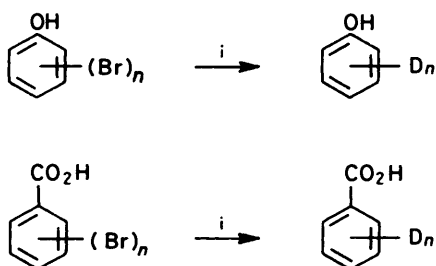


Preparation of Deuteriated 1-Phenylethanols by Reductive Dehalogenation of the Corresponding Halogenoacetophenones with Raney Alloys in an Alkaline Deuterium Oxide Solution

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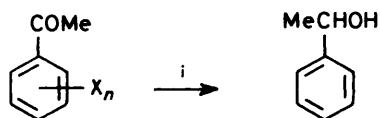
Deuteriated 1-phenylethanols were prepared by reductive dehalogenation of the corresponding halogenoacetophenones with Raney Ni–Al and Cu–Al alloys in 5% NaOD–D₂O solution. It was found that the Ni–Al alloy introduced greater than expected numbers of deuterium atoms in the phenyl ring, but the expected deuteriated 1-phenylethanols were obtained in high yield and in high isotopic purity when Raney Cu–Al alloy was used.

It has been previously reported that reductive dehalogenation of bromophenols¹ and bromobenzoic acids² with Raney Cu–Al alloy in 10% NaOD–D₂O solution afforded the corresponding deuteriated phenols and benzoic acids respectively in high yield and high isotopic purity (Scheme 1).



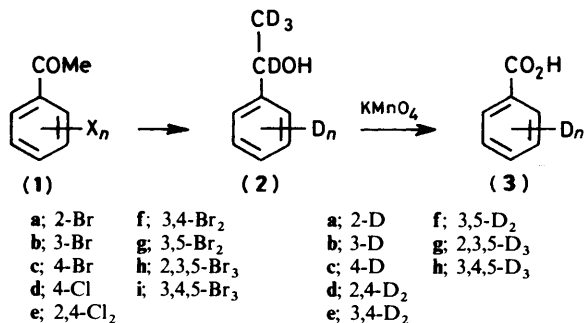
Scheme 1. Reagent: i, Cu–Al in 10% NaOD–D₂O

Recently, we found that³ treatment of halogenoacetophenones with Raney alloys in 5% NaOH–H₂O solution afforded 1-phenylethanol in good yield (Scheme 2).



Scheme 2. Reagent: i, Raney-Alloy in 5% NaOH–H₂O

As deuteriated polystyrene is of interest as plastic optical fibre and styrene can be prepared from 1-phenylethanol, the above reductive dehalogenation was applied to the preparation of deuteriated 1-phenylethanols which possess deuterium atom(s)



Scheme 3.

at specific position(s) of the aromatic ring. The results are given below.

Results and Discussion

Halogenoacetophenones (1a–i) were reduced with Raney alloys such as Ni–Al and Cu–Al in 5% NaOD–D₂O solution to give the corresponding deuteriated 1-phenylethanols (2a–h). The results are summarized in Table 1.

¹H N.m.r. spectra of compound (2) indicated that all the hydrogen atoms on the methyl group had been displaced by deuterium during the reduction under basic conditions. The deuteriated positions of the ring could not be determined on the basis of the pattern of aromatic signals of compound (2); it was therefore converted into the corresponding deuteriated benzoic acid (3a–h) and, by comparing their ¹H n.m.r. spectra with those previously reported, the deuteriated position was confirmed. The isotopic purity was determined by mass spectroscopy of compound (3).

