SYNTHESES WITH STABLE ISOTOPES: BENZIDINE-^{15}N$_2$

Thomas W. Whaley
Organic and Biochemical Synthesis Group, Los Alamos Scientific
Laboratory, University of California, Post Office Box 1663
(MS890), Los Alamos, New Mexico 87545 U.S.A.

SUMMARY

Benzidine-^{15}N$_2$ was prepared from 4,4'-biphenyldicarboxamide-
^{15}N$_2$ by the Hofmann amide degradation. The diamide, in turn,
was obtained from 4,4'-biphenyldicarbonyl chloride and
ammonium-^{15}N sulfate. An overall yield of 30-35% was obtained
for the two steps. An attempted synthesis of N-hydroxybenzidine
is also described.

INTRODUCTION

Benzidine (4,4'-diaminobiphenyl, 1) has been used in the manufacture of various

dyes and polymers and also as a reagent in certain analytical methods. The use of

the substance, which is a suspected carcinogen, is currently subject to federal

regulations in the United States. Benzidine is commonly prepared by reduction of

nitrobenzene with Zn and NaOH, followed by treatment of the resultant hydrazo-

benzene with acid (the benzidine rearrangement reaction) (1). We were interested

in preparing benzidine labeled with nitrogen-15 and chose to investigate a series

of reactions based on the Hofmann amide degradation.

DISCUSSION

The sequence of reactions used in preparing benzidine-^{15}N$_2$ is shown in Scheme 1.

Commercially available 4,4'-biphenyldicarboxylic acid (2) was smoothly converted to

diacid chloride 3 employing the SOCl$_2$-DMF method of Bosshard, et al. (2). Our

procedure for preparing 3 is considerably simpler than that of Work (3) who was

unable to effect the transformation with SOCl$_2$ and subsequently used PCl$_5$.
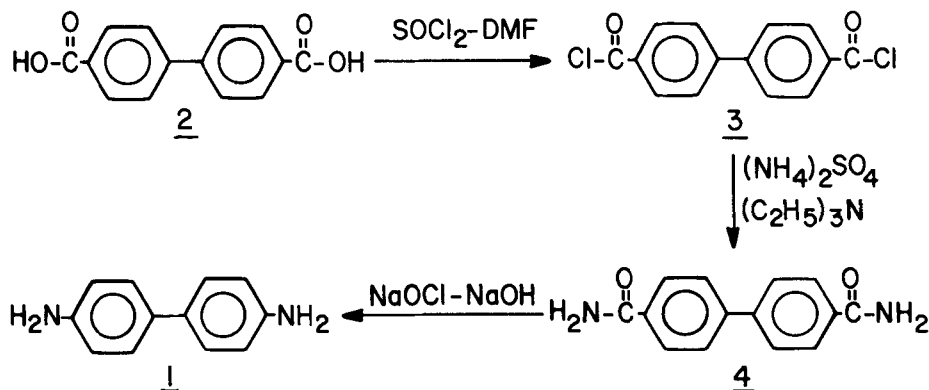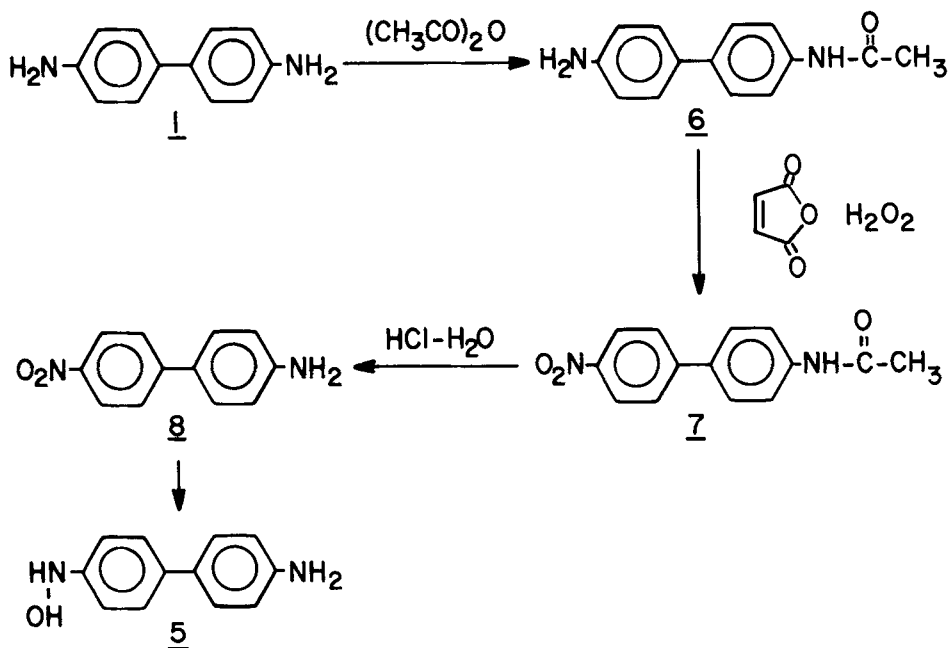
SCHEME I

