Duane A. Heyman

Sherwin Williams Chemicals, 1310 Expressway Drive, Toledo, Ohio 43608

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A method for the synthesis of 2-benzimidazolone (**1**) has been devised which does not depend on 1,2-diaminobenzene (**2**) as a starting material. This method produces **1** in good yield by the reaction of hypohalite with 2'-carbamoylphthalanilic acid (**7**), a compound readily prepared by the reaction of 2-aminobenzamide (**3**) and phthalic anhydride. Contrary to prior indications **1** can be hydrolyzed in the presence of acid at temperatures greater than 200° giving excellent yields of **2**.

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1,3-Dihydro-2*H*-benzimidazol-2-one (**1**) can be commerically prepared by heating 1,2-diaminobenzene (**2**) with a carbonyl source such as urea (2), phosgene (3), or carbon dioxide (4). The yields of **1** are good but **2** is commercially prepared from a chemical byproduct, 2-nitroaniline, a chemical whose future availability and toxicity status are uncertain. These reactions also suffer the drawback that high temperature and pressure equipment is required. There are a couple of alternate 2-benzimidazolone preparations which do not use **2** as a starting material. One method involves the heating of azides with phthalic anhydride in an appropriate solvent (5) while the second method involves heating benzenesulfonyl chloride with 2-aminobenzhydroxamic acid (6). Neither method is very attractive as a commercial process for economic or for saftey reasons.

For some time Sherwin Williams Chemicals has been interested in preparing **1** from 2*H*-3,1-benzoxazine-2,4(1*H*)-dione (**4**) (7). 2-Benzimidazolone was desired as an intermediate for the preparation of 1,2-diaminobenzene. After examining known isatoic anhydride chemistry (8), 2-aminobenzamide (**3**) appeared to be a logical starting material for the preparation of **1** as a simple Hofmann amide rearrangement should convert **3** into **1**. It also seemed that this proposed preparative method of **1** would form the basis of a commercial method as **3** is readily prepared in good yield by the reaction of ammonia with isatoic anhydride (9). A literature reference mentioning the conversion of **3** to **1** also appeared to support this initial approach to the described synthetic problem (6,10).

A study was then made of the conversion of 2-aminobenzamide to 2-benzimidazolone under Hofmann amide rearrangement conditions. During the study a number of conditions affecting the Hofmann reaction, such as temperature, base concentration, solvent, hypohalite type, and addition mode were varied. In a few instances a low yield (20% or less) of **1** was isolated but in most cases unidentified organic compounds or black tars were obtained. Apparently the predominate reaction involved a reaction of the hypohalite reagent with the amino group rather than with the amido group.

Since hypohalite appeared to preferentially react with the amino group the next avenue of the benzimidazolone preparation turned to amino protected benzamides. There are essentially three types of common amino protecting groups. The first two, acyl **5**, or benzylidene **6**, were found to react with hypohalite to give 2-substituted-4-quinazolinones rather than the desired Hofmann rearrangement (11). Apparentyl the basic conditions of the Hofmann rearrangement favored ring closure rather than rearrangement. The third type of protected amino group, a phthalimide, **8**, was prepared (12) and reacted with hypohalite giving unidentified products. This reaction was not pursued since **8** is difficult to prepare in good yield and because another highly successful route to 2-benzimidazolone was found.

