SYNTHESIS OF DEUTERIATED BENZALDEHYDES

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SUMMARY

A new method for the preparation of d_1-benzaldehydes from α-keto acids in 2 steps is reported.

Key Words: Deuterium labelling, H-D Exchange, Azines, α-deuteriated Aldehydes

INTRODUCTION

Deuterium labelled compounds are useful in tracing the course of organic and biochemical reactions.[1] Moreover, deuteriated benzaldehydes are useful as intermediates for the preparation of various deuteriated compounds.[2,3] For these reasons, it is necessary that they should be selectively deuterium labelled and of high isotopic purity.

It has been reported previously that reductive dehalogenation of halogenated acetophenones[4] and benzonitrile[5] with Raney alloys in an alkaline solution afforded 1-phenylethanol and benzylamine respectively, a dehalogenation and the reduction of the substitutent occurring at the same time. Deuteriated 1-phenylethanols have been prepared by the reduction of halogenated acetophenones in a NaOD-D_2O solution under the same conditions.[6] Also, deuteriated benzylalcohols are easily obtained by reduction of the corresponding deuteriated aldehydes.[7] Chiral deuteriated alcohols have also been prepared by asymmetric reduction.[8]

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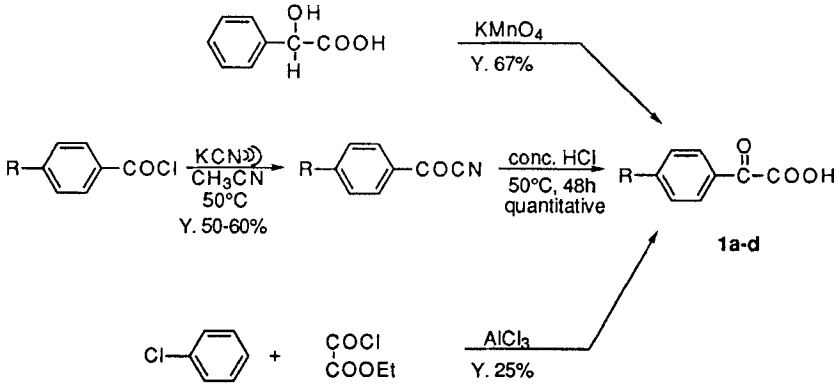
Preparation of d_1-benzaldehydes has been reported by several methods: oxidation of substituted benzyl-α-d_1-alcohols with silver carbonate[9]; deuterium oxide-hydrolysis of salts obtained from aroyl chlorides with 3-methyl-1-phenyl-2-phospholene[10]; decarboxylation of d-phenylglyoxylic acid[11,12]; hydrolysis of 2-aryl-2-deuterio-1,3-benzodithiols[13,14] and thermal decomposition of α–deuterio-methylbenzylphenyl sulfones.[15]

However, none of these reactions is entirely satisfactory and for these reasons we embarked on a study to provide a new synthetic route for *p*-substituted deuterium-labelled benzaldehydes.

RESULTS AND DISCUSSION

In a previous paper, the decarboxylation of phenylglyoxylic acid was reported to afford deuteriated benzaldehyde in high purity.[12] So, at first, we investigated the synthesis of *p*-substituted deuteriated benzaldehydes by this method using the decarboxylation of *p*-substituted phenylglyoxylic acids. α–Keto acids (**1a-d**) as the starting compounds were synthesized as shown in Scheme 1.



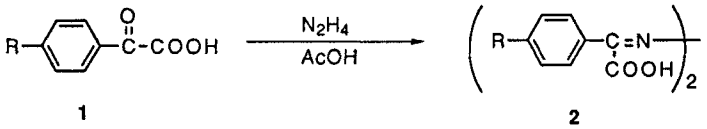
R=a: H, b: CH_3, c: CH_3O, d: Cl

Scheme 1

Phenylglyoxylic acid (**1a**) was prepared by oxidation of mandelic acid with potassium permanganate in an alkaline solution.[16] On the other hand, *p*-substituted α–keto acids (**1b-c**) were obtained by hydrolysis of the corresponding aroyl cyanides that were derived from aroyl chlorides.[17,18] The *p*-chlorobenzoyl cyanide was hydrolyzed under the same conditions, but the reaction did not give the desired *p*-chlorophenylglyoxylic acid (**1d**). Therefore, compound **1d** was prepared by Friedel-Crafts reaction of chlorobenzene with ethyloxalyl chloride.[19]

The decarboxylation of phenylglyoxylic acid (**1a**) afforded deuteriated benzaldehyde in a poor yield. We next investigated whether deuteriated benzaldehydes can be obtained by the hydrolysis of aldazines, which can be prepared by decarboxylation of azines.

