Selective Mono-C-methylations of Arylacetonitriles and Arylacettes with Dimethylcarbonate: A Mechanistic Investigation

Pietro Tundo,* Maurizio Selva, Alvise Perosa, and Sofia Memoli
Dipartimento di Scienze Ambientali, Università Ca’ Foscari, Dorsoduro 2137 - 30123 Venezia, Italy

tundop@unive.it

Received December 13, 2000

The very high mono-C-methylation selectivity (>99%) of arylacetic acid derivatives (ArCH2X; X = CN, CO2Me) with dimethyl carbonate (DMC) is due to a mechanism that involves consecutive methoxycarbonylation, methylation, and demethoxycarbonylation steps. Important aspects of this mechanism are clarified herein by a kinetic investigation. In the case of arylacetonitriles, at 140 °C, the comparison of the rate constants of model reactions involving 2-phenyl propionitrile, phenylacetonitrile, 2-methoxycarbonylphenylacetonitrile, and 2-methyl-2-methoxy carbonylphenyl acetonitrile (compounds 1a–4a, respectively) with DMC indicates that the methylation process is the fastest and the irreversible step, which drives the overall reaction to completion. The situation is reversed for arylacetic esters, where the methylation is more difficult than the demethoxycarbonylation reaction; therefore, a higher reaction temperature is required.

Introduction

Under both continuous-flow and batch conditions and in the presence of K2CO3, arylacetic acid derivatives (2: ArCH2X; X = CN, CO2Me) reacted with dimethyl carbonate (DMC) to afford the corresponding mono-C-methyl derivatives (2-aryl propionitriles and methyl 2-arylpro-}

\[ \text{ArCH}_2\text{X} + (\text{CH}_3\text{O})_2\text{CO} \xrightarrow{\text{K}_2\text{CO}_3} \text{ArCH}_2\text{CO}_2\text{Me} \]

[2]

[1]

\[ \text{ArCH(CH}_3\text{)}\text{X} + \text{CH}_3\text{OH} + \text{CO}_2 \ (\text{a}) \]

1

\[ \text{X} = \text{CN}, \text{COOCH}_3 \]

Besides the excellent synthetic outcome, this methylation method is environmentally benign in character and fits the requirements for preventing pollution of chemical processes at the source, according to the general objectives of Green Chemistry. In fact, the reaction takes place in the presence of a weak base (usually K2CO3) as a catalyst, uses a nontoxic alkylating agent (DMC), requires no solvent, and produces neither organic nor inorganic wastes to be disposed of. The only coproduct (methanol) can, in principle, be recycled for DMC production.

As far as the mechanism is concerned, our experimental investigation of DMC-mediated alkylations supports the hypothesis that the reaction does not proceed through an SN2 displacement of the ArCH(CO2Me)X on DMC (BAl2 mechanism). Rather, the selectivity arises from two consecutive reactions involving two intermediate species, that is, ArCH(CO2Me)X and Ar(CH3)(CO2Me)X (3) and Ar(C(H)2)(CO2Me)X (4), which are observed during the reaction (Scheme 1).

Initially, the carbanion [ArCH(CO2Me)X] undergoes a methoxycarbonylation reaction by attacking the acyl carbon of DMC (BAl2 mechanism); the resulting intermediate [ArCH(CO2Me)X, 3] reacts through its anion [ArC(CO2Me)X, 3] with the alkyl carbon of DMC to yield the corresponding methyl derivative [Ar(CH3)(CO2Me)X, 4; BAl2 mechanism]. Finally, compound 4 is subjected to a demethoxycarbonylation reaction to the final product [Ar(CH3)X].

With the aim of exploring this intriguing mechanism and the unusual selectivity, a detailed kinetic study of the reaction was begun: each step of Scheme 1 was considered separately, and the related kinetic constants were determined. This investigation proved to be fundamental to comprehending the reaction selectivity.

