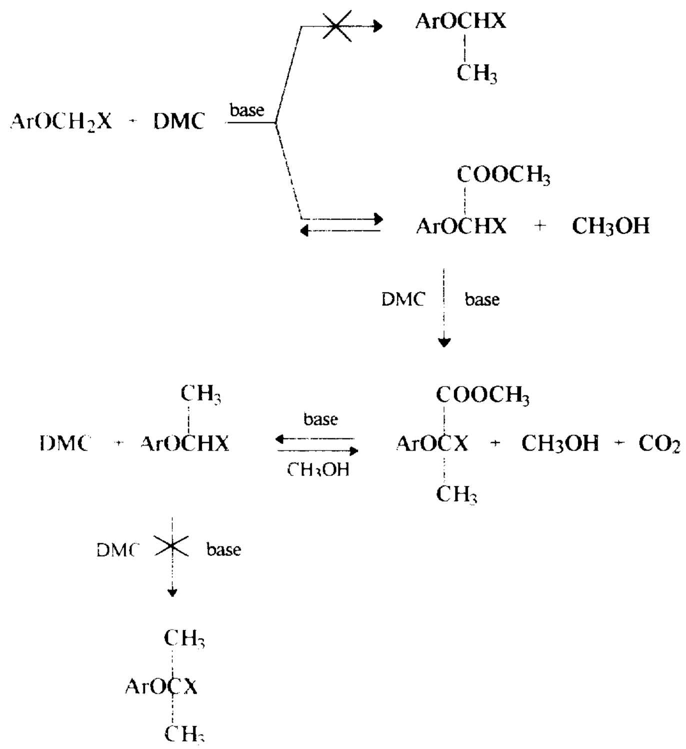
However, as the selectivity is concerned, an intriguing question still remains open; that is, why the reaction occurs through the carboxymethyl intermediates and no direct methylation takes place.

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 akylating agents (2-halo-propionitriles).

Beside 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 encourages the use of DMC in organic synthesis.



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-Phenoxy-, 2-(4-methylphenoxy)-, 2-(3-chlorophenoxy)-, and 2-(4-chlorophenoxy)- acetonitriles were prepared by reacting the corresponding substituted phenols, chloroacetonitrile, and anhyd. K_2CO_3 in refluxing

Table 1 - Reactions of Aryloxyacetic Esters and Aryloxyacetonitriles with Dimethyl Carbonate [a]

Entry	Substrate	Temp (T/°C)	Reaction time (t/h)	Conv'n (%)	Product (%) [b]	Yield [c] (%)
1	**3a**: $PhOCH_2COOMe$	190	40	99	**1a**: PhOCH(Me)COOMe (94)	80
2	**3b**: *p*-$MeC_6H_4OCH_2COOMe$	190	70	100	**1b**: *p*-MeC_6H_4OCH(Me)COOMe (92)	83
3	**3c**: *p*-$ClC_6H_4OCH_2COOMe$	190	48	100	**1c**: *p*-ClC_6H_4OCH(Me)COOMe (92)	84
4	**3d**: *m*-$ClC_6H_4OCH_2COOMe$	190	26	100	**1d**: *m*-ClC_6H_4OCH(Me)COOMe (91)	82
5	**4a**: $PhOCH_2CN$	190	32	100	**2a**: PhOCH(Me)CN (69)	62
6	**4b**: *p*-$MeC_6H_4OCH_2CN$	180	40	100	**2b**: *p*-MeC_6H_4OCH(Me)CN (51)	46
7	**4c**: *p*-$ClC_6H_4OCH_2CN$	180	41	100	**2c**: *p*-ClC_6H_4OCH(Me)CN (59)	52
8	**4d**: *m*-$ClC_6H_4OCH_2CN$	180	24	100	**2d**: *m*-ClC_6H_4OCH(Me)CN (79)	71
9	$PhOCH_2COOH$	200	48	100	**1a**: PhOCH(Me)COOMe (96)	81

[a] All reaction were carried out in an autoclave using the substrate, DMC and base (K_2CO_3: 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.

acetone soln. for a few hrs, according to an established procedure. [24] 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 cm^3), equipped with a purging valve, through which, at room temperature, air was removed before each reaction by purging with N_2 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-Claisen distillation apparatus with a fused-on Liebig condenser. All compounds were colourless liquids and their purity was >99% (by GC).

Methyl 2-phenoxypropionate **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); ^{1}H-NMR (400 Mhz, $CDCl_3$), δ, ppm: 1.62 (d, 3H, J = 6.7, CH_3), 3.76 (s, 3H, OCH_3), 4.77 (q, 1H, J = 6.7, CH), 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); ^{1}H-NMR (400 Mhz, $CDCl_3$), δ, ppm: 1.61 (d, 3H, J = 7.0, CH_3), 2.28 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 4.73 (q, 1H, J = 7.0, CH), 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); ^{1}H-NMR (400 Mhz, $CDCl_3$), δ, ppm: 1.61 (d, 3H, J = 6.8, CH_3), 3.75 (s, 3H, OCH_3), 4.72 (q, 1H, J = 6.8, CH), 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); ^{1}H-NMR (400 Mhz, $CDCl_3$), δ, ppm: 1.61 (d, 3H, J = 6.9, CH_3), 3.76 (s, 3H, OCH_3), 4.74 (q, 1H, J = 6.9, CH), 6.74-6.76, 6.87-6.88, 6.94-6.96 and 7.16-7.20 (m, 4H, Ph).

2-Phenoxypropionitrile **2a**. Starting from phenoxyacetonitrile **4a** (5.0 g), after distillation, **2a** (3.4 g, 62%) was obtained, b.p. 88-90 °C/1.00 mmHg (lit.,[13] 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); ^{1}H-NMR (400 Mhz, $CDCl_3$), δ, ppm: 1.79 (d, 3H, J = 6.7, CH_3), 4.89 (q, 1H, J = 6.7, CH), 7.00-7.1 and 7.33-7.37 (m, 5H, Ph).

2-(4-methylphenoxy)-propionitrile **2b**. Starting from 2-(4-methylphenoxy)-acetonitrile **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); ^{1}H-NMR (400 Mhz, $CDCl_3$), δ, ppm: 1.77 (d, 3H, J = 6.7, CH_3), 2.31 (s, 3H, CH_3), 4.84 (q, 1H, J = 6.7, CH), 6.91 and 7.13 (two d, 4H, J = 8.6, Ph).

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.,[2] 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); ^{1}H-NMR (400 Mhz, $CDCl_3$), δ, ppm: 1.78 (d, 3H, J = 6.8, CH_3), 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.,[2] 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); ^{1}H-NMR (400 Mhz, $CDCl_3$), δ, ppm: 1.79 (d, 3H, J = 7.0, CH_3), 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 phenoxyacetic acid (4.0 g), after distillation, **1a** (3.8 g, 81%) was obtained, b.p. 75-76 °C/0.60 mmHg (lit.,[10] b.p. 75-76 °C/0.65 mmHg).

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

$$\text{Selectivity}\ (\%) = \frac{[\mathrm{ArOCH(Me)X}]}{\{[\mathrm{ArOCH(Me)X}] + [\mathrm{ArOC(Me)_2X}]\}} \times 100$$

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