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Expedient microwave deuteration of estrone in CF_3COOD

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Abstract—A rapid and efficient deuteration procedure was developed for estrone. Irradiation of estrone in CF_3COOD in a microwave oven gave [2,4,16,16-$^2H_4$]-estrone in 95% yield. Ultrasound and CF_3COOD reflux deuterations of estrone were also studied. © 2002 Published by Elsevier Science Ltd.

The role of estrogen metabolites in the formation of cancer is under active study.[1] Isotopic dilution gas chromatography–mass spectrometry with selected ion monitoring (ID GC–MS SIM) has proved to be the most specific method for quantitation of these metabolites, and this requires the availability of deuterated internal standards. Deuterated estrone itself can be utilized as the starting material for the synthesis of many of these metabolite standards.

In the literature, [2,4,16,16-$^2H_4$]-estrone **1** has been prepared by a number of acid-catalyzed methods, many of them relying on vacuum glass ampoule techniques, however. Treatment of estrone with 0.9N DCl in dioxane for 90 h at 55°C gave a product in 35% yield of which 80% consisted[2] of **1**. Vining et al.[3] reacted estrone with D_2O without any catalyst in a vacuum ampoule at 190°C for 24 h, and reported that the d_4 species **1** was obtained in high yield. In a widely cited route to **1**, Dehennin et al.[4] used a two-step procedure involving an initial exchange of the two C-16 hydrogen atoms (0.5N NaOD in MeOD) followed by the exchange of the aromatic protons (0.5N DCl in MeOD), both steps in a glass ampoule in vacuo (24 h at 60°C). The d_4 species was present in 82.4% yield of total estrones. However Block and Djerassi[5] deuterated estrone with NaOD under reflux in D_2O for 72 h, obtaining 69% of the 4,16,16-trideuterated product.

We report here a new efficient acid catalyzed method for the deuteration of estrone, employing CF_3COOD which we have used previously for the deuteration of isoflavonoids.[6] We also show that microwave heating[7,8] is far superior to ultrasound[9] or simple reflux[10] in terms of reaction time and yield of d_4 species (see Table 1). After the reaction, the phenolic OD was back-exchanged to OH by dissolution in ethanol to avoid analytical problems resulting from uncontrolled exchanges.

Deuterated samples were analyzed with GC–MS and ^1H NMR and the spectra compared with those of unlabelled estrone to determine the deuterium content.

Optimal conditions for the d_4 species involve microwave irradiation for 8 min at 650 W with a halfway addition of a fresh portion of CF_3COOD. Almost the same yield of the d_4 product is obtained by refluxing estrone in CF_3COOD for 2×3 h. Stirring at room temperature for 2 h, or microwave irradiation for 10 s at 350 W incorporated deuterium to C-2 and C-4 only. Sonication did not improve deuteration levels compared to normal conditions. We conclude that in terms of expediency, overall yield and specific yield of the d_4 species, the method of choice for **1** consists of a treatment of estrone with CF_3COOD under microwave irradiation.

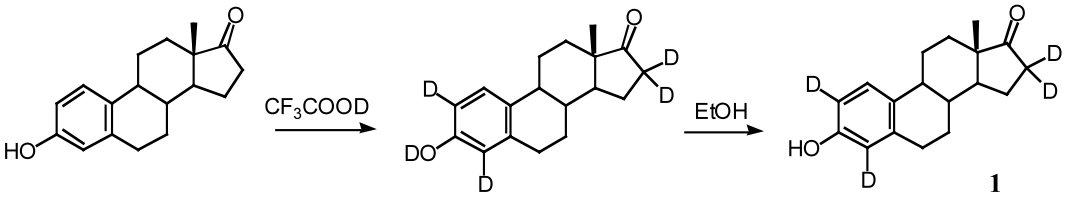

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Table 1. Deuterium distribution[a] in deuterations of estrone with CF_3COOD

Microwave power (W)	Time	d_0	d_1	d_2	d_3	d_4	d_5
350	10 s	4	5	89	2		
500	10 s	2	12	36	46	1	2
500	1 min	1	4	11	70	13	1
350	5 min	1	3	9	27	60	0
350	2×5 min[b]	1	1	4	23	69	1
500	5 min	2	2	6	11	76	2
650	5 min	1	2	6	13	79	0
650	2×5 min[b]	0	1	2	2	94	2
650	2×4 min[b]	0	0	2	2	95	1
Ultrasound temp.							
Rt	30 min	3	4	85	8		
70°C	30 min	1	4	40	50	1	3
70°C	4 h	1	3	16	52	19	10
Room temperature or under reflux							
Rt	30 min	2	18	78	2		
Rt	2 h	3	6	89	2		
70°C	4 h	0	1	9	50	28	10
Reflux	1 min	1	4	40	49	2	3
Reflux	1 h	1	1	5	35	58	0
Reflux	2 h	1	1	4	31	63	0
Reflux	3 h	1	1	2	10	81	8
Reflux	2×3 h[c]	0	0	2	2	92	5
Reflux	20 h	0	2	4	13	67	13

[a] The deuterium distribution is measured by GC–MS analysis (Varian Saturn 2000) and converted to percentages taking into account the M–1 and M+1 peaks of unlabelled estrone; figures are rounded to the nearest whole number.
[b] A fresh portion of CF_3COOD was added between irradiations.
[c] After 3 h, the mixture was evaporated and a fresh portion of CF_3COOD added.

Acknowledgements

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8. Microwave oven procedure: 20 mg (0.074 mmol) of estrone was placed in a Teflon™ tube and 0.57 ml (200 equiv.) of CF_3COOD[11] was added. The tube was heated in a microwave oven (Whirlpool Vip20, a commercial household microwave oven); for reaction times and power settings, see Table 1. After irradiation the solution was evaporated to dryness. The back-exchange of –OD to –OH was performed by dissolving the residue in ethanol and evaporation. The quantitative crude product was dissolved in ethyl acetate and filtered through silica. Recrystallization from 70% ethanol gave white crystals of [2,4,16,16-$^2H_4$]-estrone **1**, mp 258–259°C (lit.[2] 257–260°C); δ_H ($CDCl_3$, 200 MHz) 7.16 (1H, s, H-1), 4.77 (1H, Ar-OH), 2.8 (2H, m, H-6), 1.4–2.4 (11H, m), 0.91 (3H, s, CH_3); δ_C ($CDCl_3$, 200 MHz) 13.8 (C-18), 21.4 (C-15), 25.9 (C-11), 26.5 (C-7), 29.4 (C-6), 31.5 (C-12), 35 (m, C-16), 38.4 (C-8), 44.0 (C-9), 48.1 (C-13), 50.4 (C-14), 113 (t, C-2), 115 (t, C-4), 126.4 (C-1), 132.0 (C-10), 138.0 (C-5), 153.5 (C-3), 221.4 (C-17).
9. Ultrasound procedure: estrone (20 mg) and 0.57 ml (200 equiv.) of CF_3COOD were sonicated using reflux condenser (Finnsonic m03 apparatus). The mixture was then evaporated to dryness. The exchange of –OD to –OH was performed as above.
10. Reflux procedure: estrone (100 mg) was refluxed in 2.85 ml (200 equiv.) of CF_3COOD and then evaporated to dryness. The exchange of –OD to –OH was performed as above.
11. Trifluoroacetic anhydride (1 equiv.) is refluxed in 2 equiv. of D_2O for 30 min.