

Research Article

Combining microwave-enhanced deuteration reactions with parallel synthesis procedures

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Summary

The development of combined microwave-enhanced/parallel synthesis procedures and their application to the deuteration of organic compounds *via* examples of solid-state hydrogenation is reported. Other labelling procedures, such as solution state catalytic dehalogenations, hydrogenations as well as hydrogen isotope exchange reactions also benefit from the combined technology. Copyright © 2003 John Wiley & Sons, Ltd.

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Introduction

The last 15 years has seen an exponential growth in the use of microwave-enhanced methods of organic synthesis^{1,2} and these are now finding increasing application in the labelling of compounds, both with

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stable and radioactive isotopes.^{3–5} During the same time interval combinatorial/parallel synthesis procedures^{6,7} have largely replaced the customary sequential generation of individual molecules and enabled chemists to generate large chemical libraries which can then be used in high throughput screening for drug lead discovery and optimization studies. The new technology also offers considerable potential in the catalysis area^{8–12} but as far as the labelling of organic compounds with deuterium or tritium is concerned (the reactions invariably require a catalyst) there have been relatively few reported studies.^{13–15}

One of the main limitations of the combinatorial/parallel synthesis approach is that the rates of the reactions are frequently slow.^{16–18} As the use of microwaves leads to large rate accelerations it seemed logical therefore to perform parallel synthesis procedures under microwave-enhanced conditions and for this investigation we use solid-state hydrogenations as examples as well as solution state dehalogenations and hydrogenations and finally, hydrogen isotope exchange reactions.

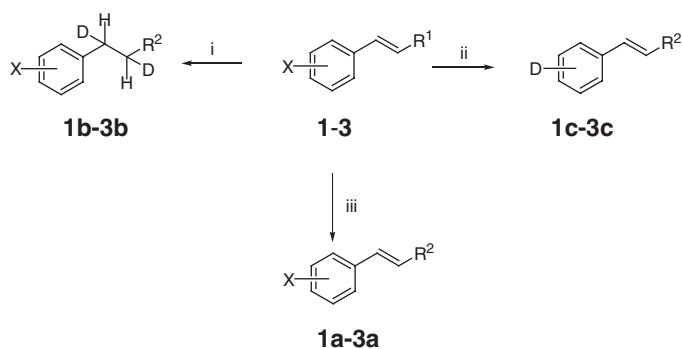
Catalytic hydrogenation reactions traditionally employ D₂ or T₂ gas in the presence of either homogeneous or heterogeneous catalysts to prepare deuterium or tritium labelled compounds.^{19,20} The development of solid-state catalytic hydrogenation by Myasoedov and co-workers^{21,22} has greatly increased the range of application. It is based on high temperature reactions with spillover deuterium/tritium, but the method has not been coupled to microwave irradiation. We have successfully demonstrated that formate salts (DCOO) are excellent solid donors and can therefore replace the customarily used D₂ gas.²³ Potassium formate is the preferred choice in our studies.

Results and discussion

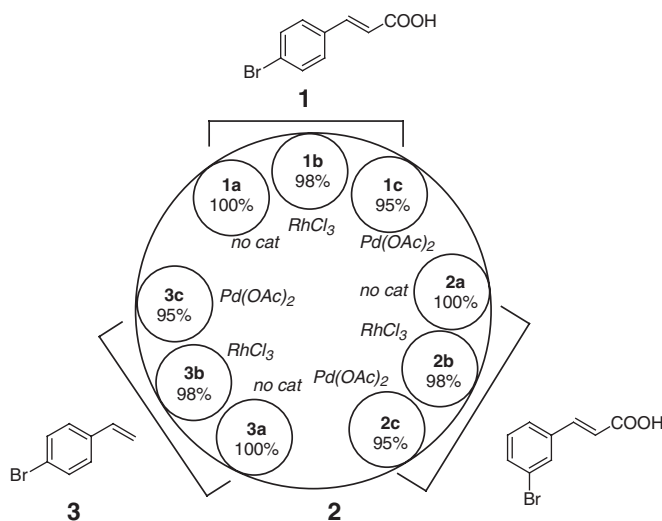
In some of our previous microwave irradiation studies^{24,25} we have employed a multimode oven (Matsui M 167 BT) and this has once again been used for the studies with the difference that a Radleys 24 place PTFE carousel is placed on the turntable and rotated at a fixed rate. Standard 10 ml tubes, 1.6 cm outside diameter and 0.18 cm thickness with polyethene caps were used in the investigations; the volume of the reaction mixture was usually in the range 0.5–3 ml.

