

## Selective and Continuous-flow Mono-methylation of Arylacetonitriles with Dimethyl Carbonate under Gas-Liquid Phase-Transfer Catalysis Conditions

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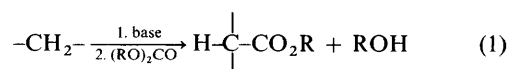
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Very high selectivity in monomethylation of arylacetonitriles is observed when dimethyl carbonate is used as an alkylating agent under g.l.-p.t.c. conditions: thus phenylacetonitrile, reacting on a catalytic bed of corundum spheres coated with K<sub>2</sub>CO<sub>3</sub> and polyethyleneglycol, yields 2-phenylpropionitrile with only 1% of bismethylated by-product. The method is a new, one-step, general route to the synthesis of 2-arylpropionitriles.

It is well known that the reaction of arylacetonitriles with alkyl halides in the presence of strong bases is not selective. In classical syntheses,<sup>1</sup> under phase-transfer conditions<sup>2</sup> or in the presence of molecular-size-discriminating inorganic matrices it yields noticeable amounts of dialkyl derivatives as by-products. In the case of methylation, moreover, it is difficult to obtain pure the mono-methyl derivative, even if the reaction is stopped before its completion.

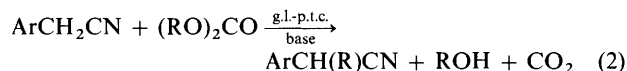
We previously reported that dialkyl carbonates behave as alkylating agents under gas-liquid phase-transfer catalysis (g.l.-p.t.c.) conditions: by flowing a gaseous mixture of aromatic primary amines,<sup>4</sup> phenols or thiophenols<sup>5</sup> and dimethyl carbonate (DMC) over a catalytic solid bed of potassium carbonate supporting polyethyleneglycol (PEG), only mono-*N*-methylanilines, aryl methyl ethers or methyl sulphides, respectively, were obtained. We report here the unusually high selective alkylation of arylacetonitriles with dialkyl carbonates.

It is reported that, working in solvent, arylacetonitriles react with dialkyl carbonates and yield the corresponding carboxy-alkyl derivatives;<sup>6</sup> a BAc2 mechanism is followed [Equation (1)]:



In contrast, operating under g.l.-p.t.c. conditions, by flowing gaseous arylacetonitriles with dialkyl carbonates through a

catalytic solid bed (potassium carbonate coated with polyethyleneglycol as a phase-transfer agent) only mono-C-alkylated compounds together with unchanged reagents (if any) are obtained. The reaction takes place according to a BA12 mechanism [Equation (2)]:



The reaction occurs with evolution of CO<sub>2</sub>: the leaving methoxycarbonate anion spontaneously decomposes, thus restoring the base on the bed and allowing the whole process to be carried out catalytically under continuous-flow conditions.

As reported in the Table, the reaction occurs very slowly in the presence of only the base (entry 1), but the phase-transfer catalyst allows almost quantitative conversion (entry 2). Both K<sub>2</sub>CO<sub>3</sub> and PEG can be supported on an inert macroporous solid bed (entries 2 and 3) with good results.

With reference to the Table phenylacetonitrile was kept in the gas phase by use of a four-fold excess of DMC. When higher boiling carbonates are used, the reaction must be performed in the presence of lower boiling diluents, in order to maintain the mixture in the gas phase. The reaction is slower but again only mono-alkylated derivatives are obtained. Thus, working in the presence of cyclohexane, diethyl carbonate produces a 28% conversion of phenylacetonitrile solely into 2-phenylbutane-

**Table.** Reaction of PhCH<sub>2</sub>CN with DMC under g.l.-p.t.c. conditions<sup>a</sup>

| Entry | Catalytic bed (g)   | Liquid flow <sup>b</sup><br>ml/h | Conversion % <sup>c</sup> |
|-------|---|----------------------------------|---------------------------|
| 1     | K <sub>2</sub> CO <sub>3</sub> alone (95) <sup>d</sup>                                    | 8.0                              | 46.0                      |
| 2     | Corundum* +<br>5 wt% K <sub>2</sub> CO <sub>3</sub> +<br>5 wt% PEG 6000 (95) <sup>e</sup> | 8.0                              | 98.0 <sup>f</sup>         |
| 3     | Corundum +<br>5 wt% K <sub>2</sub> CO <sub>3</sub> +<br>5 wt% PEG 6000 (80) <sup>e</sup>  | 16                               | 88.0 <sup>g</sup>         |

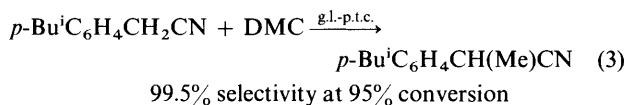
\* Al<sub>2</sub>O<sub>3</sub>. <sup>a</sup> 180 °C, atmospheric pressure. DMC-PhCH CN molar ratio = 4.0. <sup>b</sup> The mixture was sent liquid in the reactor where it vaporizes. <sup>c</sup> By g.l.c., at steady conditions. <sup>d</sup> Just granular anhydrous potassium carbonate. <sup>e</sup> For preparation of the bed and other experimental procedures see refs. 4 and 5. PEG 6000 is polyethyleneglycol with a MW of 6000. <sup>f</sup> 1% of PhC(CH<sub>3</sub>)<sub>2</sub>CN. <sup>g</sup> No traces of PhC(CH<sub>3</sub>)<sub>2</sub>CN.

nitrile (conditions of entry 2, Table but with liquid flow = 10 ml/h; cyclohexane:DEC:PhCH<sub>2</sub>CN = 60.0 ml:48.6 ml:11.5 ml; DEC:PhCH<sub>2</sub>CN molar ratio = 4.0).\*

It has been previously ascertained that in g.l.-p.t.c. the reaction occurs by a reversible partition of reagents and products between the gas phase and the stationary molten catalyst where it actually takes place. At present, however, it is premature to postulate a reaction mechanism; in any case, the very high selectivity observed in spite of the elevated temperature used, should not arise from a simple S<sub>N</sub>2 displacement; in a first examination, moreover, no promoting intermediates such as carboxymethylated derivatives were detected on the stationary catalytic phase.

Reaction 2 is a new, highly selective step for the synthesis of 2-arylpropionic acids, well known as anti-inflammatory agents. Thus, operating according to a continuous-flow process, the reaction of *p*-isobutylphenylacetonitrile with DMC yields the

mono-methyl derivative with a selectivity never observed before [Equation (3)].



2-(*p*-Isobutylphenyl)propanoic acid (Ibuprofen) is obtained from the nitrile by subsequent hydrolysis.

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\* Reactivity of phenylacetonitrile with DMC under g.l.-p.t.c. conditions is very high if compared with the reaction carried out with the same reagents and under comparable conditions but in the liquid phase: a stirred solution of PEG 6000 (30 g), of anhydrous potassium carbonate (3.0 g), phenylacetonitrile (1.1 ml, 10 mmol), and DMC (8.4 ml, 100 mmol) was heated to 100 °C. After 70 h the reaction mixtures showed only 1% conversion.