* To whom correspondence should be addressed. Fax: +39-041-234 8620.
Results and Discussion

The methylation of phenylacetonitrile (Scheme 1, 2a: \( \text{Ar} = \text{Ph}, \ X = \text{CN} \)) was used as the model reaction. Although this reaction was generally carried out at \( T \geq 180^\circ \text{C} \), the study was done at a lower temperature (140 °C) in order to decrease the reaction rate and allow a more accurate determination of the kinetic constants. All experiments were run in an autoclave since the alkylating agent (DMC) boils at 90 °C. DMC itself was used in large excess (200 molar equiv) with respect to 2a and acted as the solvent. K\(_2\)CO\(_3\) was always utilized as the base. If not otherwise specified, the reaction mixture was magnetically stirred at 650 rpm. Table 1 reports the conditions. Reactions were followed by GLC and GC/MS, on samples withdrawn at intervals from the autoclave. Steps 2, 5, and 6 of Scheme 1 were considered, while very fast acid-base equilibria (eqs 1, 3, 4, and 7) were not.

Methoxycarbonylation of 2a: Step 2. A mixture of the substrate, DMC, and K\(_2\)CO\(_3\) was made to react in a 1:200:2 molar ratio. At 140 °C, the reaction proceeded very slowly: after 25 h, only a 10% conversion was reached with the formation of the methylmethoxycarbonylated derivative \( \text{PhC(Me)(CO}_2\text{Me)CN} \) (4a) as the sole product. The corresponding kinetic constant (\( k_2 \)) was not determined.

However, under the same reaction conditions but at a higher temperature (180–200 °C), a number of different CH\(_2\)-acidic compounds such as aryloxiacetic acid derivatives (ArOCH\(_2\)X; \( X = \text{CN}, \ CO_2\text{Me} \)) and alkylbenzyl sulfones (ArCH\(_2\)SO\(_2\)R; \( R = \text{Ar, alkyl} \)) were selectively monomethylated with DMC. In all cases, reactions proceeded through methoxycarbonylated intermediates, but importantly, the direct methylation of the monomethyl derivatives [ArOCH(Me)X and ArCH(Me)SO\(_2\)R] was never observed unless at temperatures over 220 °C. R-Methylated benzyl ketones [ArCH(Me)COR] behaved similarly.

The reaction of alcohols with DMC was even more exclusive: only methoxycarbonylated products (ROCO\(_2\)H) were formed.

### Table 1. Reaction Conditions for the Investigation of Steps 2, 5, and 6 of Scheme 1

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate (mmol)</th>
<th>T (°C)</th>
<th>K(_2)CO(_3)/substrate (molar ratio)</th>
<th>MeOH/substrate (molar ratio)</th>
<th>n-decane/substrate (molar ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCH(Me)CN, 1a (1.52)</td>
<td>140</td>
<td>2</td>
<td>10</td>
<td>b</td>
</tr>
<tr>
<td>2</td>
<td>PhCH(_2)CN, 2a (1.71)</td>
<td>140</td>
<td>2</td>
<td>10</td>
<td>b</td>
</tr>
<tr>
<td>3</td>
<td>PhCH(CO(_2)Me)CN, 3a (1.14)</td>
<td>140</td>
<td>2</td>
<td>10</td>
<td>0.3</td>
</tr>
<tr>
<td>4</td>
<td>PhCH(Me)CO(_2)MeCN, 4a (1.01)</td>
<td>140</td>
<td>0.1–4(^c)</td>
<td>10–30(^c)</td>
<td>0.5</td>
</tr>
<tr>
<td>5</td>
<td>K(^+)PhCH(Me)CO(_2)MeCN, 3a (0.94)</td>
<td>140–160</td>
<td>2</td>
<td>10</td>
<td>0.2</td>
</tr>
<tr>
<td>6</td>
<td>PhCH(CO(_2)Me)(_2), 3b (0.96)</td>
<td>140–160</td>
<td>2</td>
<td>10</td>
<td>b</td>
</tr>
</tbody>
</table>

\(^{a}\) All reactions were carried out by using DMC in a 200 molar equiv excess with respect to the substrate. \(^{b}\) Internal standard was not used. \(^{c}\) Further details can be found in Table 2.

