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Microwave-assisted deuterium exchange reactions for the preparation of reactive intermediates

Katalin Fodor-Csorba,[a,]* Giancarlo Galli,[b] Sándor Holly[c] and Eszter Gács-Baitz[c]

[a] *Research Institute for Solid State Physics and Optics of the Hungarian Academy of Sciences, PO Box 49, H-1525 Budapest, Hungary*
[b] *Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Via Risorgimento 35, 56126 Pisa, Italy*
[c] *Chemical Research Center of the Hungarian Academy of Sciences, Institute for Chemistry, PO Box 17, H-1525 Budapest, Hungary*

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Abstract—Deuterium labelling of a number of ketones was achieved on a preparative scale by a microwave-assisted deuterium exchange reaction with D_2O/CF_3COOD. The reaction was rapid (<15 min) and highly isotope-efficient (ca. 100%), even though deuterium incorporation can be decreased during work-up (85–90%). No exchange reaction was observed for aryl protons of aromatic ketones. © 2002 Elsevier Science Ltd. All rights reserved.

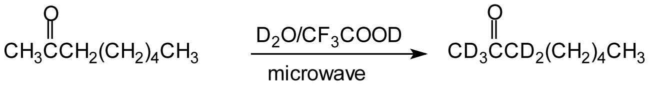
There is an ever increasing demand for the synthesis of commercially unavailable, labelled starting materials to be used in studies for a better understanding of e.g. the metabolic pathways of drugs and biologically active molecules in biological media,[1] or the order and dynamics of liquid crystals in their different mesophases.[1–3] In these latter cases, stable isotopes like deuterium have special interest, because the labelled compound is stable for a long time thus permitting more detailed investigation by specialized ^2H NMR and neutron scattering techniques.

For the preparation of deuterium labelled compounds there are several possibilities using (i) chemical reactions for connection of labelled segments to the non-labelled part of the molecule, or (ii) exchange reactions accelerated by various catalytic methods.[3–5]

Very recently, microwave-assisted deuterium labelling reactions, which are specific and faster than similar thermally activated reactions, have been introduced.[6–10] This technique may become an increasingly effective deuterium labelling reaction. However, to the best of our knowledge, no attempts have been made, so far, on microwave-assisted deuterium isotope exchange reactions on a preparative scale.

We have applied microwave-assisted deuterium labelling to a preparative scale, i.e. a few gram scale, for the synthesis of deuteriated ketones, aromatic or aliphatic, that are useful intermediates for the preparation of different classes of liquid crystals in which the deuteriated group would be directly linked to the mesogenic core. We used D_2O as the deuterium source, and CF_3COOD as a catalyst. While our test material was 2-octanone **1**, other aliphatic or aromatic ketones, such as 2-pentanone **2**, 4-methyl-2-pentanone **3**, 4-*n*-heptanoylbiphenyl **4**, and 1-(4-*n*-heptylbiphenyl)ethanone **5**, were also investigated to ascertain the versatility and selectivity of this synthetic method on different substrates (Scheme 1).

An isotopic exchange reaction on **1** has previously been carried out with D_2O under phase transfer conditions in the presence of *t*-BuOK, *n*-Bu_4NBr and benzene without microwave irradiation, but no details of the method were described.[11] According to earlier papers, the isotope exchange reactions of **1**–**3** were carried out using strong alkaline conditions, heating for 12 h, salting out the test material and repeating the procedure nine or ten times giving 100% deuteriation on the 1,1,1,3,3 positions of the ketones.[11–13]



$$CH_3\overset{O}{\overset{\|}{C}}CH_2(CH_2)_4CH_3 \xrightarrow[\text{microwave}]{D_2O/CF_3COOD} CD_3\overset{O}{\overset{\|}{C}}CD_2(CH_2)_4CH_3$$

1 **1a**

Scheme 1. Deuterium labelling of ketone derivatives.