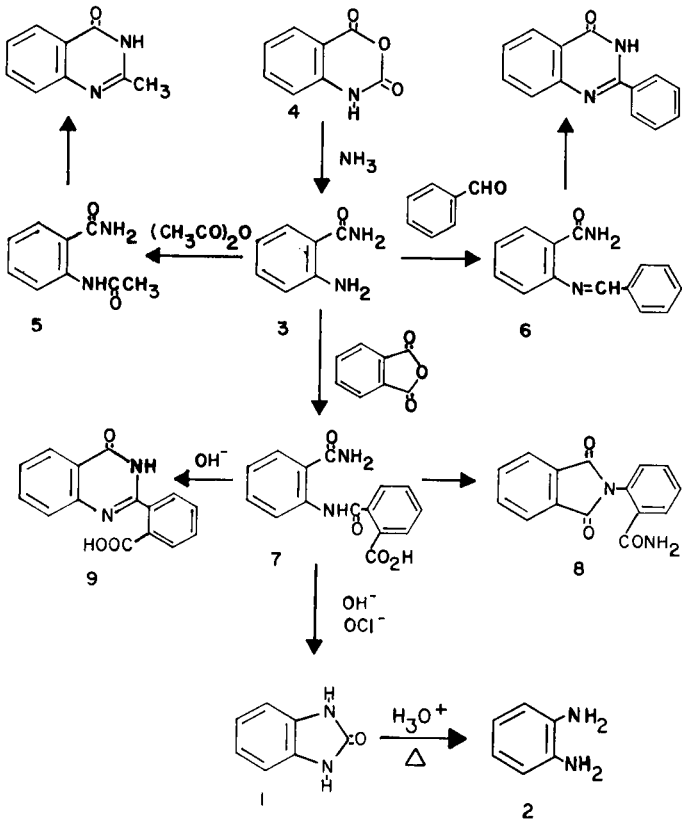

TABLE I

Solvents for the preparation of 2′-carbamoylphthalanilic acid

Solvent	% Crude Yield	M.p. °C (a)
Acetonitrile	100	184.5-185.5
Acetone	77	183.6-184.6
Chloroform (RT) (b)	92	178.5-179.0
Chloroform (warm)	94	182.0-183.0
Dimethylsulfoxide	70	183.5-184.5
Methanol (c)	95	187.1-187.4
Methylene Chloride	85	--
Tetrahydrofuran	70	182.5-183.5
Toluene	100	179.0-180.5
1,1,2-Trichlorethane	98	184.0-185.0

(a) Uncorrected melting points; Lit. (12) 186°. (b) Crystal form I precipitates from room temperature chloroform while crystal form II precipitates from warm chloroform and other solvents. (c) Twofold excess of phthalic anhydride.

An intermediate in the preparation of **8** is 2′-carbamoylphthalanilic acid, (**7**). Even though the previously described acyl protected aminobenzamides gave undesirable products, **7** was tried under the Hofmann conditions because this phthalanilic acid has a feature not shared with the prior amino substituted amterials, that is **7** contains a pendant carboxy group making it soluble in aqueous base, the conditions of a Hofmann reaction. A trial run indicated that **7** would react with hypohalite to yield benzimidazolone. This positive result prompted an investigation of the preparation of **7**. The literature preparation (12) of **7** uses *N*-methylpyrrolidone as solvent. It was soon discovered that **7** could be prepared readily in high yield by reacting 2-aminobenzamide with phthalic anhydride in a variety of warm solvents (Table I).

Previously unreported is the fact that **7** exists in at least two crystal forms. Crystal form I precipitates from room temperature chloroform and is precipitated from basic aqueous solution by acid. Crystal form II, the predominate form, precipitates from warm solvents and is also obtained by heating crystal form I in a solvent. There is a 6-8° difference in the melting points with crystal form II having the higher melting point. The infrared spectra of the two crystal forms are different across the entire spectrum especially in the N-H and carbonyl regions (see Experimental).

As mentioned previously **7** can be dissolved in an equivalent of aqueous base and reacted with hypohalite under Hofmann amide rearrangement conditions to give 80-90% crude yields of 2-benzimidazolone. To minimize hydrolysis, solutions of **7** were usually prepared at room temperature or below with about an equivalent of sodium hydroxide or sodium carbonate. Sodium hypochlorite was then added to the previously prepared phthalanilic acid solution followed by the required third equivalent or more of sodium hydroxide. (A second equivalent of base is generated in the reaction of hypohalite with the amide group of **7**.) The reaction of **7** with hypohalite is mildly exothermic with the addition of the last portions of base being more exothermic. The reaction can be allowed to proceed adiabatically but to assure the completion of the reaction mild heating is applied for about thirty minutes after the second exotherm has peaked.

2-Benzimidazolone can be separated from the impurities generated in the reaction by *p*H control during workup. Compound **1** precipitates below about *p*H 10 while most of the impurities remain in solution above *p*H 6. The impurity fraction consists of at least 3-5 components of which two have been identified. One has been identified as 2′-carboxyphthalanilic acid while the second compound and major component is the ring closed 2-(2′-carboxyphenyl)quinazolin-4-one (**9**). Another impurity which may contain one or more components is a highly colored gummy solid. At this stage the origin of these impurities is unknown. They could arise as natural side reactions in this Hofmann reaction or they could arise by reaction of hypohalite with any unreacted 2-aminobenzamide present in **7**.