4,4'-Biphenyldicarboxamide-$^{15}N_2$ (4) was prepared in good yield by the reaction of

3 with ammonia-^{15}N (generated in situ from ammonium-^{15}N sulfate and triethylamine)

in CH_2Cl_2 solution. The Hofmann amide degradation (4) of the diamide 4 to give

benzidine-$^{15}N_2$ was accomplished in 40-45% yield by treatment with alkaline hypo-

chlorite solution using the dioxane co-solvent modification described by Magnien

and Baltzly (5). Another modification of Hofmann's reaction using methyl hypo-

bromite has been described by Radlick and Brown (6), but this modification was not

investigated in the current studies.

The overall yield for the two steps of the synthesis involving isotopic com-

pounds was 30-35%. This yield is not particularly high, but there are several

advantages to the method outlined here. First, the procedures are operationally

simple and can be carried out on almost any reaction scale. Second, since the

4,4'-orientation of the substituents is determined by the starting material, the

benzidine prepared in this manner is uncontaminated by positional isomers of

diaminobiphenyl which are also produced when the benzidine rearrangement is

employed.

A synthesis of N-hydroxybenzidine (5) from benzidine, as shown in Scheme 2,

was investigated, but suitable conditions for the last step were not found.

However, the reactions comprise a convenient synthesis of the various inter-

mediates and are reported here. N-Acetylbenzidine (6) was prepared in 85-90%

SCHEME 2

yield by the slow addition of acetic anhydride to a slurry of benzidine in a minimal volume of ether at room temperature. Since 6 is fairly insoluble in ether, this method avoids appreciable diacetylation which was observed when the benzidine was completely dissolved in the Et_2O. Further purification of 6 was accomplished by precipitation of the sulfate from EtOH. Conversion of 6 to 4-acetamido-4'-nitrobiphenyl (7) was effected in 55-80% yield with the permaleic acid reagent described by White and Emmons (7) employing an oxidant:substrate ratio of 6:1 and a reaction period of 20 hr. Hydrolysis of the amide function of 7 (1:1 conc. HCl-EtOH, reflux 3 hr) gave 4-amino-4'-nitrobiphenyl (8) in 80% yield. Attempts to reduce 8 to 5 using NH_3 and H_2S (8) or Zn and NH_4Cl (9) were unsuccessful. Thin-layer chromatography of the reaction mixtures showed only benzidine and the starting material (8), with no evidence of intermediate-oxidation state products.

The polarographic reduction behavior of substituted nitrobenzenes might suggest a reason for the failure of the chemical reduction of 8 to 5. Most aromatic nitro compounds display a four-electron polarographic wave corresponding to

reduction of the nitro compound to the aryl hydroxylamine and a two-electron wave

corresponding to reduction of the aryl hydroxylamine to the aromatic amine; how-

ever, p-nitrophenol and p-nitroaniline both exhibit only a single six-electron

wave representing reduction of the aromatic nitro compound to the aromatic amino

without observation of the intermediate hydroxylamine (10). In other words, a

strong electron-releasing group in the para-position facilitates the polarographic

reduction of an aryl hydroxylamine to the aromatic amine. To the extent that

polarographic trends extrapolate to chemical reductions, the structural similar-

ity of 5 to p-nitroaniline would account for overreduction of 8 to benzidine.

