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Microwave-enhanced aromatic dehalogenation studies: a rapid deuterium-labelling procedure

John R. Jones,[a,*] William J. S. Lockley,[b] Shui-Yu Lu[a] and Stewart P. Thompson[b]

[a]*Department of Chemistry, University of Surrey, Guildford, Surrey GU2 7XH, UK*
[b]*Medicinal Chemistry Department, AstraZeneca R&D Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5RH, UK*

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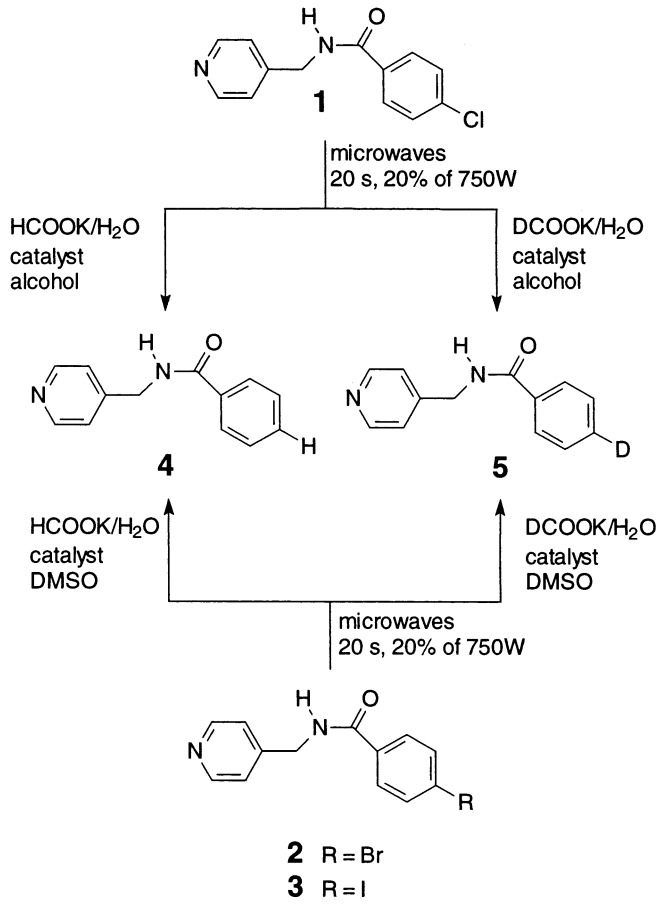
Abstract—Rapid (<1 min) and specific deuterium labelling is achieved through the microwave-enhanced dehalogenation of a number of *N*-4-picolyl-4-halogenobenzamides using deuterated formate as solid deuterium donor and either homogeneous or heterogeneous catalysts; the percentage deuterium incorporation is a function of the kind of solvent used.

Of the various methods used to prepare deuterium and tritium labelled compounds aromatic dehalogenation is second only to hydrogenation in importance.[1] Nevertheless, like hydrogenation, the reaction suffers from several limitations. For example the low solubility of both D_2 and T_2 gas in many organic solvents lead to slow rates and inefficient isotope usage. Moreover in the case of tritium the storage of the radioactive waste is becoming an increasingly serious and expensive issue. Hence there is a need for cleaner, faster and more isotope-efficient procedures.

We have modified[2] the classical hydrogenation procedure by replacing D_2/T_2 gas with solid isotope donors, such as formates and when these reactions are coupled to microwave irradiation[1,3–5] large accelerations in rates are achieved. The donors can be used in stoichiometric concentrations so that in the case of tritium little or no radioactive waste is produced. It seemed logical therefore to investigate whether these improvements could be extended to aromatic dehalogenation reactions and here we report our initial deuteration findings. Some examples of the use of formates in dehalogenation studies have been reported,[6–8] however none describe the utility of these agents for labelling organic compounds under microwave irradiation.

The *N*-4-picolyl-4-halogenobenzamide system (**1**–**3**) was chosen as the basic substrate structure because (a) the Cl, Br, and I derivatives were all easily synthesised,



Scheme 1. Dehalogenation under microwave conditions.

