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Development of a microwave-enhanced isotopic labelling procedure based on the Eschweiler–Clarke methylation reaction

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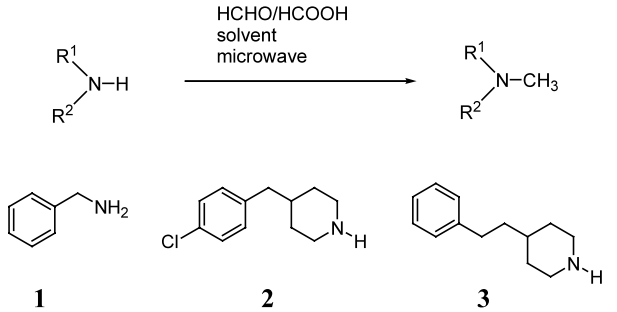
Abstract—A number of primary and secondary amines have been rapidly methylated under microwave-enhanced conditions using formic acid-formaldehyde mixtures, providing a route to $^{2}H(D)$-containing compounds and the potential for $^{3}H(T)$, ^{11}C, ^{13}C and ^{14}C labelling.

All of the most widely used deuteriation/tritiation procedures—hydrogen isotope exchange,[1,2] hydrogenation,[3] aromatic dehalogenation,[4,5] and borohydride reduction[6]—with the exception of methylation, have benefited from the introduction of microwave-enhanced procedures.[7,8] Faster, cleaner reactions can be achieved without the need for a gas handling facility when the familiar donors D_2 and T_2 are replaced by solid, polar donors such as formate. Furthermore, in the case of tritium the amount of radioactive waste produced can be greatly reduced and, if need be, converted to useful by-products on further microwave treatment.[9]

Methyl iodide, despite its many disadvantages (a low boiling liquid of poor stability and accompanying health hazard, especially if it is radioactive), is still the most widely used methylating agent. Our thoughts therefore turned towards a replacement made up of both a primary and secondary donor.

The combination of formic acid and formaldehyde methylation of amines—known as the Eschweiler–Clarke reaction,[10,11]—is a method of wide synthetic utility and has been the subject of critical investigation[12] in which a series of substituted benzylamines were used as model compounds. This, together with a recently reported study[13] in which the reaction was subjected to microwave irradiation prompts us to report our findings using amines **1**–**3** as model compounds for non-isotopically labelled reactions and on the preparation of the corresponding deuteriated compounds for amines **4**–**5**. This represents the first application of the microwave-enhanced reaction in the labelling area (Scheme 1).

Three different types of instruments were used—the Smith Creator focused MW synthesiser, the Synthewave S402 monomode reactor and a Matsui BT 169 oven. Whilst reactions were carried out sequentially using the first two devices, parallel reactions can be studied using the latter. In a typical experiment, *trans*-cinnamyl piperazine (16 mg, 0.08 mmol), HCHO (6 μl, 37% aqueous solution, 0.08 mmol), HCOOH (3 μl, 0.08 mmol) together with DMSO (0.2 ml) were mixed in a 5 ml Pyrex glass tube. The tube was subjected to microwave irradiation at 120 W for 1 min. The reaction mixture was dissolved in $CHCl_3$ (2 ml). The chloroform solution was washed with NaOH (10% aqueous solution, 6 ml) and dried over Na_2SO_4. Removal of solvent by blowing a stream of N_2 gas afforded methylated



1 **2** **3**

Scheme 1.

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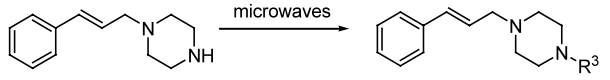
products as a colourless oil (16 mg, 93%). The products were characterised by ^{1}H NMR spectroscopy and mass spectrometry.

The salient features of the results are as follows:

(a) In all cases methylation was extremely rapid and was usually complete within 1–3 min. This contrasts with the 24 h at 80°C that was used for the thermal methylation.[12] Whilst the ratio[13] of formaldehyde to amine and that of formic acid to amine had previously been in the range 1.5–4, the present 1:1:1 ratio does away with the need for excess reagents; this will be particularly advantageous for radiochemical work.

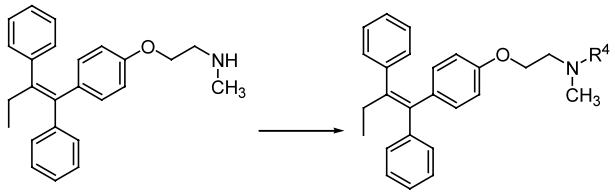
(b) The reactions could be performed in the absence of solvent when the amine was soluble in the formic acid–formaldehyde mixture, failing this DMSO was used.

(c) As for the earlier hydrogenation work[3] the deuterium distribution in the primary and secondary donors could be easily varied thereby providing a convenient route to three isotopomers (Scheme 2). Formaldehyde supplies the *N*-Me group with two deuterium atoms whilst the formic acid provides one. Only when the fully deuteriated mixture—DCDO+DCO_2D—is employed are three deuterium atoms incorporated. Early work[14] with ^{14}C had also established that the carbon of the *N*-Me group derived from the aldehyde. No isotope exchange between DCDO and HCOOH or HCHO and DCOOD was observed.



4 **4a** $R^3 = CH_2D$; **4b** $R^3 = CHD_2$; **4c** $R^3 = CD_3$

Reaction conditions: HCHO, DCOOD, DMSO for **4a**; DCDO, HCOOH, DMSO for **4b**; DCDO, DCOOD, DMSO for **4c**.



5 **5a** $R^4 = CH_3$; **5b** $R^4 = CD_3$

Reaction conditions: HCHO, HCOOH, DMSO for **5a**; DCDO, DCOOD, DMSO for **5b**.

Scheme 2.

(d) The final compound to be methylated is desmethyl Tamoxifen (**5**) to produce Tamoxifen-d_3, a drug that has found wide use for the treatment of cancer and where the labelled form has many applications in metabolism and pharmacokinetic studies.

(e) Simple modification of the methylation procedure would allow ^{3}H compounds to be prepared. Similarly compounds containing the $-^{13}CD_3$ group, for which there is an increasing demand, could be easily synthesised. Finally, the rapidity of the methylation reaction and the increasing availability of key ^{11}C building blocks suggest new opportunities in the rapidly expanding PET radiopharmaceutical area.[15]

In summary, we have developed an extremely rapid microwave-enhanced methylation procedure using a combination of primary and secondary donors that has initially been used for deuterium labelling, but which has considerable potential for incorporating other isotopes, both stable and radioactive.

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