***SHORT PAPER***

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# Microwave enhanced decarboxylations of aromatic carboxylic acids: improved deuteriation/tritiation potential†

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Decarboxylation of aromatic carboxylic acids under microwave enhanced conditions is an increasingly attractive method of preparing deuterium/tritium labelled compounds.

For many years the most widely used methods for preparing deuterium[1] and tritium[2] labelled compounds–hydrogen isotope exchange, hydrogenation and dehalogenation with $D_2$ or $T_2$ gas in the presence of a transition metal catalyst, borohydride reductions and methylations–have remained essentially unchanged. Now through the application of microwaves[3] it is becoming possible to greatly accelerate the reactions, to carry them out in a different manner by *e.g.* replacing $D_2/T_2$ with solid donors[4] such as formates and, in some cases, perform reactions such as borohydride reductions entirely in the solid state[5]. In the case of tritium the much cleaner reactions and reduced levels of radioactive waste produced represent additional improvements. A further consequence is that the relative merits of the various methods no longer remain the same and that some hitherto rarely used methods now become considerably more attractive. Such is the case for decarboxylation reactions where, in the few quoted examples[6] of the method having been used for tritiation purposes, the overriding feature is the harsh experimental conditions employed.

2-Unsubstituted indoles, widely used intermediates in organic chemistry, are commonly synthesised through decarboxylation of the parent acid.[7] This is achieved by prolonged heating in the presence of Cu (metal/salts) as catalyst and a basic solvent such as quinoline. In our studies (Table 1) prior washing of the acid with $CH_3OD$ to exchange the carboxy proton with deuterium, followed by brief microwave activation, is sufficient to achieve decarboxylation/deuteriation in ~100% yield. The procedure was equally successful for α-methylcinnamic acid **(2)** and three substituted benzoic acids **(3-5)**, although only in one case was the deuterium incorporated regiospecifically.

Further improvements in the procedure for labelling these compounds can be anticipated as it has been shown that by using thick wall glass tubes capable of withstanding high pressures and a commercial reactor decarboxylation proceeds in the absence of the environmentally undesirable copper catalysts.[8] Furthermore quinoline can be replaced with water[9-11].

Our approach was to replace $H_2O$ by $D_2O$ and to use N-ethylmorpholine as catalyst, the substrates now being one or more benzoylformic acids **(6,7)**. By comparison with a previously quoted thermal example[12] the microwave enhanced decarboxylation/deuteriation occurs very rapidly and is complete within 4 minutes.

The range of compounds that can be labelled in this manner has been further widened by the recent observation[13,14] that tributylphosphine and other trivalent phosphorus compounds ($R_3P$; R = Bu, Ph, $Me_2N$, OEt) catalyse the decarboxylation of α-iminoacids. By using deuteriated/tritiated acetic acid as a $D^+/T^+$ donor several labelled imines have been prepared; these in turn can be used to label β-lactams and other biologically interesting compounds such as α-aminophosphates.[15]

Finally, it is worth noting that the corresponding phosphites[16] ($R_2HP{=}O$; R = OEt, OMe), cheap, non-toxic hydrogen-atom donors and attractive alternatives to organic tin hydrides, have been identified as effective radical reducing agents for organic halides, thioesters and isocyanides. The labelled versions of these reagents thus provide new opportunities.[17]

## Experimental

Two different microwave instruments (a CEM MDS system and a Matsui M169BT unit) were used for the decarboxylation studies of which the former was a commercial design and the latter was a household kind. $^1H$ (300 MHz) and $^2H$ ($^1H$ decoupled, 46 MHz) NMR spectra were obtained using a Bruker AC300 spectrometer.

A typical decarboxylation procedure for acids **1–5** was as follows: Acid (*e.g.* indole-2-carboxylic acid, 153 mg, 1.2 mmol), catalyst [$CuCO_3$. $Cu(OH)_2$, 227 mg, 1.3 mmol] and quinoline (1 $cm^3$) were mixed in a heavy walled glass tube. The tube was sealed under vacuum and placed in a beaker containing vermiculite, then irradiated in the CEM MDS microwave oven. On completion of microwave irradiation, the contents were diluted in EtOAC (50 $cm^3$), and washed with HCl (1% aqueous, 3 × 50 $cm^3$), followed by $H_2O$ (50 $cm^3$), NaOH (0.1 M aqueous, 3 × 40 $cm^3$) and finally saturated aqueous $Na_2CO_3$ (2 × 25 $cm^3$). Removal of solvent afforded the crude product which was then purified using column chromatography (silica gel, 4:1 hexane/diethyl ether mixture as solvent).

Decarboxylations of benzoylformic acids **(6,7)** were carried out using the Matsui 169BT microwave oven. Typically benzoylformic acid (0.10 g, 0.66 mmol), N-ethylmorpholine (0.16 g, 1.33 mmol) and deuterium oxide ($D_2O$, 66 μl, 3.3 mmol) were placed in a pear-shaped flask (25 $cm^3$) fitted with a septum. The flask was evacuated, then placed in a beaker containing vermiculite and irradiated in the microwave oven at 300 W power for 4 minutes. On completion, the flask was allowed to cool. 0.1 $cm^3$ of the contents were taken up in $CDCl_3$ (0.5 $cm^3$), washed with water, dried, and analysed by $^1H$ NMR spectroscopy (Bruker AC300). As the chemical shift for the two protons in the *ortho*-position of the aromatic ring of benzoylformic acid (δ ~ 8.00 ppm) is somewhat higher than those for benzaldehyde (δ ~ 7.80 ppm) this served as a means of calculating the decarboxylation yield which was consistantly > 90%. Comparison of the $^1H$ and $^2H$ NMR spectra gave the isotopic incorporation.

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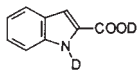
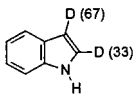
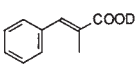
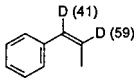
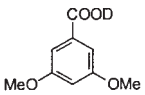
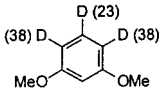
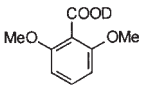
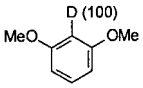
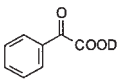
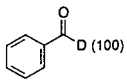
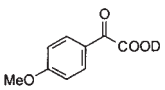
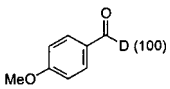
**Table 1.** Examples of successful microwave enhanced decarboxylations/deuteriations

| Entry | Reactant | Catalyst/ solvent | Power/ heating time | Product/Deuterium incorporation (relative %) |
|---|---|---|---|---|
| **1** |  | $CuCO_3.Cu(OH)_2$ Quinoline | 560W, 16 min |  |
| **2** |  | " | 560W, 14 min |  |
| **3** |  | " | 560W, 16 min |  |
| **4** |  | " | 560W, 16min |  |
| **5** |  | " | 560W, 18 min |  |
| **6** |  | N-ethylmorpholine $D_2O$ | 300W, 4min |  |
| **7** |  | " | 300W, 4min |  |

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