Although **7** readily underwent a Hofmann amide rearrangement under the appropriate conditions it too could by cyclized to quinazolinone (note quinazolinone formation is a side reaction of amide rearrangement). Heating **7** in aqueous methanol containing base for a short period gave a 94% yield of **9**. Quinazolinone also becomes the predominate product if the phthalanilic acid-hypohalite reaction is carried out above about 70°.

2-Benzimidazolone is generally considered to be inert to hydrolysis, even with acid or base catalysts, under normal conditions ($\leqslant 100°$) (13). Because of an interest in converting **1** to **2** it was decided to investigate whether **1** could be hydrolyzed in the presence of catalysts under more forcing conditions than had been reported previously.

The first system examined was the reaction of **1** with sodium hydroxide-potassium hydroxide mixtures under fusion conditions at temperatures up to 315° for as long as six hours. 2-Benzimidazolone was recovered unchanged from these reaction conditions suggesting that **1** is truly resistant to base hydrolysis. A second explanation for the failure to obtain **2** from the hydrolysis of **1** may be that any **2** formed in the reaction reacts with carbonate to reform **1** thus undergoing an invisible reaction (14). Studies of this reaction have been too brief to date to select between the two possible explanations for the failure of base to catalyze the hydrolysis of **1**.

The next avenue of investigation was a study of the acid catalyzed hydrolysis of **1**. Above temperatures of about 190° **1** was found to hydrolyze to **2** in the presence of an acid catalyst. The results of a brief parameter study are

TABLE II

Acid Hydrolysis of 2-Benzimidazolone (a)

Time (hr.)	Temperature °C (b)	[Acid]	Mole Ratio $[H^+]$/**1**	% Yield **2** (c)	Recovered **1**
1	195	12	32/1	1	95
5	255	12	32/1	100	0
2	243	4.8	6.4/1	80	20
2	265	4.8	6.4/1	95	0
1	263	4.8	6.4/1	93	5
2	273	4.8	6.4/1	93 (f)	0
2	277	2.4	3.2/1	85 (f)	0
1	273	4.8	6.4/1	93 (f)	0
2	252	6	8/1	98	2
2	255	3.6	4.8/1	90	10
2	252	1.2	1.6/1	50	50
3.5 (d)	305	0	0	4	96
1 (e)	250	9	24/1	85	10

(a) The reactions were done with 1.0 g. (0.075 mole) of recrystallized 2-benzimidazolone in 10-20 ml. of aqueous hydrochloric acid. (b) Temperature of heating bath. (c) Recovered yields of unpurified product. (d) No added acid. (e) Aqueous sulfuric acid. (f) Unidentified black materials were also recovered.

outlined in Table II. These results suggest that within limits the acid hydrolysis reaction is favored by increasing temperature, acid concentration and acid strength. To obtain a quantitative conversion of 1,2-diaminobenzene in one hour requires a temperature of about 260-265° and about 6*M* hydrochloric acid. Higher temperatures (270-280°) appear to promote side reactions or decomposition and at lower temperatures (195°) the conversion to **2** is very slow. Acid concentrations below 6*M* hydrochloric acid result in lower conversions to **2** at constant temperature while a high concentration of sulfuric acid (above 75 volume precent) results in the undesirable side reaction of ring sulfonation. The rate of reaction also appears to be dependent on acid strength as sulfuric acid seems to yield the fastest rate while the telatively weak acid, water gave very low amounts of **2** under the conditions studied. The ratio of protons to **1** is believed to be important for complete conversions to **2** in a reasonable length of time. Under two equivalents of acid per mole of **1** significantly reduces the rate of conversion (see Table II) of **2** from **1**.

In summary 2-benzimidazolone can be prepared from 2-aminobenzamide and then hydrolyzed to 1,2-diaminobenzene. Thus an independent synthesis of 1,2-diaminobenzene not dependent on the chemical byproduct, 2-nitroaniline, has been generated.

EXPERIMENTAL

Melting points (uncorrected) were determined using a Thomas Hoover melting point apparatus. Infrared spectra were measured using a Perkin-Elmer 337 spectrometer. Proton nmr spectra were recorded using a Varian Associates T-60 instrument. Recrystallized 2-aminobenzamide (Sherwin Williams Chemicals) of melting point 110.6-111.2° was used as the starting material for the 2-benzimidazolone synthesis.

2'-Carbamoylphthalanilic Acid (**7**).