First, we re-examined the catalytic activity of RhCl₃ and Pd(OAc)₂ towards the reduction or dehalogenation of 4-bromocinnamic acid and structurally similar compounds under microwave-enhanced parallel conditions. A 9-reaction matrix was used as illustrated in Scheme 1. The

short reaction times and easy optimization of reaction conditions are attractive features. When DMSO- d_6 was used as reaction solvent the reaction mixture, after simple filtration, can be used directly for NMR analysis. HPLC with an autosampler, would be an obvious alternative to evaluate the reactions in a high throughput manner. As robotics comes to play an increasingly important role in chemistry, one can immediately see the way to design more sophisticated labelling



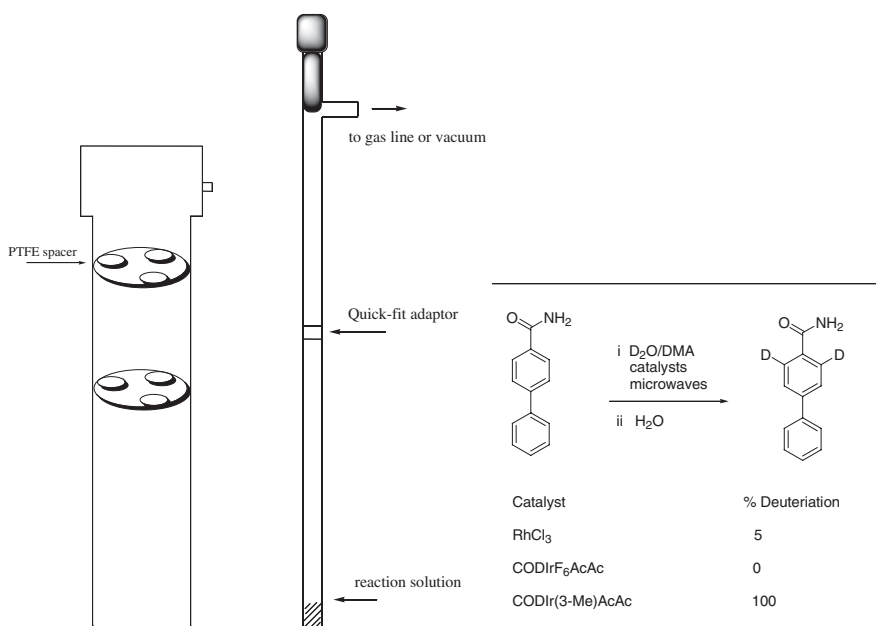
where X = Br
 R¹ = H, COOH
 R² = H, COOK



Scheme 1. Schematic representation of the parallel blank, dehalogenation and hydrogenation reactions under microwave-enhanced conditions. Yields are calculated using ¹H NMR spectroscopic method. Reaction conditions: (i) DCOOK/D₂O, RhCl₃, DMSO; (ii) DCOOK/D₂O, Pd(OAc)₂, DMSO; (iii) DCOOK/D₂O, DMSO

Efficient deuterium labelling was achieved when DCOOK was used under microwave-enhanced solventless conditions. Peaks in the ^2H (^1H decoupled) NMR spectra at 2.47 and 2.87 ppm are unambiguous evidence that deuterium was introduced equally on both the α and β positions. Initially the incorporation of D is around 50% at each site, but when a secondary deuterium source such as $\text{MgSO}_4 \cdot 7\text{D}_2\text{O}$ was introduced into the reaction medium, the D incorporation increased to close on 100%. This suggests that the reaction in the solid state follows a similar mechanistic pattern to that in solution where the secondary donor was water (or D_2O) from the surrounding environment.²³

The hydrogen isotope exchange reactions were carried out with 4-phenylbenzamide as substrate and three catalysts [RhCl_3 , cyclooctadienyliridium(I)-1,1,1,5,5,5-hexafluoropentan-2,4-dionate (CODIrF₆AcAc) and cyclooctadienyliridium(I)-3-methylpentan-2,4-dionate (CODIr(3-Me)AcAc)] using the monomode microwave cavity. In order that the reactions to be studied under parallel conditions the instrument was modified as shown in Scheme 3. A 6 pulse sequence of 30 s on, 30 s off was used at 600 W microwave power input. The results showed that the iridium catalyst, CODIr(3-Me)AcAc, was extremely efficient. RhCl_3 has