---

\(^{10}\) Although we already demonstrated that K\(_2\)CO\(_3\) could certainly act as a catalyst (in a 5% molar amount with respect to ArCH\(_2\)X),\(^{2,4}\) in order to follow the reactions more conveniently, they were all performed using an excess of the base (2 molar equiv).
strongly suggested that the direct methylation of (18 h).

Moreover, it was observed that the reaction of DMC with 2-phenylpropionitrile [PhCH(CH₃)CN, 1a] did not yield the doubly methylated derivative [PhC(CH₃)₂CN] even operating at 160 °C and for prolonged reaction times (18 h).

In light of these results, structural and acidity factors strongly suggested that the direct methylation of 2a (via a B₃Al₂ mechanism) with DMC could also be reasonably ruled out. Therefore, the formation of the product 4a in the investigated reaction (step 2) had to occur through the initial methoxycarbonylation of the reagent (2a) followed by a subsequent methylation.

Presently, there are no clear reasons why the anion 3a⁻ undergoes methylation while 2a⁻ does not. A possible explanation could lay in the hard–soft character of the involved moieties: the methoxycarbonylation of the more stabilized anion 3a⁻ is probably much slower (and reversible) than that of the less hindered (and more reactive) 2a⁻. Therefore, the observed behavior would be due to the high acidity of 3a rather than to a high reactivity of 3a⁻. Also, a factor that should account for the different nucleophilicity of 2a⁻ and 3a⁻ is that the reaction takes place in the presence of a solid base: therefore, surface phenomena may affect the reaction outcome (see later). Indirect evidence comes from the DMC-methylation of arylacetonitriles, promoted by homogeneous strong bases (phosphazenes). In this case, the reaction is no longer selective since the double methylation of the substrates occurs to a large extent.

These aspects are, however, beyond the scope of the present work, the aim of which is to understand and describe the reaction selectivity through a kinetic investigation.

**Demethoxycarbonylation and Methylation of 3a: Steps 2 and 5.** 2-Methoxycarbonylphenylacetonitrile (3a), the key intermediate of both equilibrium 2 and reaction 5, was used for the investigation of these two steps. Experiments were carried out by reacting a mixture of 3a, DMC, K₂CO₃, and methanol in a 1:200:2:10 molar ratio. Methanol was used to make experimental conditions of reactions 2 and 5 comparable to those of reaction 6, which requires this reagent (see later).

From a kinetic standpoint, reactions 2 and 5 are a set of competitive reactions (eq b):

\[ \text{2a} \xrightleftharpoons[k_2]{k_5} \text{3a} \rightarrow \text{4a} \]

where \( k_2, k_5 \), and \( k_9 \) are the corresponding kinetic constants. However, since the methoxycarbonylation reaction of 2a (2a → 3a) was much slower than its reverse reaction (3a → 2a), eq b was simplified by placing \( k_2 \ll k_5 \) (eq c):

\[ \text{2a} \xrightarrow[k_2]{k_5} \text{3a} \rightarrow \text{4a} \]

Eq c yields a first-order law expression for the disappearance of 3a with time (eq d):

\[ -d[3a]/dt = k_{-2}[3a] + k_5[3a] = (k_{-2} + k_5)[3a] = k[3a] \]

where \( k = k_{-2} + k_5 \). According to eq d, the substance 3a follows a pseudo-first-order rate law (Figure 1). This reaction was repeated three times, and an average \( k_{\text{disp}} \) of 1.1 × 10⁻³ min⁻¹ was calculated.

The formations of 2a and 4a [PhC(CH₃)(CO₂CH₃)CN] are given, respectively, by (Scheme 1):

\[ \text{d}[2a]/dt = k_{-2}[3a] = k_{-2}[3a]e^{-kt} \] or \[ \text{2a} = [2a]₀ + (k_{-2}/k)[3a]₀(1 - e^{-kt}) \]

and

\[ \text{d}[4a]/dt = k_5[3a] - k_9[4a] + k_{-5}[1a] \]

where \( 1a \) was the monomethyl derivative [PhCH(CH₃)CN].