Phthalic anhydride, 15.5 g. (0.10 mole) was dissolved in 80 ml. of warm 1,1,2-trichloroethane (45°), filtered to remove a small amount of insouble material (phthalic acid) and the filtrate mixed with an additional 70 ml. of solvent. To the room temperature phthalic anhydride solution was added with efficient mechanical stirring, a warm (60°) solution of 13.6 g. (0.10 mole) of 2-aminobenzamide in 150 ml. of 1,1,2-trichloroethane. Within minutes of benzamide addition a solid precipitated. The white suspension was stirred at 60-70° for thirty minutes and then allowed to cool to room temperature with stirring. The white reaction mixture was filtered, washed with solvent, air dried and dried 16 hours at 50°. There was collected 25.9 g. (91%) of white solid which was shown to be the desired product (crystal form II) by infrared spectroscopy and melting point, 184.0-185.0° [Lit (12), 186°]. An additional 2.1 g. of product was collected from the filtrate.

The same general procedure was used with the other solvents listed in Table I.

The following gives characteristic infrared bands (uncorrected) in cm^{-1} of the N-H and carbonyl regions for the two crystal forms of **7**: Crystal Form I - 3375, 3260, 3215, 1730, 1660, 1640, 1625, 1605, 1590, 1540. Crystal Form II - 3390, 3355, 3225, 1700, 1680, 1660, 1615, 1595, 1560, 1540.

2-Benzimidazolone (**1**).

To a 400 ml. beaker was added 125 ml. of distilled water, 7.2 ml. of 50% aqueous sodium hydroxide and 25.2 g., (0.089 mole) of 2'-carbamoylphthalanilic acid. The reaction mixture was stirred two minutes at room temperature with most of the solid dissolving. Then 60 ml. of cool 1.48 *N* sodium hypochlorite was added immediately turning the reaction mixture brown and exhibiting an exotherm from 30° to 37°. Within one minute of hypochlorite addition 7.4 ml. of additional 50% aqueous sodium hydroxide was added causing a rapid exotherm from 37° to 52°.

The reaction mixture was stirred an additional thirty minutes without external heating, cooled, acidified with concentrated hydrochloric acid to *p*H 8.5, filtered, washed with water and dried. There was collected 11.6 g. (97.8%) of tan solid which was shown by infrared (6) and nmr spectra to be crude 2-benzimidazolone.

Crude benzimidazolone was purified by the following procedure. Crude **1** was dissolved in aqueous base, treated with a small amount of sodium dithionite, carbon treated and then reprecipitated with acid. The reprecipitated material was recrystallized from *N,N*-dimethylformamide-water giving a white solid of good purity.

2-(2′-Carboxyphenyl)-4-quinazolone (**9**).

2′-Carbomoylphthalanilic acid, 2.8 g. (0.01 mole) was mixed with 20 ml. of methanol and 3 ml. of 50% aqueous sodium hydroxide. The reaction mixture was heated at 50° for 15 minutes and then stirred an additional hour without heating. The cooled reaction mixture was acidified to *p*H 3.8 with 5 *N* hydrochloric acid. The resulting precipitate was filtered, washed with water and dried. There was collected 2.5 g. (94%) of white solid which was identified as the desired quinazolone by an infrared spectrum and melting point, 230.5-232.0°, Lit. 229-231 (15).

Acid Hydrolysis (**1**).

Recrystallized 2-benzimidazolone, 1.0 g. (0.0075 mole), 6 ml. of distilled water and 4 ml. of concentrated hydrochloric acid was charged into a 200 mm pyrex test tube. The tube, containing an off-white suspension, was cooled with Dry-Ice, sealed and placed in a bomb reactor along with methanol (heat transfer and pressure equalization agent). The sealed bomb was placed in an oil bath and heated to 265° (two hours to reach temperature). The bath was held at 265 + 5° for two hours and then cooled to room temperature. Upon opening the bomb the sealed glass tube was found to contain a dark green reaction mixture. The tube was cooled with Dry-Ice and opened with caution. (The tube is under pressure with a potential for shattering!) The contents of the tube were washed into a beaker, cooled with an ice bath, neutralized to *p*H 7 with 50% aqueous sodium hydroxide, filtered, washed with water and dried. The filtrate was extracted with five 25 ml. portions of methylene chloride and then the extracts were reduced to dryness on a rotorary film evaporator. A total of 0.85 g. (100% yield) of tan-purple solid was collected and identified by an infrared spectrum as being crude 1,2-diaminobenzene.

The same general procedure was used when varying the reaction time, temperature and reactant concentrations.

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