Preparation of Cinnamic Acids Labelled with Deuterium or Tritium at the α-Position

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Summary (*E*)-[α-^{2}H]- and (*E*)-[α-^{3}H]Cinnamic acids can be easily obtained from the corresponding α-trimethylammonio-acids (or their ester halides) *via* Hofmann elimination in deuteriated and tritiated water respectively.

We report here a simple method for the synthesis of (*E*)-cinnamic acids (III) labelled with isotopic hydrogen at the α-position based on the Hofmann decomposition of α-trimethylammonio-acids (I) or their ester halides (II) in deuteriated or tritiated water (Scheme).

The following procedures for the exchange and elimination stages were employed:† (A) The α-amino-acid hydrochloride (2 mmol) was heated with an excess of MeI and dry Ag_2O in D_2O (99·75% D; 5 ml) under reflux for 2 h; this mixture was filtered, acidified with conc. HCl, filtered again, made alkaline with solid NaOH (30%) and kept at room temperature for 24 h and at 100° for 2 h: phenylalanine, 4-methoxyphenylalanine, and 3,4-dimethoxyphenylalanine gave (*E*)-[α-^{2}H]cinnamic acid (63% yield; 0·82 D atom/molecule), (*E*)-4-methoxy[α-^{2}H]cinnamic acid (59%; 0·89), and (*E*)-3,4-dimethoxy[α-^{2}H]cinnamic acid (41%; 0·88) respectively. (B) The α-dimethylamino-acid[1] (0·5 mmol) was treated with MeI (0·8 mmol) in alkaline D_2O (1 ml, 30% NaOH) and kept at r.t. for 24 h and at 100° for 2 h: *NN*-dimethylphenylalanine gave (*E*)-[α-^{2}H]cinnamic acid (96%; 0·78). (C) The α-trimethylammonio-acid ethyl ester iodide[2] (0·5 mmol) was dissolved in alkaline D_2O (2 ml, 30% NaOH) and kept under N_2 at 0° for 1 h and at 100° for 2 h: (II; Ar = *p*-OH-C_6H_4, R = Et, X = I; m.p. 185—186°) gave (*E*)-[α-^{2}H]-*p*-coumaric acid (54%; 0·90). Procedure (C) is recommended for preparing acids containing groups which are readily methylated under exhaustive methylation conditions.

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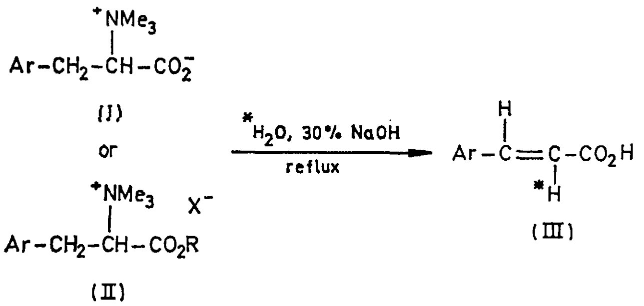
† In each case, after acidification of the reaction mixture, the αβ-unsaturated acid was extracted with ether, washed with natural water, and checked for identity and purity by elemental analysis, t.l.c., and g.l.c. of its methyl ester. The specificity of labelling determined by n.m.r. and m.s. Deuterium content was measured by m.s. (only $^{2}H_{0}$ and $^{2}H_{1}$ species were found).



Scheme

These results, together with the finding that neither phenylalanine nor cinnamic acid exchange their α-hydrogen for deuterium when heated in alkaline D_2O, are consistent with a base-catalysed formation of stable ammonium ylides[3] from (I) and (II); in addition, the specificity of labelling (as shown by n.m.r. and m.s.) indicates that the Hofmann elimination proceeds by the *E*2 mechanism without significative contribution of the *E*1c*B* route.[4]

(*E*)-[2-^{3}H]Cinnamic acid (spec. act. 7·5 mCi/mmol) has been obtained by procedure (B) (98% yield; 1 ml ^3H_2O act. 5 Ci). The synthesis of other (*E*)-[2-^{3}H]cinnamic acids is under way.

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