Carbonyl compounds can be reacted with hydrazine hydrate to give aldazines and ketazines.[18] We investigated whether α–keto acids reacted with hydrazine hydrate under the same reaction conditions. The azines **2** were prepared as shown in Scheme 2 and Table 1.



1 **2**

Scheme 2

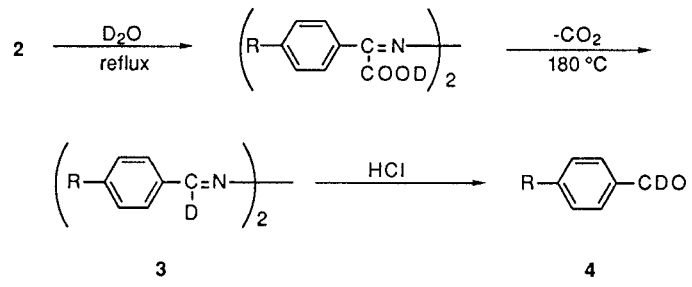
Table 1. Preparation of azine **2a-d**.

2	R	Yield(%)	m.p.(°C)(decomp.)
a	H	87	167-169
b	CH_3	87	188-189
c	CH_3O	81	172-173
d	Cl	89	171-172

When the α–keto acid **1** was treated with hydrazine hydrate in acetic acid at 0°C, azine **2** was precipitated. After filtration, azine **2** was dried in vacuo, and it was obtained in quantitative yield and in a pure state, requiring no further recrystallization.

After the azine **2** was hydrogen-deuterium exchanged by the use of deuterium oxide under argon, it was pyrolyzed at 180°C. From the reaction mixture the α–deuteriated benzaldehyde **4** was afforded by steam distillation. These results are summarized in Scheme 3 and Table 2. The azines **2a–c** were converted to α–deuteriated benzaldehydes **4a–c** in 55-65% yield and in > 93% isotopic purity. However, the reaction of azinidi-*p*-chlorophenylacetic acid **2d** under the same conditions leads to *p*-chlorobenzaldehyde **4d** in only 17% yield but 97% isotopic purity, together with *p*-chlorobenzaldazine **3d** in 41% yield and 97% of isotopic purity.

In conclusion, α–deuteriated benzaldehydes were conveniently prepared in high isotopic purities *via* their corresponding azines which could easily be prepared from the corresponding α–keto acids by reaction with hydrazine hydrate.



Scheme 3

Table2. Preparation of α-Deuterated Aldehydes **4**

	R	Yield (%)		m.p. or b.p./torr (°C)		D content of **4** by ^{1}H NMR (%)
		3	**4**	**3**	**4**	
a	H	–	65	–	48 / 0.5	93
b	CH_3	–	55	–	62 / 2.5	93
c	CH_3O	–	64	–	145 / 5	96
d	Cl	41	17	212-3	47-48	97

EXPERIMENTAL SECTIONS

Melting points were determined on a Yanagimoto micro-melting apparatus. Infrared spectra were measured on a JASCO A-102 or IR-700. Nuclear magnetic resonance spectra were obtained with a Nippon Denshi JEOL EX 270 n.m.r. spectrometer with tetramethylsilane as an internal standard.