Eq f was simplified by applying the following considerations. (i) The reaction of 3a with DMC showed that the concentration of 1a was low compared to that of 3a until the latter was present, being \([3a] \approx 7[1a]\) throughout all the reaction. (ii) An independent investigation of step 6 indicated that the methoxycarbonylation of the monomethyl derivative (1a → 4a) occurred very slowly: \( k_9 \) has to be very small in comparison to \( k_2 \). Therefore, eq f gives eq g by omitting the term \( k_{-5}[1a] \):

\[ \text{d}[4a]/dt = k_5[3a] - k_9[4a] \]

Since \([4a]₀ = 0\), one may assume that the condition \( k_5[3a] \gg k_9[4a] \) can be verified for a certain reaction time (see later). If so, eq g is further simplified to the following:

\[ \text{d}[4a]/dt = k_5[3a] \]

and considering that also \([2a]₀ = 0\), the combination of eqs e and h yields:

\[ \text{(13) Scheme 1 should dictate the use of carbanion concentrations (2a⁻, 3a⁻) rather than [2a] and [3a] in kinetic equations. However, whatever the concentrations of 2a and 3a are, ratios 2a/2a and 3a/3a must be constant throughout the reaction (steps 2 and 5); the apparent simplification of eq b, which serves as a working hypothesis, does not alter kinetic results.} \]
Eq i means that the ratio between 2a and 4a should remain constant and independent from the concentration of the reagent 3a. Eq i was validated experimentally. As can be seen in Figure 2a (solid line), when 3a was made to react with DMC, the ratio [2a]/[4a] remained unaltered (0.3). Moreover, the plot of the concentration of the product 2a versus (1 – e^{-kt}) showed a good linear correlation (Figure 2b), which proved the pseudo-first-order assumed by eq e.

Since the investigated reactions take place in the presence of a heterogeneous catalyst (K2CO3), it should be noted that the rate may also depend on diffusion phenomena of reactants/products on the solid surface. We have already reported this in the particular case of phenylacetonitrile, for which it was shown that conversions were dependent on the stirring rate of the reaction mixture.6 To account for this fact, the reaction of 3a with DMC was also investigated by applying different stirring rates (v_{stir}). Results are reported in Table 2.

A mass transport limitation seemed to occur at low v_{stir} (compare conversion/time in entries 1–3). However, the ratio [2a]/[4a] was substantially the same (0.3) in all cases, meaning that the ratio between rates of demethoxycarbonylation and methylation of 3a was also free from a diffusion control. Even if the amount of the anion 3a (from which both compounds 2a and 4a are derived) did depend on the stirring, it was not necessary to measure its actual concentration in the reaction mixture (and hence, the equilibrium constant of eq 4 in Scheme 1).

Therefore, for kinetic calculations, the reagent concentration measured (by GC) as [3a]_{meas} = ([3a]_{react} + [3a]_{eq}) (where [3a]_{react} was the reagent concentration in solution) appeared to be adequate.14 Bearing this in mind, we were able to determine the rate constants k_{-2} and k_{5} from the combination of eqs d and i:

\[
\begin{align*}
    k_{-2} &= k_2 + k_5 \\
    [2a]/[4a] &= k_{-2}/k_5
\end{align*}
\]

The solution of this system gave \( k_{-2} = 2.5 \times 10^{-3} \pm 3 \times 10^{-4} \text{ min}^{-1} \) and \( k_5 = 7.9 \times 10^{-3} \pm 2 \times 10^{-4} \text{ min}^{-1} \).

