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Articles

A New Route for the Preparation of 5-Hydroxyisophthalic Acid

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Abstract:

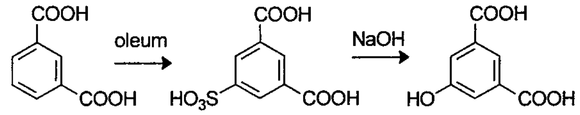
A new, simple and practical, two-stage process for the preparation of 5-hydroxyisophthalic acid (5-HIPA) from isophthalic acid is described. In the first stage, isophthalic acid is brominated by bromine in oleum, in the presence of an iodine catalyst, to give crude 5-bromoisophthalic acid (5-BIPA). In the second stage the crude 5-BIPA is hydrolyzed with aqueous NaOH, in the presence of a copper catalyst, to give crude 5-HIPA, with a purity of ca. 98%. Both stages of the process were optimized. A single crystallization of the crude 5-HIPA from water gives the product in a purity of more than 99%. The overall yield of pure 5-HIPA is 65−70%.

Introduction

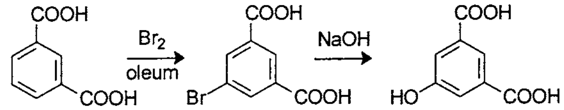
5-Hydroxyisophthalic acid (5-HIPA) is used as a starting material for a variety of products such as drugs, agrochemicals, and polymers.[1] Lately, the interest in 5-HIPA as an intermediate for drugs has increased, as it is used in the production of X-ray contrast materials (radiopaques) for example, iomeprol.[2−5]

Various methods for the preparation of 5-HIPA are described in the literature. The main published methods for preparing 5-HIPA include (1) sulfonation of isophthalic acid (IPA) followed by caustic fusion,[6] (2) a method based on the diazotization of 5-aminoisophthalic acid,[7] and (3) oxidation of a substituted xylene.[8] (4) Alkaline rearrangement of tropone−carboxylic acids, for example, from 6-methoxy-3-oxo-cyclohepta-1,4,6-trienecarboxylic acid, with aqueous KOH at 250 °C[9a] and from 6-bromo-3-methoxy-5-oxo-cyclohepta-1,3,6-trienecarboxylic acid, with aqueous KOH at 200 °C, (5) from hydroxyanthraquinones with KOH, in the melt, for example, from rufigallic acid (1,2,3,5,6,7-hexahydroxy anthraquinone)[10a] or from chrysophanic acid (dihydroxy-2-methyl-anthraquinone).[10b]

Scheme 1. **Industrial method for the preparation of 5-HIPA**



Scheme 2. **New method for the preparation of 5-HIPA**



Among the prior art processes, the one based on sulfonation and caustic fusion appears to be the most effective, and it is used as an industrial process for manufacturing 5-HIPA (Scheme 1).

The main feature of this process is the need for a high reaction temperature together with a strong basic medium. Such severe reaction conditions lead to corrosion of the equipment and the necessity for its frequent replacement.

The aim of this work was to develop a simple, economical, and practical process, with industrial potential, for the preparation of 5-HIPA in a high yield and with a high purity, which can be carried out under relatively mild temperature conditions.

5-HIPA was prepared by the bromination of IPA to obtain 5-bromoisophthalic acid (5-BIPA), followed by hydrolysis to 5-HIPA and purification of the final product (Scheme 2). This method is new and was patented by us in 1997.[11]

Preparation of 5-BIPA. *Literature Search.* A literature review has been carried out on the preparation of 5-BIPA.

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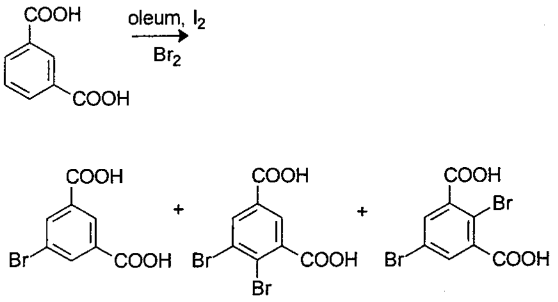
Scheme 3. **Main products of IPA bromination**



The main methods are (1) bromination of IPA in oleum, to yield predominantly 4-bromoisophthalic acid.[12] If, however, a small amount of iodine and a compound of copper, silver, lead, or mercury are present, the bromination occurs selectively at the 5-position. The amount of I_2 or metal can be from 0.02 to 2 mol % of the IPA. The oleum initially contains from 25 to 65% SO_3, and 4.5−8.5 parts by weight of oleum can be used. The reaction is carried out at 100 °C over 5 h when I_2 is present, or 24 h without I_2. (This publication is only an abstract and does not give any additional details). (2) 5-BIPA was prepared in 40% yield by diazotizing dimethyl 5-aminoisophthalic acid and then reacting the diazonium salt with copper bromide and HBr (the Sandmeyer reaction).[13] (3) The dimethyl ester of 5-BIPA was obtained from dimethyl 5-aminoisophthalate in a manner similar to that described previously,[13] in a yield of ca. 50%.[14] (4) 5-BIPA was obtained by the bromination of IPA with bromine and silver sulfate, in concentrated sulfuric acid. The silver was employed in an equimolar quantity. The bromination was carried out at 100−110 °C over 32 h.[15]