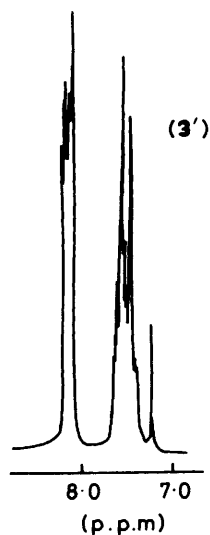
The expected deuteriated 1-phenylethanols (2a–h) were obtained in high yield and in high isotopic purity when Raney Cu–Al alloy was used. However, a greater number of deuterium atoms than expected were introduced into the phenyl ring in the reduction with Ni–Al alloy and compound (2c) was obtained in low isotopic purity from *p*-bromo- (1c) and *p*-chloro-acetophenone (1d). The same phenomenon was observed in the reductive dehalogenation of halogenophenols¹ and halogenobenzoic acids.² The over-introduction of deuterium atoms was partially suppressed by irradiation with ultrasound during the reduction but this resulted in low isotopic purity. When acetophenone itself was treated with Ni–Al alloy in 5% NaOD–D₂O solution, a mixture of the deuteriated 1-phenylethanols (2') was obtained. In the ¹H n.m.r. spectrum of the corresponding mixture of benzoic acids (3') shown in the Figure, the relative ratio of the peak area of *ortho* (centred at 8.10 p.p.m.) and *meta* and *para* protons (centred at 7.50 p.p.m.) is ca. 1:1. This means that hydrogen-deuterium exchange reaction occurs mainly at the *para* and *meta* positions in acetophenone as well as in benzoic acid,² thus supporting the previously proposed mechanism,² and confirming that the mixture (3') contains mainly (3b) and (3c), and the mixture (2') contains (2b) and (2c).

The reductive method may be applicable to the preparation of [²H₉]1-phenylethanol (2i), but pentahalogenoacetophenones are not easily accessible. On the other hand, the easily obtainable 2,4,6-trichloroacetophenone (1j) was expected, on treatment with Ni–Al alloy, to give compound (2i) by reductive dehalogenation and coincident hydrogen-deuterium exchange on *meta* positions of the ring, however the results were un-

Table 1. Reduction of halogenoacetophenones (1a–i) with Raney alloys in 5% NaOD–D₂O solutions at 50 °C for 30 min^a

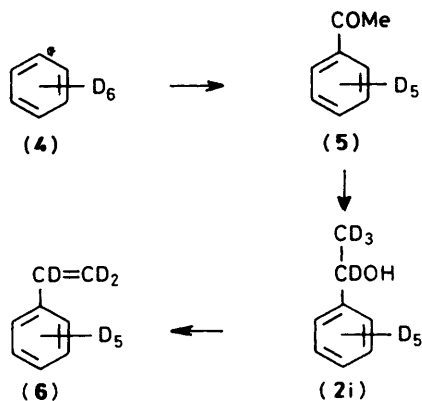
Run	Substrate	Alloy	Product (2) (%) ^b	Composition of (3) ^c					
				D ₀	D ₁	D ₂	D ₃	D ₄	D ₅
1	(1a)	Cu–Al	(2a) 89	8	89	1	0	0	0
2	(1b)	Cu–Al	(2b) 86	5	95	0	0	0	0
3	(1c)	Ni–Al	(2c) 86	4	19	27	30	14	16
4	(1c) ^d	Ni–Al	(2c) 87	18	67	9	4	1	1
5	(1c)	Cu–Al	(2c) 90	6	93	1	0	0	0
6	(1d)	Ni–Al	(2c) 86	4	19	29	31	14	3
7	(1d) ^d	Ni–Al	(2c) 88	15	54	18	8	4	1
8	(1d)	Cu–Al	(2c) 86	8	92	0	0	0	0
9	(1e)	Cu–Al	(2d) 81	0	8	91	1	0	0
10	(1f)	Cu–Al	(2e) 85	0	7	91	1	0	0
11	(1g)	Cu–Al	(2f) 86	0	6	91	3	0	0
12	(1h)	Cu–Al	(2g) 81	0	0	7	91	1	1
13	(1i)	Cu–Al	(2h) 82	0	2	22	76	0	0

^a To a mixture of (1) (5 mmol) in 5% NaOD–D₂O (10 ml) was added 0.125 g of the alloy [per atom of the halogen of (1)] at 10 min intervals, 10 times. ^b Isolated yields are shown. ^c The compositions were obtained by mass spectroscopy. ^d Irradiated with ultrasound.

**Figure.**

satisfactory; both yield (23%) and isotopic content (86%) of the obtained compound (2i) were low.

Compound (2i) was therefore prepared in high isotopic content from [²H₆]benzene via [²H₅]acetophenone (5),⁴ (Scheme 4 and Table 2) and converted into [²H₈]styrene (6) with 92% isotopic content.