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* Corresponding author. Fax: +36-1-392-2215; e-mail: fodor@szfki.hu

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2,2,2-Trideuterio-1-phenylethanone was obtained either in alkaline conditions[14a,b,d] or by heating 1-phenylethanone at 400–410°C in deuterium oxide for 12 hours under supercritical pressure.[14c]

According to our investigations, the acid-catalyzed exchange reaction on **1** with thermal activation yielded less deuteriation even under more drastic experimental conditions (480 min at reflux) (Table 1). Similar results were obtained with analogous ketones such as **2** and **3**. A lower deuterium incorporation was achieved with aromatic ketones **4** and **5**, with no interference from the aromatic protons using either power or thermal control of the microwave reaction (Table 1). We suggest that acid promoted enolization of the ketone takes place, which can accelerate the exchange in the strong deuteriating medium.

For high efficiency, deuterotrifluoroacetic acid and heavy water were applied in large excess to facilitate exchange of the protons of 2-octanone. After 15 min irradiation, essentially quantitative deuteriation of the carbon atoms alpha to the carbonyl group was detected by ^{1}H NMR. During work-up of the reaction mixture under acidic conditions a significant decrease down to 90–85% of the deuterium content occurred. Therefore, 2-octanone-d_5 **1a** had to be extracted very quickly and the mixture neutralized in order to avoid the back-exchange reaction.

In conclusion, in this work microwave-assisted deuterium exchange has been used on a preparative scale and shown to be rapid, selective and isotope-efficient.

1,1,1,3,3-Pentadeuterio-2-octanone 1a: 2-octanone (2.0 g, 15.6 mmol), CH_3COOD (5 ml, 64.9 mmol) and D_2O (20.00 ml) were introduced into a tube equipped with a mechanical stirrer, reflux condenser and placed in a Prolabo Synthewave 402 focused microwave reactor (600 W). The reaction mixture was irradiated for 15 min with power control at about 90°C (2 min 100% and 13 min 20%). The reaction mixture was extracted quickly with carbon tetrachloride, washed with 5% $NaHCO_3/D_2O$ solution, dried over anhydrous sodium carbonate, evaporated and distilled at 173°C, 1.6 g, (80%). IR (neat): 2957 ($\nu_{as}CH_3$), 2931 ($\nu_{as}CH_2$), 2874 (ν_sCH_3), 2859 (ν_sCH_2), 2253 ($\nu_{as}CD_3$), 2216 ($\nu_{as}CD_2$), 2176 (ν_sCD_3), 2121 (ν_sCD_2), 1713 ($\nu C{=}O$) cm^{-1}. ^{1}H NMR (400 MHz, δ ppm, $CDCl_3$): 0.84 (t, 3H, H8), 1.56 (m, 2H, H7), 1.25–1.32 (m, 6H, H6+H5+H4), 2.12 (s+m, 0.3H, H1), 2.40 (t+m, 0.2H, H3). MS *m*/*e*: 133 (M^+).

1,1,1,3,3-Pentadeuterio-2-pentanone 2a: 2-pentanone (2.9 g, 33.4 mmol), heavy water 6.0 g (300.0 mmol) and trifluoroacetic acid (4.9 g, 42.5 mmol) were irradiated in the same reaction flask at 90°C with power control (2 min 100% and 13 min 25% of power). After cooling to room temperature, the reaction mixture was extracted with diethyl ether, dried over anhydrous sodium hydrogencarbonate and distilled at 100.0–102.4°C on 300 mm Vigreux column. The deuteriation rate was 98%, (2.4 g. 84%). IR (neat): 3000–2800 ($\nu_{as}CH_3$, $\nu_{as}CH_2$, ν_sCH_3, ν_sCH_2), 2254 ($\nu_{as}CD_3$), 2218 ($\nu_{as}CD_2$), 2181 (ν_sCD_3), 2142 (ν_sCD_2), 1713 ($\nu C{=}O$), 1254 (δ_sCD_3) cm^{-1}. ^{1}H NMR (400 MHz, δ ppm, $CDCl_3$): 0.93 (3H, t, C5-H3), 1.60 (2H, q, C4-H2), 2.10 (0.8H, m, C1-H3), 2.38 (0.54 H, m, C3-H2).

