

PREPARATION OF DEUTERIATED BENZYLAMINES AND PHENETHYLAMINE WITH RANEY ALLOYS IN AN ALKALINE DEUTERIUM OXIDE SOLUTION

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SUMMARY

Benzyl- α,α -²H₂-amine, 2-²H₁-Benzyl- α,α -²H₂-amine, 3-²H₁-Benzyl- α,α -²H₂-amine, 4-²H₁-Benzyl- α,α -²H₂-amine, 2, 5-²H₂-Benzyl- α,α -²H₂-amine, and phenethyl- $\alpha,\alpha,\beta,\beta$ -²H₄-amine were prepared in high isotopic purities from the corresponding benzonitrile, bromobenzonitriles, and phenylacetonitrile by reduction with Raney Cu-Al alloy in an alkaline deuterium oxide solution.

Key Words: Deuterium Labelling, Synthesis, Raney Cu-Al Alloy, NaOD-D₂O

INTRODUCTION

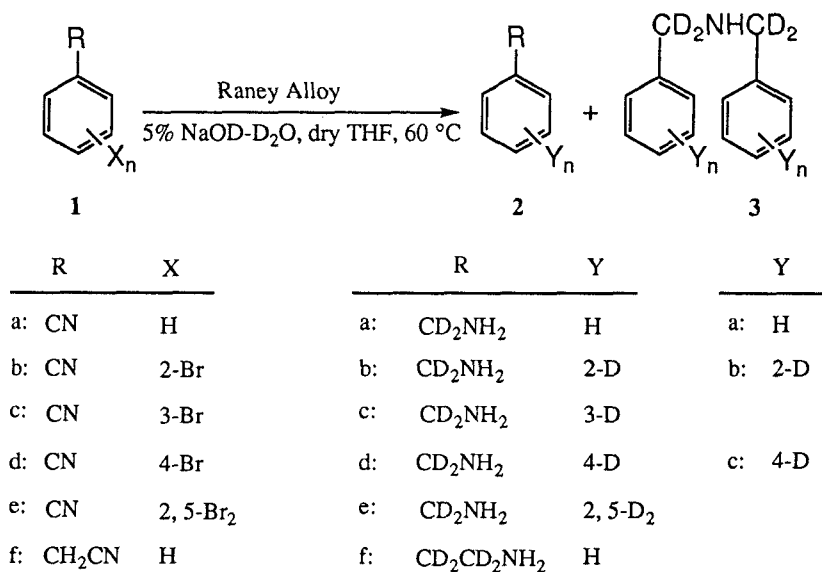
The preparation of benzyl- α,α -²H₂-amine using LiAl²H₄ has been reported.^{1),2)} This method has to be carried out under inert atmospheric conditions and generally reaction times are long. Furthermore, with this method, deuterium cannot be introduced to specific position(s) of the aromatic

ring at the same time as the reduction of the substituent. Phenethyl- $\alpha,\alpha,\beta,\beta$ - $^2\text{H}_4$ -amine can also be prepared using LiAl^2H_4 to introduce deuterium. However, the reaction sequence takes four steps from benzoic acid as the starting material.³⁾ Thus the experimental procedures mentioned above are complicated and conditions need to be chosen very carefully.

Recently we have reported that in the case of the deuteration of halogenated acetophenones and benzaldehyde by the reduction with Raney Cu-Al alloy in an alkaline deuterium oxide solution, deuteriated 1-phenyl ethanols⁴⁾ and benzy1- α - $^2\text{H}_1$ -alcohol⁵⁾ were obtained respectively, dehalogenation and the reduction of the substituent occurring at the same time. In order to determine the scope of this method using Raney alloys in an alkaline deuterium oxide solution, the preparation of the titled deuteriated compounds was carried out using the readily available benzonitrile, bromobenzonitriles, and phenylacetonitrile as starting materials. The titled deuteriated compounds have been used as tracers in metabolic studies.⁶⁾

RESULTS AND DISCUSSION

Benzonitrile (**1a**), bromobenzonitriles (**1b-e**), and phenylacetonitrile (**1f**) were reduced with Raney alloys such as Ni-Al and Cu-Al in 5% NaOD- D_2O solution to give the corresponding deuteriated benzylamines (**2a-e**) and phenethylamine (**2f**) respectively. The results are summarized in Table 1.