<div align="center">EXPERIMENTAL</div>

Materials and Methods--Ammonium-^{15}N sulfate (ca. 95 mol % ^{15}N) was produced

at this Laboratory (Los Alamos Scientific Laboratory Isotope Separation Facility,

Group CNC-4). Melting points were determined using a Fischer-Johns melting

point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-

Elmer 710 spectrophotometer using polystyrene calibration lines.

4,4'-Biphenyldicarbonyl chloride (3)--A mixture of 4,4'-biphenyldicarboxylic

acid (24.2 g, 100 mmol), chlorobenzene (150 ml), $SOCl_2$ (72 g, 600 mmol), and DMF

(1 g) contained in a flask equipped with a condenser and drying tube was heated

on a steam bath for 4 hr, at which time an orange solution was obtained. The

warm solution was diluted with cyclohexane (300 ml) to give a precipitate which

was filtered, washed with cyclohexane, and dried to yield 26.3 g of yellow

needles, mp 180-192°. Recrystallization from methylene chloride-cyclohexane

(Norit) gave 21.3 g (76%) of 3 as off-white needles, mp 188-190° [reported (3)

184°]. Ir (KBr): 1770, 1600, 1395, 1205, 1180, 880, 865, 830 cm^{-1}.

4,4'-Biphenyldicarboxamide-^{15}N$_2$ (4)--A mixture of 4,4'-biphenyldicarbonyl

chloride (23.3 g, 83.5 mmol), ammonium-^{15}N sulfate (12.3 g, 91.8 mmol), and CH_2Cl_2

(800 ml) was prepared in a round-bottom flask. Triethylamine (38.1 g, 377 mmol)

was added, the flask was securely stoppered, and the mixture was stirred at room

temperature for 72 hr. The cream-colored mixture was poured into water (300 ml),

and the CH_2Cl_2 was evaporated with a stream of air and gentle warming. The

resulting solid was filtered, washed with water, MeOH, and Et$_2$O, and dried to give 16 g (79%) of $\underline{4}$ as a tan powder, mp > 300°. Ir (KBr): 3370, 3170, 1640, 1610, 1390 cm^{-1}. The material was used in the next reaction without further purification.

Benzidine-^{15}N$_2$ ($\underline{1}$)--A mixture of 4,4'-biphenyldicarboxamide-^{15}N$_2$ (4.84 g, 20 mmol), dioxane (200 ml), and aqueous NaOH-NaOCl solution [240 ml, $\underline{ca}$. 60 mmol NaOCl, prepared from 4.86 g KMnO$_4$ and 63 ml conc. HCl with the liberated Cl$_2$ collected in 300 ml 10% (w/v) NaOH solution (4)] was heated to 80° for 3 hr. The reddish-brown reaction mixture was cooled, acidified with 10% HCl (200 ml), treated with Norit, and filtered through Celite. Treatment of the filtrate with aqueous Na$_2$SO$_4$ (1 $\underline{M}$, 100 ml) precipitated crude benzidine-^{15}N$_2$ sulfate which was filtered, washed with water, EtOH, and Et$_2$O, and dried to give 4.22 g of a tan powder. In order to regenerate the free base, the above solid was stirred with 10% NaOH solution (100 ml) and Et$_2$O (300 ml) for 30 min. Following separation of the Et$_2$O layer and extraction of the aqueous layer with Et$_2$O (3 x 200 ml), the combined Et$_2$O extracts were dried (MgSO$_4$) and the Et$_2$O evaporated to give a solid residue which was crystallized from aqueous ethanol, yielding 1.66 g (45%) of benzidine-^{15}N$_2$ as a light-tan powder, mp 124-125° [reported (1) 128°]. Ir (KBr): 3315, 3185, 1600, 1490, 1255, 1170, 815 cm^{-1}.

T.W. Whaley

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