The same reaction mixture was heated under reflux for 6 h at normal pressure. The reaction mixture was worked up the same way as above. Repeated treatment for 2 h under the same conditions using a new deuterium source gave 98% deuteriation on the C1 and C3 carbons, 2.2 g (75%).

1,1,1,3,3-Pentadeuterio-4-methyl-2-pentanone 3a: 4-methyl-2-pentanone (2.4 g, 24.00 mmol), trifluoroacetic acid-d_1 (5.9 g, 56.2 mmol) and heavy water (7.0 g, 350.0 mmol) were irradiated with the power control (as above **1a**) for 15 min. The reaction mixture was extracted with carbon tetrachloride, dried over anhydrous sodium carbonate, and distilled on a Vigreux column (300 mm). Fractions boiling at 126–127°C were collected, 1.9 g (77%).

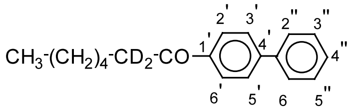
The thermal treatment of the reaction mixture gave a similar result after 9 h reflux. The work up of the

Table 1. Typical deuterium incorporation extent (D) with D_2O/CF_3COOD under different conditions

Substrate	Method	Power	Temperature (°C)	Time	D (%)
1	Microwave	90	90	15 min	96
	Thermal	–	Reflux	480 min	85
	Thermal	K_2CO_3	Reflux	120 h	99[12a]
2	Microwave	80	90	15 min	90
	Thermal	–	Reflux	480 min	75
	Thermal	K_2CO_3	Reflux	120 h	99[13a,b]
3	Microwave	80	90	15 min	85
	Thermal	–	Reflux	540 min	90
4	Microwave	90	90	20 min	75
	Thermal	–	20	1 month	66
	Thermal	–	Reflux	24 h	68
5	Microwave	80	90	20 min	95
	Thermal	–	Reflux	540 min	90
	Thermal	–	20	1 week	66

reaction mixture was similar as described above. IR (neat): 3000–2800 ($\nu_{as}CH_3$, $\nu_{as}CH_2$, ν_sCH_3, ν_sCH_2), 2254 ($\nu_{as}CD_3$), 2216 ($\nu_{as}CD_2$), 2169 (ν_sCD_3), 2133 (ν_sCD_2), 1713 (νC=O) 1251 (δ_sCD_3) cm^{-1}. ^{1}H NMR: (400 MHz, δ ppm, $CDCl_3$) 0.92 (6H, d, $J=6.8$ Hz, C4-H, C5-H3), 2.08 (0.42H, m, C1-H3), 2.10 (1H, m, $J=6.8$ Hz C4-H), 2.28 (0.33H, m, C3-H2).

2,2-Dideuterio-4-*n*-heptanoylbiphenyl 4a: Trifluoroacetic acid-d_1 (11.5 g, 100 mmol) and 4-*n*-heptanoylbiphenyl **4** (2.7 g, 10.0 mmol) were irradiated for 15 min using the same conditions as described under **1a**. The acid was removed by distillation and the residue was treated with ethanol until it became neutral 2.3 g, (86%). IR (KBr): 3000–2800 ($\nu_{as}CH_3$, $\nu_{as}CH_2$, ν_sCH_3, ν_sCH_2), 1674 (νC=O), 1601 ($\nu C_{Ar}C_{Ar}$), 1280 (β_sCD_2), 839 ($\gamma C_{Ar}H$, *p*-disubst.), 761 ($\gamma C_{Ar}H$, phenyl) cm^{-1}.



