

## Specific Monodeuteration of Chalcones and Related Compounds

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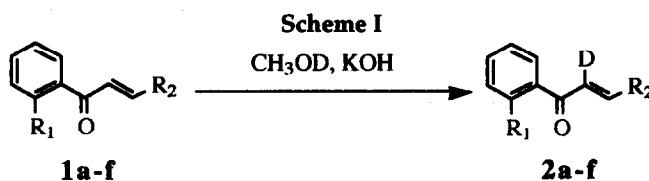
**Abstract:** The selective deuterations of several chalcones and related flavonoids were carried out with a catalytic amount of KOH in methanol-d<sub>1</sub>. Product formation showed exclusively  $\alpha$ -deuteration with the exception of 2-styrylchromone, which was completely deuterated at the  $\gamma$  position. Product formations were verified by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy and several reactions were monitored by <sup>1</sup>H NMR spectroscopy.

The flavonoids are a class of heterocyclic natural products that are prevalent throughout the plant kingdom. Both natural and synthetic flavonoids are known to possess important biological properties and are used in the agricultural, food, and pharmaceutical industries.<sup>1</sup> The newest class of natural flavonoids, 2-styrylchromones, have exhibited potent cytotoxicity against several human cancer cells *in vitro*.<sup>2</sup>

Frequently, the selective incorporation of an isotopic label into pharmacologically active compounds is necessary in order to evaluate the metabolic fate of these molecules *in vivo*. In our work on the synthesis and biological assessment of several chalcones, flavones (2-phenylchromones), and 2-styrylchromones,<sup>3</sup> a general, specific  $\alpha$ -deuteration reaction was unveiled. To our knowledge, this is the first chemical (non-enzymatic) approach to such labeling.

The general reaction involves the treatment of an  $\alpha,\beta$ -unsaturated ketone type compound (1) with KOH in CH<sub>3</sub>OD according to the conditions in Scheme I. The reactions typically resulted in a virtual quantitative transformation with 95-100% conversion to the

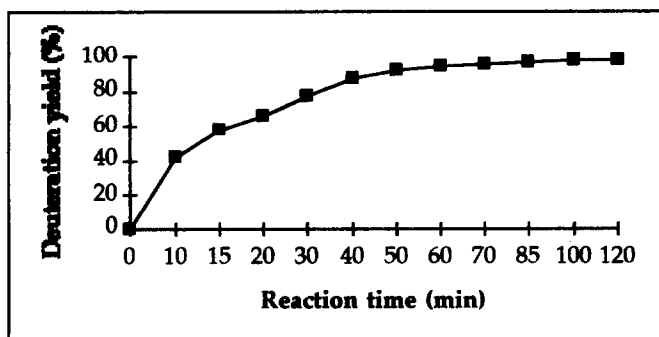
corresponding  $\alpha$ -D labeled compounds (**2**). All products were characterized by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy.<sup>4-6</sup>



Starting Material <sup>a</sup>	R <sub>1</sub>	R <sub>2</sub>	Product	mol equiv. of KOH	Time (h)	Temp. (°C)
<b>1a</b>	H	<i>o</i> -OMeC <sub>6</sub> H <sub>4</sub>	<b>2a</b>	0.25	24	r.t.
<b>1a</b>			<b>2a</b>	0.25	2	50
<b>1b</b>	H	<i>p</i> -OMeC <sub>6</sub> H <sub>4</sub>	<b>2b</b>	0.25	2	50
<b>1c</b>	H	C(CH <sub>3</sub> ) <sub>3</sub>	<b>2c</b>	0.25	2	50
<b>1d</b>	OH	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	<b>2d</b>	1.5	2	50
<b>1e</b>	OH	C(CH <sub>3</sub> )=CHC <sub>6</sub> H <sub>5</sub>	<b>2e</b>	1.5	2	50
<b>1f</b>	OH	CH=CHC <sub>6</sub> H <sub>5</sub>	<b>2f</b>	1.5	2	50

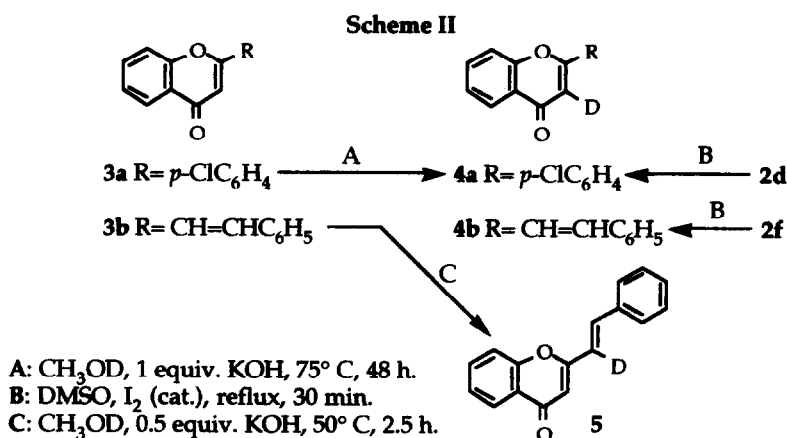
<sup>a</sup> Reactions were usually run with 50 mg of ketone in 2-3 mL of CH<sub>3</sub>OD.