Scheme 3. Metal catalyzed hydrogen isotope exchange reaction using an apparatus where three tubes (right) are inserted in the quartz single-body flask (left) and held in position by the PTFE spacers

turned out to be a good catalyst for hydrogen isotope exchange studies²⁶, but these typically would involve heating at $> 120^{\circ}\text{C}$ for up to 16 h. Now we can employ catalysts that are able to perform the same reactions in less than 5 min under microwave-enhanced conditions.

The developments reported here have proved to be extremely useful in our deuteration studies. In particular they allow us to:

- determine the best catalyst in acid, base and metal catalyzed hydrogen isotope exchange reactions, under both homogeneous and heterogeneous conditions;
- optimize the catalyst concentration/weight;
- study the benefits that arise from using mixed catalysts;
- determine the best solvent to use;
- use several carousels in a sequential manner, so that the irradiation times and power levels can be varied in a systematic manner.

The main disadvantage of both systems is that neither the temperature nor the pressure can be monitored. However, the reactions invariably attain equilibrium fairly rapidly and for solid-state reactions the pressure is not as important as it is for solution studies.

Experimental

General methods

The Matsui M169BT (750 W) and Prolabo Synthewave 402 (600 W) are the two microwave instruments used in this work. The 24-place PTFE carousel was provided by Radleys Discovery Technologies Ltd. All reagents were used as received unless otherwise stated. ^1H NMR spectra were recorded on a Bruker AC300 spectrometer. PTFE spacers and reaction tube for the Synthewave 402 set-up were designed and made in house.

Parallel solution state reaction in the multimode microwave cavity

Typically, *p*-bromocinnamic acid (4.1 mg), $\text{Pd}(\text{OAc})_2$ (5.1 mg) [or RhCl_3 (2.6 mg), or without catalyst], $\text{DCOOK}/\text{D}_2\text{O}$ (10 mg/10 μl , 15 μl) and $\text{DMSO}-d_6$ (0.5 ml) were mixed in a 10 ml glass tube. Nine reaction tubes were placed on the PTFE carousel; it was not necessary to use the full capacity for the present experiments. The reaction mixtures were irradiated in the Matsui microwave oven (750 W) for 40 s at level I (25%) power setting. On completion and after cooling, the solutions were filtered and transferred to standard NMR sample tubes for

analysis. ^1H NMR (validated by LC-MS) analysis was used to evaluate the reactions. Yields of isolated compounds were $>95\%$.

Parallel solid-state reaction under microwave-enhanced conditions

Typically, the procedure involves grinding cinnamic acid (20 mg), rhodium trichloride (25 mg) and DCOOK-alumina (30% w/w, 95 mg) in the solid state and transferring the powdery mixture to a loosely capped glass tube. Eight such vials with different catalysts and substrate/formate ratios were placed in the carousel and irradiated in a Matsui M169BT microwave oven at 750 W for 3 min. The products were extracted into D_2O or other appropriate solvents. The ratio of hydrocinnamic acid (with two characteristic triplets at 2.87 and 2.47 ppm) to unreacted cinnamic acid (characterized by two doublets at 7.58 and 6.48 ppm) was calculated from their respective ^1H NMR spectrum integrals. Reaction mixture of compound **8** was extracted using $\text{DMSO-}d_6$.

Parallel solution state hydrogen deuterium exchange reaction in the monomode microwave cavity

A stock solution of 4-phenylbenzamide in $\text{D}_2\text{O}/\text{DMA}$ (1:2 v/v) was prepared at a concentration of 6.67 mg/ml for general use. Typically, 4-phenylbenzamide stock solution (0.5 ml), catalyst (1.0 mg) was mixed in the reaction tube. Three such reactions were prepared and inserted into the Synthewave 402 quartz single-body flask. The reaction mixtures were irradiated using 6 pulse sequences of 30 s on – 30 s off at 600 W microwave power input. At the end of the reaction, H_2O (1 ml) was added to precipitate the amide. The product was collected by filtration and then redissolved in $\text{DMSO-}d_6$ for ^1H and ^2H (^1H decoupled) NMR analysis.

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