Reactions with Dimethyl Carbonate. Part 3.[1] Applications and Mechanism of Mono- or Bis-methylation of Aromatic Amines with Dimethyl Carbonate

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As part of our research on the replacement of highly toxic chemicals in synthesis, we required a less toxic but economic substitute for dimethyl sulphate and methyl iodide.[1] A comparison of the toxicological values of this reagent with those for dimethyl carbonate show that for dimethyl sulphate LD_{50}(rat) for oral dose is 440 mg kg^{-1}, while for subcutaneous injection it is 30 mg kg^{-1}.[6] The corresponding values for dimethyl carbonate are: oral, 12 800 mg kg^{-1}; subcutaneous injection, 8500 mg kg^{-1}.[5] The dermal LD_{50}(guinea pig) value is above 10 ml kg^{-1}.[6] After inhalation of 1000 ppm of dimethyl carbonate by rats for 6 h no toxic signs are observed; 5000 ppm for 6 h give some toxic signs but a rapid recovery after exposure is reported with an autopsy showing no abnormalities of the internal organs.[6] In comparison, the lethal dose for inhalation of dimethyl sulphate is 30 ppm during 4 h.[6]

It is advantageous that aromatic amines give mono- or bis-methylation by simple variation of the reaction conditions. In the presence of potassium carbonate as base, the reaction with dimethyl carbonate gave methoxycarbonylation–methylation, the corresponding *N*-methylarylcarbamate being isolated as the sole product. Hydrolysis and decarboxylation gave the monomethylated amine. Thus dimethyl carbonate serves to activate, protect, and methylate in one step. In the absence of base the reaction gave the bismethylated amine only.

The usefulness of dimethyl carbonate is demonstrated in the preparation of *N*-methylaminoantipyrine (**2**), the active substance in many drugs having antipyretic and analgesic effects. Generally, (**2**) is prepared from aminoantipyrin (**1**) and dimethyl sulphate; however, because the reaction cannot be stopped at the monomethylation stage, it is necessary to protect the amino function.[7] The simple and convenient formation of (**2**) by use of our conditions is shown in Scheme 1.

To explain our results we propose a mechanism in analogy with the established one. Experiments with substituted anilines confirm this mechanism and indicate the possibilities and limitations of the procedure.

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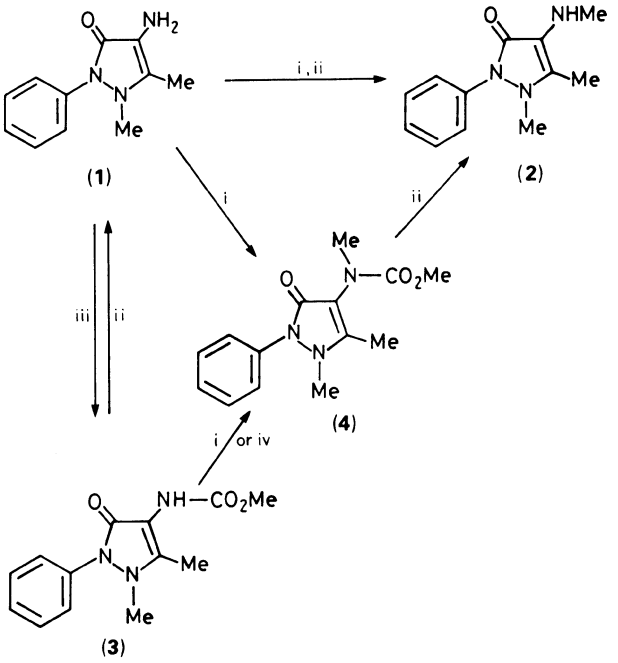

Scheme 1 *Reagents:* i, dimethyl carbonate, K_2CO_3 (or NaH, $NaNH_2$), 18-crown-6 or Aliquat 336, 90 °C; ii, 10% KOH; iii, as i but at 50 °C; iv, MeI–NaH

Table 1: Reaction of aniline with dimethyl carbonate

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