Scheme 1

Table 1. Preparation of deuteriated benzylamines (2a-e) and phenethylamine (2f) from benzonitrile (1a), bromobenzonitriles (1b-e), and phenylacetone nitrile (1f) by the reduction with Raney alloys in 5% NaOD-D₂O and THF.¹⁾

Run	Substrate	Raney alloy	Product (yield %) ²⁾	Composition of 2 and 3 (%) ³⁾							
				D ₀	D ₁	D ₂	D ₃	D ₄	D ₅	D ₆	D ₇
1	1a	Cu-Al	2a (58)	0	4	96	0	0	0	0	0
2	1a	Ni-Al	2a (34)	0	16	57	20	4	3	0	0
			3a (30)	0	0	0	21	60	10	9	0
3	1b	Cu-Al	2b (51)	0	9	91	0	0	0	0	0
			3b (14)	0	0	0	0	0	0	92	8
4	1c	Cu-Al	2c (42)	0	0	11	89	0	0	0	0
5	1d	Cu-Al	2d (62)	0	4	13	83	0	0	0	0
			3c (9)	0	0	0	0	23	2	75	0
6 ⁴⁾	1e	Cu-Al	2e (64)	0	0	0	12	88	0	0	0
7	1f	Cu-Al	2f (56)	0	0	4	6	90	0	0	0

1) The amount of alloy used: for (1a-d, f)=0.25 g/mmol, for 1e=0.5 g/mmol. The detailed conditions are shown in the experimental section. 2) Isolated yields are shown. 3) Compositions were obtained from mass spectral data. The positions of the deuterium labelling were confirmed by ¹H n.m.r. spectra obtained from the N-acetyl derivatives of 2. 4) Under ultrasonic irradiation.

The desired benzyl- α,α -²H₂-amine (2a) was obtained in 58% 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 Raney Ni-Al alloy and compound (2a) was obtained in low isotopic purity (²H₂=57%) from 1a (Run 2). The same phenomenon was observed in the reductive dehalogenation of halogenoacetophenones⁴⁾, halogenophenols⁷⁾, and halogenobenzoic acids⁸⁾. The reductive deuteration of monobromobenzonitriles (1b-d) afforded the corresponding 2-, 3-, and 4-²H₁-benzyl- α,α -²H₂-amines in acceptable yields (42-62%) and in isotopic purities of more than 83%. When Raney Cu-Al alloy was used, dehalogenation and the reduction of the nitrile-group occurred at the same time. Furthermore, 2,5-²H₂-benzyl- α,α -²H₂-amine (2e) was obtained from 2,5-dibromobenzonitrile (1e) by reduction with Raney Cu-Al alloy in 5% NaOD-D₂O solution under ultrasonic irradiation. In the case of the reduction of 1a with Raney Ni-Al alloy (Run 2) dibenzyl- $\alpha,\alpha,\alpha',\alpha'$ -²H₄-amine (3a) was also produced. In the reaction of 1b and 1d with Raney Cu-Al alloy (Run 3 and 5), 2-²H₁-dibenzyl- $\alpha,\alpha,\alpha',\alpha'$ -²H₄-amine (3b), and 4-²H₁-dibenzyl- $\alpha,\alpha,\alpha',\alpha'$ -²H₄-amine (3c) were obtained as a by-product, respectively, besides 2b and 2d. The formation of the deuteriated dibenzylamines in a one pot reaction, albeit as a by-product and in low

yield, is interesting. Before, **3a** was prepared in three steps from benzamide.²⁾ The reason for the formation of **3a**, **3b**, and **3c** by using this method is not clear at present, though it is suggested that the products form by an addition of the deuteriated benzylamine to an intermediate imine with subsequent reduction.⁹⁾

Using the same method phenylacetonitrile (**1f**) could be converted to phenethyl- $\alpha,\alpha,\beta,\beta$ - $^2\text{H}_4$ -amine (**2f**). The reduction of the nitrile group and a hydrogen-deuterium exchange at the benzylic position occur at the same time, making this a very effective method for introducing four deuterium atoms to the α - and β positions of phenethylamine in one step.

In conclusion, we obtained the desired five deuteriated benzylamines and phenethylamine in 83-96% isotopic purities by the reduction of halogenated benzonitriles and phenylacetonitrile with Raney Cu-Al alloy in 5% NaOD-D₂O solution. Only in the deuteriation of **1e** was ultrasonic irradiation needed. These results broaden the application^{4),5)} of using Raney Cu-Al alloy on halogenated arenes carrying a reducible substituent in order to introduce deuterium to specific position(s) of the aromatic ring with the concurrent reduction of the substituent.

EXPERIMENTAL

The boiling points of the deuteriated compounds, obtained in this study, were virtually the same as those of the corresponding parent compounds. The ¹H N.M.R. (internal SiMe₄) spectra were measured on a Nippon Denshi JEOL-FT 100 n.m.r. spectrometer. The Mass spectra were recorded on a Nippon Denshi JMS-O1SG-2 mass spectrometer at 75 eV using a direct-inlet system. A Branson model ATH1012-12 ultrasound laboratory cleaner was used for ultrasonication during reduction.

Materials.

Compounds (**1a-d, f**) are commercially available and (**1e**)¹⁰⁾ was prepared according to a literature procedure.

Procedure for the reduction of benzonitrile (**1a**), bromobenzonitriles (**1b-e**), and phenylacetonitrile (**1f**) Three types of procedures are given below.