These data show that \( k_5 \approx k_{-2} \), i.e., the methylation of 3a (step 5) occurs faster than its demethoxycarbonylation (step 2). This also proved that kinetic analyses of the reactions of DMC with 2a and 3a were in good agreement: when compound 3a was formed from 2a, it readily reacted to give 4a; again, the direct reaction of 3a with DMC afforded 4a faster than 2a. The methyla- tion step being more rapid than the methoxycarbonylation and the demethoxycarbonylation ones pushed the reaction onward.

This behavior may also explain some results previously reported:4 for a set of different acetonitriles (ArCH2CN; Ar: XCH2H2, X = H, Me, OMe, F, Cl, OMe, MeO, m-OMe), it was observed that the concentration of the methoxycarbonyl intermediate [ArCH(CO2Me)CN, 3] was always much lower than that of the methylmethoxycarbonyl intermediate [ArC(Me)(CO2Me)CN, 4].16

It should be stressed, however, that all the above considerations as well as the evaluation of constants k_{-2} and k_{5} rely on the occurrence of the inequality \( k_{-2}[3a] > k_5[4a] \). Under which conditions does this relation hold? Obviously, the answer requires the determination of the k_{5} constant related to the demethoxycarbonylation of 4a.

**Demethoxycarbonylation of 4a: Step 6.** The reaction of 2-methoxycarbonyl-2-phenylpropionitrile (4a) with methanol was investigated by using a mixture of the substrate, DMC, K2CO3, and MeOH in a 1:30:2:10 molar ratio. The disappearance of the substrate with time

---

14. Before GC analysis, all samples of the reaction mixture were acidified.

15. Since the reaction of 3a with DMC was repeated three times, three different k values were available. The system i was solved by coupling the corresponding k value to a set of six values of the [2a]/[4a] ratio (calculated for each sample analyzed during such reactions). Thus, the determination of both k_{-2} and k_{5} was averaged over a total of 18 solutions of i.

16. However, electron-withdrawing substituents (i.e., p-Cl and p-F) seemed to speed up the overall reaction, probably through a stabilization of the involved carbanions.
Hence, $k_{\text{obs}} = 2.9 \times 10^{-3} \text{ min}^{-1}$.

From Scheme 1, the rate of disappearance of $4a$ with DMC was extremely slow (only 8% conversion after 25 h), $k_{-6} \ll k_6$. Hence, $k_{\text{obs}} = k_6$.

With both constants $k_6$ and $k_5$ determined, the range of validity for eq h (i.e., of the inequality $k_6[3a] \gg k_5[4a]$) can be estimated through the integrated form of eq g:

$$[4a] = k_6/k_5 (3a)_0 [e^{-k_6 t} - e^{-k_5 t}]$$

(18) The concentration $[3a]_0$ was known, being compound 3a the reagent.

(19) To gauge this discrepancy, the ratio $[2a]/[4a]$ can also be expressed with the assumption that $k_{-2} = k_6 = k_{-5} = k_5 = k_{-6} = k_6$.

Table 3. Demethoxycarbonylation of 2-Methoxycarbonyl-2-phenylpropionitrile (4a): Influence of Methanol and Potassium Carbonate

<table>
<thead>
<tr>
<th>entry</th>
<th>MeOH:4a (molar ratio)</th>
<th>K$_2$CO$_3$:4a (molar ratio)</th>
<th>no. of runs</th>
<th>$k_{\text{obs}} \times 10^{-3}$ (min$^{-1}$) $^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>2</td>
<td>3</td>
<td>3.0</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>2</td>
<td>3</td>
<td>7.6</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>0.1</td>
<td>2</td>
<td>1.5</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>1</td>
<td>3</td>
<td>1.9</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>3</td>
<td>2</td>
<td>3.1</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>4</td>
<td>3</td>
<td>3.1</td>
</tr>
</tbody>
</table>

$^a$ All reactions were carried out at 140 °C using a DMC/substrate molar ratio of 200. $^b$ $k_{\text{obs}}$ values were averaged over the number of runs.