The deuteration of **1a** was monitored by  $^1\text{H}$  NMR spectroscopy. After approximately one hour, the reaction was nearly complete (Fig. I).



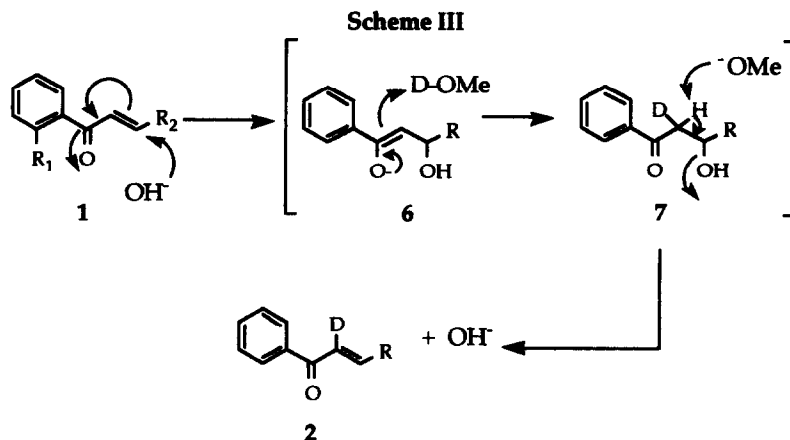
**Figure I:** Reaction of 2-methoxychalcone (**1a**) with 0.25 equiv. of KOH in CD<sub>3</sub>OD at 50 °C.

In an attempt to determine the scope of this reaction, a flavone (3a) and a 2-styrylchromone (3b) were subjected to reaction conditions similar to those in Scheme I. The unreactivity of the C<sub>2</sub>-C<sub>3</sub> double bond in these molecules is well documented,<sup>7</sup> and thus it was not surprising that more rigorous reaction conditions were required to obtain the 3-deuterio derivatives. In the case of flavone 3a, after 48 hours at 75° C with 1.0 equivalent of KOH, 96% α-deuteration was observed. The same deuterated product could also be obtained efficiently *via* the oxidative cyclization<sup>3</sup> of 2d (Scheme II).



Treatment of 2-styrylchromone 3b under the deuteration conditions shown in pathway C, Scheme II, resulted in complete deuteration at the γ position (compound 5) in 2.5 hours. However, a small amount of α-deuteration was also observed. This is in contrast to the α-deuteration results obtained from dienone 1f which shows no γ substitution. And α-D-2-styrylchromone (4b) was prepared *via* the oxidative cyclization<sup>3</sup> of 2f (Scheme II).

When 1a was heated in CH<sub>3</sub>OD at reflux without any amount of KOH no deuteration occurred. A mechanism that is consistent with the observed α deuteration (and γ deuteration in the formation of compound 5) involves initial attack of OH<sup>-</sup> at the β (or δ for 3b) position to give an enolate-like intermediate (6, Scheme III). Low-temperature <sup>1</sup>H NMR studies of the α-deuteration of 1a did not show any new aliphatic proton signals; thus, the tetrahedral intermediate 7 appears to be short-lived relative to the NMR timescale. The recovery of KOH at the end of the reaction (typically 0.25-0.5 mol equiv.) suggests a catalytic mechanism.



Determination of the optimum reaction conditions as well as studies with other nucleophiles and compounds are currently underway.

**Acknowledgements:** The authors would like to thank "Centro de Química" of the University of Aveiro for support of this project. Thanks are also due to JNICT, Lisbon, for the grant 1M/90 to buy the Bruker AMX 300 spectrometer. W.A.P. thanks the J. William Fulbright Foundation for a research fellowship to the University of Aveiro.

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4.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were determined at 300 and 75 MHz respectively. For compounds **2a-f**, the chemical shifts ( $\delta$ , ppm from TMS) of H- $\beta$  in the  $^1\text{H}$  NMR and C- $\alpha$  in  $^{13}\text{C}$  NMR spectra are listed. Coupling constants were determined when possible ( $J$ , Hz): **2a**. 8.12 (t,  $J$  2.0); 122.5 (t,  $J$  24). **2b**. 7.76 (s, br); 119.5 (t,  $J$  23). **2c**. 7.06 (t,  $J$  2.1); 120.7 (t,  $J$  24). **2d**. 7.87 (s, br); 120.3 (t,  $J$  22). **2e**. 7.74 (s, br); 119.1 (t,  $J$  23). **2f**. 7.76 (m, br); 123.1 (t,  $J$  24).
5. C- $\alpha$  in  $^{13}\text{C}$  NMR spectrum: **4a**. 107.4 (t,  $J$  26). **4b**. 110.4 (t,  $J$  26).
6. H- $\delta$  in  $^1\text{H}$  NMR and C- $\gamma$  in  $^{13}\text{C}$  NMR spectra: **5**. 7.68 (s, br); 120.0 (t,  $J$  24).
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