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Development of combined microwave-enhanced labelling procedures for maximising deuterium incorporation

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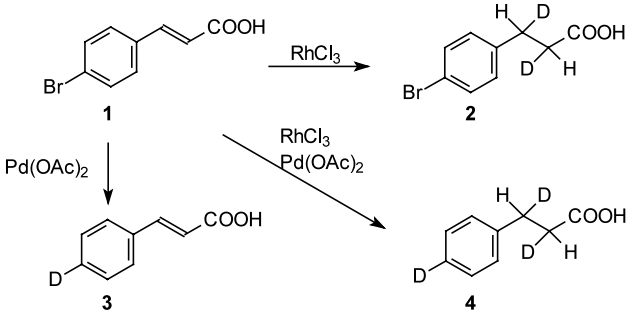
Abstract—Combined hydrogenation/aromatic dehalogenation under microwave-enhanced conditions provides a rapid route to deuterium labelled compounds with enhanced isotopic incorporation.

As the demand for deuterium- and tritium-labelled compounds continues to grow so does the search for rapid, more selective, one-step, catalytic procedures, leading to increased isotopic incorporation.[1] Microwave-enhanced reactions[2] have an important part to play as they can lead to dramatic rate accelerations whilst also offering alternative, environmentally friendly routes with, in the case of tritium, the formation of much reduced levels of radioactive waste. Catalytic transfer hydrogenation[3] and aromatic dehalogenations[4] with solid donors, rather than the customary T_2 gas, are both good examples. More recently we have shown how the adoption of parallel hydrogenation procedures can provide further benefits[5] and in the present study we take the development of the new labelling technology one step further.

Within the pharmaceutical industry the need for both stable and radioactive versions of the same compound is dictated by the increasingly stringent requirements of the various drug approval agencies. Although there are differences in scale the most popular methods for preparing ^{2}H- and ^{3}H-labelled compounds are the same. These are hydrogen isotope exchange,[6] hydrogenation,[3] aromatic dehalogenation,[4] borohydride reduction[7] and methylation.[8] These reactions are usually performed separately but there is no reason why, given careful choice of substrate, two or even three reactions cannot be carried out concurrently.

Here we illustrate the possibilities by reference to an example of combined catalytic transfer hydrogenation/aromatic dehalogenation under microwave-enhanced conditions. The substrate chosen was *p*-bromocinnamic acid (**1**). With microwave irradiation and $RhCl_3$ as catalyst hydrogenation is complete within 60 s. Similarly when using $Pd(OAc)_2$ as the catalyst under the same conditions debromination is complete within 60–90 s. Use of the combined catalyst [$RhCl_3$–$Pd(OAc)_2$] and microwave irradiation leads to quantitative hydrogenation plus debromination (Scheme 1). Under thermal conditions these kind of reactions need more than 2 h to reach equilibrium.[3]

Typically, *p*-bromocinnamic acid (4.1 mg), $Pd(OAc)_2$ (5.1 mg), $RhCl_3$ (2.6 mg), HCOOK/H_2O (10 mg/10 μl, 15 μl) and DMSO-d_6 (0.5 ml) were mixed in a 15 ml glass vial. The reaction mixture was irradiated in a Matsui microwave oven (750 W) for 40 s at level I (25%) power setting. Black solids were filtered off, and the clear brown solution was transferred into a standard NMR tube. The ^{1}H NMR (validated by mass



Scheme 1. All reactions use DCOOK in D_2O as D donor, DMSO as solvent and microwave irradiation.

Keywords: deuterium; labelling; dehalogenation; hydrogenation; microwaves.

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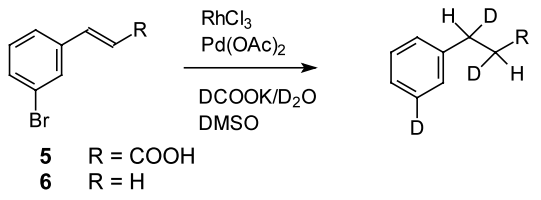
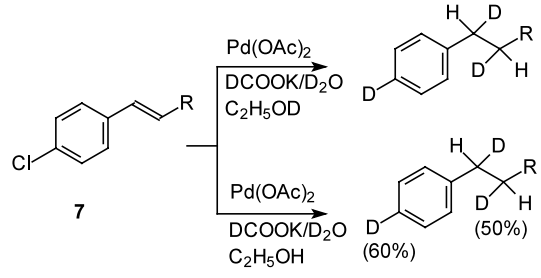
spectroscopy) analysis showed that both reactions were complete. The yield of isolated compound was 96%.

When $HCOOK/H_2O$ was replaced by $DCOOK/D_2O$, three deuterium atoms are incorporated and their positions are confirmed by the ^1H and ^2H NMR ($CHCl_3$, 7.31, 2.87 and 2.47 ppm) spectra. The isotopic incorporation was >95% in all three positions. When $DCOOK/H_2O$ was used an equally high yield (~96%) was achieved. The isotopic incorporation remained at the same level for the aromatic and α-positions but in the β-position it was approximately 50%. Clearly no hydrogen isotope exchange occurs between DCOOK and H_2O prior to the reactions taking place, consistent with previous findings.[4]

Simple structural modification of the substrate (Scheme 2) led to equally satisfactory results but an attempted dechlorination and hydrogenation of **7** was partially successful, only hydrogenation taking place. Changing the solvent from DMSO to ethanol overcame these difficulties so much so that only one catalyst (Scheme 3) was now necessary to effect combined dechlorination and hydrogenation. On microwave irradiation for 2×20 s at power level I (25%) equilibrium for both was established. To ensure maximising isotope incorporation at all sites it was necessary to use C_2H_5OD as well as D_2O.



Scheme 2.



Scheme 3.

The scope for transferring the technology to the tritiation of compounds is dependent on the required specific activity. Whilst tritiated formate can be readily prepared at high specific activity (Ci $mmol^{-1}$) the use of tritiated water at such level is precluded. Consequently there is much interest in the development of new donors, such as ionic liquids,[9] which interact very effectively with microwave irradiation.

In summary, rapid M+3 deuterium labelling of bifunctional molecules can be achieved using a combination of hydrogenation/aromatic dehalogenation and microwave irradiation. The new technology lends itself to other combinations of deuterium labelling reactions.

Acknowledgements

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