However, the further point is why the ratio $[2a]/[4a]$ seems to be constant throughout the reaction (Figure 2a, solid line). This can be discussed through the combination of eqs e and g:

$$[2a]/[4a] = \frac{(k_{-2}/k_2 + k_6/k_5)}{(k_6/k_5 - k_6) \times (1 - e^{-(k_{-2} + k_6)t})/ (e^{-k_6 t} - e^{-k_5 t})}$$

whose corresponding plot (using the $k_{-2}$, $k_6$, and $k_5$ values) is the dashed line of Figure 2a. Eq n exhibits a rather good overlap to the experimental curve. However, at a high reaction time (>250 min), the two plots tend to diverge. Equation n correctly predicts that $[2a]/[4a]$ should increase with time: in fact, 4a is consumed via the demethoxycarbonylation process (step 6, see also Figure 4), while the amount of 2a remains constant since its methoxycarbonylation does not take place at 140 °C (step 2, Scheme 1). This behavior appears less evidently from the experimental dots probably because of the smooth slope of the curve.

In summary, the comparison between $k_{-2}$, $k_5$, and $k_6$ showed that the methylation step (3a - 4a) took place faster than both demethoxycarbonylation reactions (3a - 2a and 4a - 1a), which in turn had comparable kinetic constants. Therefore, the methylation step was responsible for driving both equilibria 2 and 6 to the right and accounted for the observed selectivity. The methoxycarbonylation step (2a - 3a) was instead the rate determining process of the overall reaction.

Step 6 was further investigated to explore whether the reaction rate could be affected by both the base and the coproduct methanol. Thus, in separate experiments, the amount of K$_2$CO$_3$ and the volume of methanol were changed. Reactions were all of pseudo-first order with respect to the substrate. Results are reported in Table 3 and show the following. (i) The rate constants doubled when the K$_2$CO$_3$/4a ratio ranged from 0.1 to 2 (entries 1 and 3, $k_{\text{obs}} = 1.5$ and $3 \times 10^{-3} \text{ min}^{-1}$, respectively); a further increase of the base amount (K$_2$CO$_3$/4a > 2) did
The described mechanism evinces the crucial action of the methoxyacarbonyl group, which by increasing the acidity of 3 increases the concentration of the corresponding anion, $\text{ArCl}^-(\text{CO}_2\text{CH}_3)\text{R}^- (3^-)$, thereby allowing step 5 to occur rapidly. This being established, a key aspect still remains unclear: why 3 undergoes direct methylation, while 1 or 2 does not. Steric and stability factors of the involved anions can be considered, but a more in-depth investigation is necessary. Also, the specific influence of the heterogeneous catalyst must be addressed.

 Arylacetoesters behave differently with respect to the nitriles. The reaction of dimethyl phenylmalonate with DMC proves that the demethoxyacarbonylation step is easier than the methylation reaction. This fact could be the reason esters need higher temperatures for the reaction to be completed. However, the nonmethyl selectivities are comparable (≈99%) for both of the two classes of ary lacetic acid derivatives, even using a large excess (200 molar equiv) of the methylating agent.

**Conclusions**

The kinetic analysis of the mechanism of Scheme 1 allows the following general considerations. (i) The similarity of $k_2$ and $k_6$ reveals that both the starting reagent 2a and its methyl derivative 1a undergo demethoxyacarbonylation reactions at comparable rates, while the methylation step of the intermediate 4a is the fastest reaction. (ii) The rate determining step of the overall transformation is the methoxyacarbonylation reaction, which is so slow for both 2a and 1a that the determination of the related kinetic constants ($k_2$ and $k_6$) is impracticable at 140 °C. This is probably due to the low concentration of nucleophiles 2a- and 1a- attainable in the presence of a weak base such as K$_2$CO$_3$.

On the whole, the comparison of the kinetic behavior of the investigated steps reveals that the nonequilibrium methylation reaction is crucial for driving the overall process to completion. In fact, the higher rate of step 5 allows both the rapid consumption of 3a and the accumulation of 4a, which serves as a reactant for step 6; in other words, both equilibria 2 and 6 are controlled by the irreversible reaction 5.