Results and Discussion

Bromination Stage. Our investigations commenced with optimization of the temperature, required amounts of I_2 and catalyst, and the quantity and concentration of oleum.

The criterion of a “good” bromination was maximum reaction conversion with a minimum amount of dibrominated by-products. In the hydrolysis stage, the latter leads to the formation of both a certain quantity of IPA, with the resulting crude 5-HIPA being a darker color. The main product of the bromination in all the experiments is 5-BIPA. Two isomers of dibromoisophthalic acid are obtained together with 5-BIPA. These dibromo products were separated by preparative HPLC and identified by ^{1}H NMR spectra. One of them was shown to be 2,5-dibromoisophthalic acid (DBIPA-1), while the other is 4,5-dibromoisophthalic acid (DBIPA-2) (Scheme 3). It is worth mentioning that the solubility of the 2,5-isomer in water is higher than that of the 4,5-isomer. In addition, a small amount of iodoisophthalic acid (IIPA) is formed by iodination of the IPA. However, IIPA does not present a problem as an impurity, since it also gives 5-HIPA in the subsequent hydrolysis stage. Additional impurities formed, in very small amounts (<1%, GC area), during the bromination, are bromoiodoisophthalic acids and tribromoisophthalic acid. Their structures were determined by GC/MS analyses.

Table 1. **Influence of the quantity of iodine catalyst and the temperature on the reaction (IPA 50 g, 0.3 mol; oleum 239 g, 20% SO_3; Br_2/IPA molar ratio 0.64; washing with 0.8 L of H_2O at 80−90 °C)**

expt	iodine % w/w IPA	temp, °C	time, h	composition, GC, % IPA	BIPA	IIPA	DBIPA[b]
1[a]	−	102−105	5.0	89.0	9.8	−	−
2	1.0	102−105	5.0	3.6	82.2	0.5	12.5
3	2.0	102−105	4.0	1.0	81.7	1.1	15.5
4	3.0	102−105	3.0	0.9	81.0	2.2	15.1
5	2.0	79−80	5.0	15.5	81.1	0.8	2.6
			14.0	5.0	88.2	0.7	6.1
6	3.0	84−88	9.0	7.9	85.9	1.7	4.4
			11.5	5.9	87.2	1.6	4.8

[a] 5% $CuSO_4$. [b] Herein and below, DBIPA represents the sum of DBIPA-1 and DBIPA-2.

Table 2. **Influence of the quantity of oleum and the temperature on the reaction (IPA 50 g, 0.3 mol; oleum 20% SO_3; I_2 2% w/w IPA; washing with 0.8 L of H_2O at 80−90 °C)**

expt	oleum/IPA w/w IPA	Br_2/IPA mol. ratio	temp, °C	time, h	composition, GC, % IPA	BIPA	IIPA	DBIPA
3	4.8	0.64	102−105	4	1.0	81.7	1.1	15.5
5	4.8	0.64	79−80	5	15.5	81.1	0.8	2.6
7	5.6	0.64	86−89	6	9.8	84.8	0.8	4.6
8	3.2	0.64	118−123	9	15.3	79.9	1.4	3.4
9[a]	2.8	0.55	102−105	4	1.2	89.2	1.7	7.1

[a] The oleum concentration was 40% SO_3.

Several experiments were carried out to study the influence of the quantity of I_2 and the temperature of the reaction (Table 1).

Attempts to carry out the bromination with a $CuSO_4$ catalyst, but without iodine, were unsuccessful, due to the slow reaction rate (expt no. 1). On the other hand, the use of $CuSO_4$ turned out to be unnecessary, and all further experiments were carried out without $CuSO_4$.

The use of 1% I_2 leads to a slow reaction rate and incomplete conversion (expt no. 2). The same results were obtained when the reaction temperature was reduced (expt nos. 5 and 6).

It seems that the optimum, after consideration of the reaction time and cost of raw materials, is to use 2% I_2 at 102−105 °C (expt no. 3).

A number of experiments were carried out at different temperatures, studying the influence of the quantity of oleum on the bromination products (Table 2). The aim of these investigations was to find the minimum quantity of oleum required to obtain crude 5-BIPA with the specified impurity content.