Azine(**2**). General procedure

To a stirred solution of phenylglyoxylic acid **1a** (30 g) in acetic acid (60 ml) was gradually added hydrazine hydrate (5.0 ml) at 0 °C, and then the reaction mixture was stirred for 15 min. The yellow product was separated from the solution by filtration, washed with cold water, and dried *in vacuo* to afford the azine **2a** (25.7 g, 87%).

azinodi-phenylacetic acid(**2a**)

yellow powder; m.p. 167-169°C(decomp.) (lit.[21] 168°C); ν (KBr) 3000, 1720, 1660, 1605, 1450, 1410, 1215, 865 cm^{-1}.

azinodi-*p*-toluylacetic acid(**2b**)

yellow powder; m.p.188-189°C(decomp.)(lit[22]. 183°C); ν (KBr) 2970, 1675, 1565, 1510, 1400, 1270, 1120, 1010 cm^{-1}.

azinodi-*p*-anisylacetic acid(**2c**)

yellow powder; m.p. 188-189°C(decomp.) ; ν (KBr) 2970, 1675, 1563, 1510, 1400, 1272, 1010 cm^{-1}; δ (DMSO-d_6) 2.43(s, 3H, CH3), 7.32-7.35(m, 2H, Ar), 8.27-8.30(m, 2H, Ar)

azinodi-*p*-chlorophenylacetic acid(**2d**)

yellow powder; m.p. 171-172°C(decomp.)

ν (KBr) 1710, 1590, 1480, 1090, 1010, 825 cm^{-1}; δ (DMSO-d_6) 7.55-7.58(m, 4H, Ar), 7.93-7.97(m, 4H, Ar), 13.16(brs, 2H, COOH)

Preparation of α–deuteriated benzaldehyde (**4**). General procedure

A mixture of azine **2a** (20 g) and deuterium oxide (30 ml) was heated at reflux for 30 min under argon, and then deuterium oxide was removed by distillation at atmospheric pressure from the reaction mixture. The residue was pyrolyzed at 180°C for 30 min. After the pyrolysate was cooled to room temperature, conc. HCl (5 ml) was added to it and the mixture was subjected to steam distilled. The distillate was extracted with ether, dried over $MgSO_4$, and evaporated *in vacuo* to afford 9.4 g (65%) of the α–deuteriated benzaldehyde **4a** as a colorless oil.

benzaldehyde-d_1(**4a**)

colorless oil; b.p. 48°C/0.5torr (lit [9]78°C/18torr); δ ($CDCl_3$) 7.5-7.9(m, 5H, Ar), 10.0(s, CHO)

p-tolualdehyde-d_1(**4b**)

colorless oil; b.p. 62°C/2.5torr (lit[9] 130°C/20torr); δ ($CDCl_3$) 2.44(s, 3H, CH3), 7.32-7.35(m, 2H, Ar), 7.78-8.01(m, 2H, Ar) 9.98(s, CHO)

p-anisaldehyde-d_1(**4c**)

colorless oil; b.p. 145°C/5torr (lit[9]165°C/18torr); δ ($CDCl_3$) 3.89(3H, s, OCH3), 6.98-7.27(2H, m, Ar), 7.82-7.86(2H, m, Ar), 9.88(s, CHO)

p-Chloro α-d_1-benzaldehyde (**4d**)

A mixture of azine **2d** (1.4 g) and deuterium oxide (3 ml) was heated at reflux for 30 min under argon, and then deuterium oxide was removed by distillation at atmospheric pressure from the reaction mixture. The residue was pyrolyzed at 180°C for 30min. After the pyrolysate was cooled to room temperature, conc. HCl (5 ml) was added to it and the mixture was subjected to steam distilled. The distillate was extracted with ether, dried over $MgSO_4$, and evaporated *in vacuo* to afford 184 mg (17%) of the α-deuteriated aldehyde **4d** as colorless needles. The residue in the steam distillation flask was extracted with CH_2Cl_2, dried over MgSO4, and evaporated *in vacuo* to afford 442 mg (41%) of *p*-chlorophenylaldazine-d_2(**3d**) as yellow plates.

p-chlorobenzaldehyde-d_1(**4d**)

colorless needles; m.p. 47-48°C (lit[9] 47°C); ν (KBr) 2120, 1665, 1225, 1155, 1090 cm^{-1};

δ ($CDCl_3$) 7.40-7.45(m, 2h, Ar), 7.75-7.80(m, 2H, Ar), 9.98(s, CHO)

p-chlorophenylaldazine-d_2(**3d**)

yellow plates (EtOH); m.p. 212-13°C

ν (KBr) 3060, 2220, 1605, 1490, 1400, 1090, 1000, 845 cm^{-1}; δ ($CDCl_3$) 7.40-45(4H, m, Ar), 7.75-80(4H, m, Ar), 8.60(0.06H, s, -CH=N-)

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