Procedure A (Runs 1, 2, 3, and 5 in Table 1)

To a stirred mixture of **1a** (1.54 g, 15 mmol), Raney Cu-Al alloy (3.75 g), D₂O (35 ml), and dry THF (2.5 ml) at room temperature was added gradually dropwise a 40% NaOD-D₂O solution (5 ml) within a period of 10 min. After the reaction mixture was stirred at 60 °C for 1 hr (2 hrs in the case of Run 4), the Cu powder formed was filtered and the filtrate was extracted with CH₂Cl₂. The extract

was washed with water, dried over MgSO_4 , evaporated *in vacuo* to leave a residue, which was distilled on a Kugelrohr apparatus (oven temperature: 115 °C) under reduced pressure (18 mmHg), to afford 936 mg (58%) of **2a** as colourless liquid (lit.,¹¹) b.p. 185-187 °C as for $^2\text{H}_0$ form). In the case of runs 2, 3, and 5 in Table 1, 556 mg (34%) of **2a**, 848 mg (51%) of **2b**, and 1.02 g (62%) of **1d** were obtained, respectively. A residue was redistilled on a Kugelrohr apparatus (oven temperature: 170 °C) under reduced pressure (5 mmHg), to afford 452 mg (30%) of **3a**, 209 mg (14%) of **3b**, and 137 mg (9%) of **3c** as colourless liquids (lit.,¹²) b.p. 113-114 °C/0.1 mmHg as $^2\text{H}_0$ form) respectively.

Procedure B (Runs 4 and 7 in Table 1)

To a stirred mixture of **1c** (2.74 g, 15 mmol) in a 5% $\text{NaOD-D}_2\text{O}$ solution (40 ml), and dry THF (2.5 ml) at 60 °C was added Raney Cu-Al alloy (0.25 g per portion) over a period of 10 min (15 portions of alloy with a total amount of 3.75 g). After the reaction mixture was stirred at 60 °C for 2 hrs, the Cu powder formed was filtered and the filtrate was extracted with CH_2Cl_2 . The extract was washed with water, dried over MgSO_4 , evaporated *in vacuo* to leave a residue, which was distilled on a Kugelrohr apparatus (oven temperature: 115-117 °C) under reduced pressure (18 mmHg), to afford 694 mg (42%) of **2c** as colourless liquid (lit.,¹¹) b.p. 185-187 °C as for $^2\text{H}_0$ form).

Procedure C (Run 6 in Table 1)

To a stirred mixture of **1e** (3.90 g, 15 mmol), Raney Cu-Al alloy (7.5 g), D_2O (70 ml), and dry THF (14 ml) at room temperature was added gradually dropwise a 40% $\text{NaOD-D}_2\text{O}$ solution (10 ml) within a period of 10 min under ultrasonic irradiation. After the reaction mixture was stirred at 60 °C for 2 hrs, the Cu powder formed was filtered and the filtrate was extracted with CH_2Cl_2 . The extract was washed with water, dried over MgSO_4 , evaporated *in vacuo* to leave a residue, which was distilled on a Kugelrohr apparatus (oven temperature: 115°C) under reduced pressure (18 mmHg), to afford 1.06 g (64%) of **2e** as colourless liquid (lit.,¹¹) b.p. 185-187 °C as for $^2\text{H}_0$ form).

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REFERENCES

- 1) Fraser R. R., Raza M. A., Renaud R. N. and Layton R. B. - *Can. J. Chem.* 53: 167 (1975)
- 2) Axenrod T. and Milne G. W. A. - *Tetrahedron* 24: 5775 (1968)
- 3) Davis B. - *J. Labelled. Compd. Radiopharm.* 24: 199(1986)
- 4) Tashiro M., Mataka S., Nakamura H. and Nakayama K. - *J. Chem. Soc., Perkin Trans. I* 173 (1988)
- 5) Tsukinoki T., Ishimoto K., Tsuzuki H., Mataka S. and Tashiro M. - *J. Labelled. Compd. Radiopharm.* 33: 987 (1993)
- 6) Husain M., Edmondson D. E. and Singer T. P. - *Biochemistry.* 21: 217 (1982)
- 7) Tashiro M., Iwasaki A. and Fukata G. - *J. Org. Chem.* 43: 136 (1978)
- 8) Tashiro M., Nakayama K. and Fukata G. - *J. Chem. Soc., Perkin Trans. II* 2315 (1983)
- 9) Tashiro M., Mataka S., Nakayama K. and Tsukinoki T. - *Rep. Res. Inst. Ind. Sci. (Kyushu Daigaku Seisan Kagaku Kenkyusho Houkoku)* 82: 117 (1987)
- 10) Pearson D. E., Stamper W. E. and Suthers B. R. - *J. Org. Chem.* 28: 3147 (1963)
- 11) Ing H. R. and Manske R. H. F. - *J. Chem. Soc.* 2348 (1926)
- 12) Juday R. and Adkins H. - *J. Am. Chem. Soc.* 77: 4559 (1955)