**Scheme 4.****Table 2.** Deuterium content of compounds (5), (2i), and (6)

Compound	Deuterium content (%)			
	Ring	1-position	2-position	Total
(5)	94–96 ^a			
	93–96 ^b			
(2i) ^c	96	96	96	96
(6) ^c	94	91	91	92

^a Determined by ¹H n.m.r. ^b By mass spectroscopy. ^c By ¹H n.m.r. with CHCl=CCl₂ as an internal standard.

Experimental

N.m.r. spectra were determined at 100 MHz on a Nippon Denshi JEOL FT-100 n.m.r. spectrometer with Me₄Si as an internal reference. Mass spectra were obtained on a Nippon Denshi JMS-01-SA-2 spectrometer at 75 eV by using a direct-inlet system.

Halogenoacetophenones.—Compounds (1a), (1b), (1d), and (1e) were commercially available and (1c),⁵ and (1f),⁶ were prepared according to literature methods.

Preparation of 3,5-Dibromoacetophenone (1g).—Concentrated sulphuric acid (7.5 ml) was added gradually to a solution of 4-amino-3,5-dibromoacetophenone (8.78 g, 30 mmol) in benzene (15 ml) and ethanol (100 ml) at 50 °C. The reaction mixture was refluxed for 3 h, after which 20 ml of the solvent was distilled off. To the residue was added gradually, below 10 °C, a solution of sodium nitrite (4.3 g, 62 mmol) in a small amount of water, followed by copper powder. The mixture was refluxed for a further 3 h, the insoluble materials were filtered off and water (100 ml) was added to the filtrate. Extraction with dichloromethane, washing with water, drying (Na₂SO₄) and evaporation under reduced pressure gave the crude compound (1g) (8.2 g, 98%) which was chromatographed on silica gel using benzene as eluant to afford pure (1g) as pale yellow needles (ethanol), m.p. 61–61.5 °C (lit.,⁷ m.p. 68 °C).

Preparation of 3,4,5-Tribromoacetophenone (1i).—Sodium nitrite (1.1 g, 16 mmol) was added to conc. sulphuric acid (11.8 ml) at below 0 °C and the reaction mixtures gently warmed on a water-bath⁸ to dissolve the sodium nitrite. A solution of 4-amino-3,5-dibromoacetophenone (4.0 g, 13.7 mmol) in acetic acid (60 ml) was added at below 20 °C and the reaction mixture

warmed for a further 1 h at 30 °C. A solution of CuBr (4.5 g, 31 mmol) in 36% HBr (30 ml) was added gradually to the reaction mixture with ice-water cooling; the solution was then heated at 80 °C until evolution of N₂ ceased. The reaction mixture was poured into a large amount of water and the insoluble materials collected and extracted with hot methanol. The methanol solution was evaporated under reduced pressure to leave the residue which was extracted with ethanol. The ethanol solution was evaporated under reduced pressure to leave the residues which were chromatographed on silica gel using benzene as eluant to give (1i) as pale yellow needles (ethanol), m.p. 130–132 °C (lit.,⁷ 134–135 °C).

Preparation of 2,3,5-Tribromoacetophenone (1h).—Preparation of (1h) from 2-amino-3,5-dibromoacetophenone was carried out and worked up as described above: (1h), pale reddish prisms (light petroleum), m.p. 54–55 °C; δ (CDCl₃) 2.58 (3 H, s), 7.35 (1 H, d, *J* 2.5 Hz), and 7.82 (1 H, d, *J* 2.5 Hz); *m/z* 354, 356, 358, and 360 (*M*⁺) (Found: C, 26.8; H, 1.65. C₈H₅Br₃O requires C, 26.93; H, 1.41).

General Procedure for Reduction of Halogenoacetophenones (1).—To a mixture of (1) (10 mmol) and 5% NaOD–D₂O (40 ml) was added gradually the alloy (0.125 g per atom of the halogen) at 50 °C (bath temperature) during 10 min, and the procedure was repeated 10 times. The total amount of the

alloy was 1.25 g per halogen atom of (1). After addition of the alloy was complete, the reaction mixture was stirred at 50 °C for 30 min, and the insoluble materials filtered off. The filtrate was extracted with dichloromethane, the extract was dried (Na₂SO₄) and evaporated under reduced pressure to afford the deuteriated 1-phenylethanol (2) in the yield shown in Table 1.

Oxidation of compound (2) with KMnO₄ was carried out according to the literature method⁸ to give the corresponding deuteriated benzoic acids² in almost quantitative yield.

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