* Corresponding author. Tel.: +00-44-1483-259313; fax: +00-44-1483-876851; e-mail: j.r.jones@surrey.ac.uk

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Table 1. Typical percentage deuterium incorporation (D%) under different conditions

Substrate	Catalyst	D-donor	Solvent	D%
1	Pd/C	$DCOOK/H_2O$	C_2H_5OH	50–67
	Pd/C	$HCOOK/D_2O$	C_2H_5OH	5
	Pd/C	$HCOOK/H_2O$	C_2D_5OD	15
2, **3**	$Pd(OAc)_2$	$DCOOK/H_2O$	DMSO	>95
	$Pd(OAc)_2$	$HCOOK/D_2O$	DMSO	0

(b) satisfactory purification procedures were to hand, (c) they yield strong pseudomolecular ions in both positive and negative ion HPLC–MS and (d) have simple NMR spectra.

In a typical labelling reaction aqueous DCOOK solution (5 mg/10 μl, 31 μl, 0.18 mmol), the substrate **2** (35 mg, 0.12 mmol) and palladium acetate catalyst (5.4 mg, 0.024 mmol) were mixed with DMSO (1.0 cm^3) in a borosilicate glass test tube. The latter was purged with nitrogen gas, then placed in a beaker (250 cm^3) in an upright position and subjected to microwave heating (20 s, 20% power setting, Matsui BT 169 microwave oven) under atmospheric pressure (Scheme 1). On completion, the black suspension was filtered off, and the filtrate diluted in dichloromethane (DCM, 10 cm^3). The DCM solution was then washed with water (3×5 cm^3), and dried over anhydrous Na_2SO_4. Removal of the solvent afforded deuterated product **5** as yellow crystals (24 mg, 94%). The product was dissolved in acetone-d_6 to record the ^1H NMR spectrum, and in acetone to record the ^2H NMR spectrum. For HPLC–MS analysis, reaction mixtures were used without further separation except where the heterogeneous catalyst was used in which case the solids were filtered off before analysis.

The salient features of the results are as follows:

1. No dehalogenation takes place in the absence of the formate donor.
2. Dehalogenation proved to be extremely rapid and was complete within 1 min. This contrasts with the 90–270 min at 100°C required for the thermal debromination of 2-bromonaphthalene.[8]
3. The chemical yields (>90%) and isotopic purity of the products obtained using ^1H and ^2H NMR spectroscopy (proton in **4** or deuterium label in **5** at 7.53 ppm) were in agreement with the results of the HPLC–MS analysis ($MH^+ = 213$ for **4** and 214 for **5**).
4. For debromination and deiodination DMSO is a very effective solvent. Hardly any deuterium incorporation takes place when the deuterium is located in the co-solvent rather than the donor (i.e. $HCOOK + D_2O$). Such results imply that no H/D exchange takes place between them prior to the reaction of the substrate with the hydrido-metal species that is formed as a result of the decomposition of the formate or during the reduction process.[9] No dechlorination was observed in DMSO.
5. Alcohols, such as C_2H_5OH, i-C_3H_7OH and n-C_4H_9OH, are good solvents for the dehalogenation of all three types of substrates, but the percentage deuterium incorporation is always lower[10] than when the aprotic solvent DMSO is used (Table 1).
6. Both homogeneous [$Pd(OAc)_2$ and Wilkinson's catalyst] and heterogeneous (Pd/C) catalysts are effective for all three substrates but the ease of separation in the latter case is counterbalanced by a tendency for biphenyl by-product formation[7] via palladium-mediated coupling. $RhCl_3$ is only effective for debromination and deiodination in DMSO and caused decomposition of **1** in alcohol.

Even with our simple experimental procedure it is still possible to perform parallel reactions. For example, three test tubes each containing substrate, DCOOK and solvent, but different catalysts, can be irradiated in the microwave oven. Coupled with the rapidity of the reactions, this option provides a useful method for high though-put screening of reduction reactions since large numbers of substrates or catalysts can now be investigated without the need to handle gaseous hydrogen donors.[11,12]

In conclusion, rapid and specific deuterium labelling can be achieved through microwave-enhanced catalytic dehalogenation using deuterated formate. The dehalogenation procedure described will also have applications in other areas of organic synthesis, since the reaction can be carried out in alternative microwave-effective protic solvents such as water.

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