^{1}H NMR (400 MHz, δ ppm, $CDCl_3$): 0.9 (3H, t, CH_3), 1.3–1.8 (m, 4×CH_2), 2.98 (m, 0.65H, CO-C(HD)$_2$), 7.4 (m, 1H, H4″), 7.48 (m, 2H, H3″+H5″), 7.62 (d, 2H, H2″+H6″), 7.68 (d, 2H, H3′+H5′), 8.02 (d, 2H, H2′+H6′).

The same reaction mixture was heated under reflux for 24 h, its work-up was the same as above, 2.1 g (79%). Similar deuteriation rate was achieved, when the reaction mixture was allowed to stand at room temperature for one month, 2.4 g (89%).

2,2,2-Trideuterio-1-[4-*n*-heptylbiphenyl]ethanone 5a: Trifluoroacetic acid-d_1 (11.5 g, 100.0 mmol) and **5** (2.0 g, 6.8 mmol) were irradiated for 15 min in a microwave oven with power control (20% of 300 W). Finally the trifluoroacetic acid-d_1 was distilled off, then ethyl methyl ketone was added and distilled to remove the traces of the acid. The solid residue was crystallized from absolute ethanol, 1.8 g (90%). IR (KBr): 3054, 3034 ($\nu C_{Ar}H$), 3000–2800 ($\nu_{as}CH_3$, $\nu_{as}CH_2$, ν_sCH_3, ν_sCH_2), 1678 (νC=O), 1602 ($\nu C_{Ar}C_{Ar}$), 1294 (β_sCD_3), 826 ($\gamma C_{Ar}H$, *p*-disubst.) cm^{-1}. ^{1}H NMR (400 MHz, δ ppm, $CDCl_3$): 0.89 (t, 3H, CH_3), 1.25–1.40 (m, 8H, 4×CH_2), 1.62 (m, 2H, CH_2), 2.64 (m, 0.1H, $COCD_3$), 7.27 (m, 2H, H2′, H6′), 7.54 (m, 2H, H3′+H5′), 7.67 (m, 2H, H2″+H6″), 8.01 (m, 2H, H3″+H5″).

2,2-Dideuterio-1-[4-*n*-heptylbiphenyl]ethanone 5b: Heavy water (99%) (2.7 g, 130.0 mmol) was added dropwise under cooling to trifluoroacetic anhydride (27.4 g, 130.4 mmol) and the resulting trifluoroacetic acid-d_1 (30.0 g, 260.0 mmol) was used for the exchange reaction of **5** (10.0 g, 34.01 mmol) at room temperature for 1 week, 9.5 g (95%).

IR (KBr): 3054, 3034 ($\nu C_{Ar}H$), 3000–2800 ($\nu_{as}CH_3$, $\nu_{as}CH_2$, ν_sCH_3, ν_sCH_2), 1678 (νC=O), 1602 ($\nu C_{Ar}C_{Ar}$), 1294 (β_sCD_2H), 826 ($\gamma C_{Ar}H$, *p*-disubst.) cm^{-1}. ^{1}H NMR (400 MHz, δ ppm, $CDCl_3$): 0.89 (t, 3H, CH_3), 1.25–1.40 (m, 8H, 4×CH_2), 1.62 (m, 2H, CH_2), 2.64 (m, 1H, $COCD_2H$), 7.27 (m, 2H, H2′, H6′), 7.54 (m, 2H, H3′+H5′), 7.67 (m, 2H, H2″+H6″), 8.01 (m, 2H, H3″+H5″). MS: $M^+=296$, M^+-$CD_2H=279$.

^{1}H NMR spectra were recorded on a Varian XL-400 instrument in $CDCl_3$ solution at room temperature. ^{1}H assignments, if necessary, were performed with the aid of homonuclear spin-decoupling experiments. IR spectra (resolution 4 cm^{-1}) were recorded on a Nicolet Magna 750 FT-IR spectrometer on KBr discs.

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