Experimental Section

All compounds used were ACS grade and were used without further purification. $^1$H and $^{13}$C NMR spectra were recorded using a Bruker Ac 200 spectrometer (200 and 50 MHz.

---

(20) Maskill, H. In The Physical Basis of Organic Chemistry; Oxford University Press: Oxford, 1989; p 258. h and $k_a$ are Planck and Boltzmann constants. The activation energy was calculated from the gradient of Figure 4 ($\Delta H^*/R$) using the equation $E_a = \Delta H^* + RT$ (by placing $T = 423 \, \text{K}$, as the mean absolute temperature of the range over which $k_{obs}$ values were determined).
respectively) using CDCl₃ as the solvent with TMS as the internal standard. GC analyses were performed on a Varian GC 3400 CX apparatus using a 30 m, DB5 capillary column. GC/MS analyses were performed at 70 eV on an HP 5971 mass detector coupled to an HP 5890-Series II gas chromatograph fitted with a 30 m, DB5 capillary column. Melting points were determined on a Büchi 535 melting point apparatus and are uncorrected.

Reactions Carried Out in Autoclave: General Procedure. A stainless steel (AISI 316) autoclave (internal volume of 250 cm³) was loaded with a mixture of DMCh the substrate (0.2 g), the base (K₂CO₃), methanol (where indicated), and n-decane as the internal standard in the molar ratios reported below (Table 3). At room temperature and before each reaction, air was removed by a purging valve with a N₂ stream. The autoclave was placed in a tubular oven heated by an oil-circulating jacket, while the mixture was kept under magnetic stirring. 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 in stainless steel suction pipe that, in turn, was immersed into the reaction mixture. In this way, samples (0.3 cm³) could be withdrawn during the reaction and analyzed by both GC and GC/MS.

2-Methoxycarbonylphenylacetonitrile (3a) and 2-Methoxycarboxylmethyl-2-phenylpropionitrile (4a) were synthesized according to established procedures, while a gentle N₂ stream (0.5 cm³/min) was allowed in and finally, filtered. The salt 3a was obtained in a 59% yield (23.2 g). ¹H NMR (DMSO-d₆): δ ppm 7.55 (d, 2H, J = 7.4 Hz, ortho aromatic), 7.01 (t, 2H, J = 7.4 Hz, meta aromatic), 6.81 (t, 1H, J = 7.4 Hz, para aromatic), 3.39 (s, 3H, COOCH₃). ¹³C NMR (DMSO, d₆): δ ppm 168 (CO), 127, 121, 117 (C, aromatics), 48 (OCH₃). The literature reported the formation of the sodium salt Na⁺(COOCH₃)CN obtained in a methanol solution of sodium methoxide and 3a.

Calibration Curves. The evaluation of rate constants for the steps of Scheme 1, required a high degree of accuracy in the GC analyses. Thus, calibration curves were determined for both compounds 3a and 4a–3a by using n-decane as the internal standard. The general procedure is as follows. A 0.05 M solution of each substrate was prepared using DMCh as the solvent. Four aliquots of 5, 10, 15, and 20 cm³ were taken and placed separately into four volumetric flasks. Each solution was added with 20 cm³ of a 0.026 M solution of sodium methoxide and then each solution was analyzed twice by GC. In the case of 3a, analytical samples of 0.2 cm³ were acidified and extracted with diethyl ether as described in the above preparation of 3a. The calibration curves were obtained by plotting, for each solution, the ratio of the chromatographic areas of the substrate and the standard versus the concentration of the substrate. Linear fits with r ≥ 0.99 were obtained in all cases.

Acknowledgment. Murst (Italian Ministry of University and Scientific and Technological Research) and INCA (Interuniversity Consortium Chemistry for the Environment) are gratefully acknowledged for financial support. Prof. Achille Giacometti is also gratefully acknowledged for his helpful discussion and suggestions on the mathematical aspects of the work.