In expt no. 3, (at 102−105 °C and an oleum/IPA weight ratio of 4.8) a satisfactory result was obtained. An attempt

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Table 3. **Influence of oleum concentration and temperature on the reaction (IPA 50 g, 0.3 mol; oleum/IPA molar ratio 4.8; I_2 2% w/w IPA; washing with 0.8 L of H_2O at 80−90 °C)**

expt	oleum concn %	Br_2/IPA mol. ratio	temp °C	time h	concentration, GC, % IPA	5-BIPA	IIPA	DBIPA
10	65	0.55	102−105	2.0	0.8	86.7	1.7	10.7
11	40	0.55	102−105	3.0	1.5	90.1	1.6	6.3
12	30	0.60	102−105	4.0	1.5	89.2	0.7	7.5
13	20	0.64	102−105	4.0	1.0	81.5	1.0	15.3
14	15	0.64	102−105	4.5	3.1	82.9	1.0	12.8
15	15	0.64	120−125	3.0	1.9	80.1	1.5	16.0
16	10	0.64	120−125	7.5	60.6	36.9	1.9	0.6

to reduce the DBIPA formation by reduction of the reaction temperature was carried out in expt no. 5, but it resulted in both a slow reaction rate and low conversion. A similar result was obtained at a temperature of 86−89 °C and an oleum/IPA weight ratio of 5.6 (expt no. 7).

Reduction of the oleum/IPA weight ratio to 3.2, even at a higher temperature, results in a reduction of both the reaction rate and conversion (expt no. 8).

The best results were obtained when 40% oleum was used. In this case, only 7.1% DBIPA was obtained at 102−105 °C and an oleum/IPA weight ratio of 2.8.

A number of experiments were carried out to study the influence of the oleum concentration on the bromination products. The results (presented in Table 3) show the following: (a) A high IPA conversion (>97%) cannot be reached at a temperature of 102−105 °C when the oleum concentration is less than 20% free SO_3. (b) The quantity of DBIPA by-products is reduced when the oleum concentration is increased from 20 to 40% free SO_3 and then increased again at 65%. The best result was obtained when 40% free SO_3 oleum was used.

Work-Up of the Bromination Mixture. The procedure for the work-up of the bromination mixture appears to have a significant effect on the IPA and DBIPA content of the product. Various work-up procedures were checked. The yield of crude BIPA by all methods was ca. 77−83% based on IPA.

Precipitation by Feeding the Reaction Mixture into the Water. The first attempted work-up method involved pouring the reaction mixture into H_2O at 80−100 °C, followed by filtration of the precipitated crude 5-BIPA at 40−90 °C. The filtration was fast in comparison with precipitation in cold water. Three variations of the work-up continuation were checked. (a) Filtration of the precipitated, crude 5-BIPA was carried out at 80−90 °C. The wet, crude 5-BIPA cake was boiled for 1 h with a fresh batch of H_2O and then filtered at 80−90 °C. This work-up method gave crude 5-BIPA containing 0.3−1.0% IPA, 88−94% 5-BIPA, 1.5−2.0% IIPA, and 5−10% dibrominated products. A relatively small content of DBIPA was present, due to the higher solubility of DBIPA in H_2O in comparison with 5-BIPA. The content of DBIPA in the crude 5-BIPA essentially depends on the quantity of H_2O used, both for the first precipitation stage and the following re-slurry stage. A serious disadvantage of this work-up method is the large amount of acid wastes (ca. 20−25 kg of 20% H_2SO_4 together with organic impurities, Na_2SO_4 and NaBr, per kg of 5-BIPA). (b) Filtration of the precipitated, crude 5-BIPA was carried out at 80−90 °C. The wet, crude 5-BIPA cake was washed on the filter with fresh H_2O at 80−90 °C without additional treatment. In this case, the crude 5-BIPA contained ca. 0.5−1.0% IPA, 83−86% 5-BIPA, 1.4−1.6% IIPA, and 13−16% DBIPA. The amount of acid wastes in this method was less than in method (a) and amounted to ca. 12−15 kg of 30% H_2SO_4 (together with organic impurities, Na_2SO_4 and NaBr) per kg of 5-BIPA. (c) The reaction mixture was fed into H_2O at 80−100 °C. Less H_2O was used than in methods (a) and (b). Filtration of the precipitated, crude 5-BIPA was carried out at 40−50 °C. The wet, crude 5-BIPA cake was washed on the filter with fresh H_2O at 40−50 °C. The impurity content in the crude 5-BIPA by this method was similar to that in method (b), but the quantity of acid waste by this method was less than in methods (a) and (b) and amounted to ca. 8−10 kg of 40% H_2SO_4 (together with organic impurities, sodium sulfate and sodium bromide) per kg of 5-BIPA.

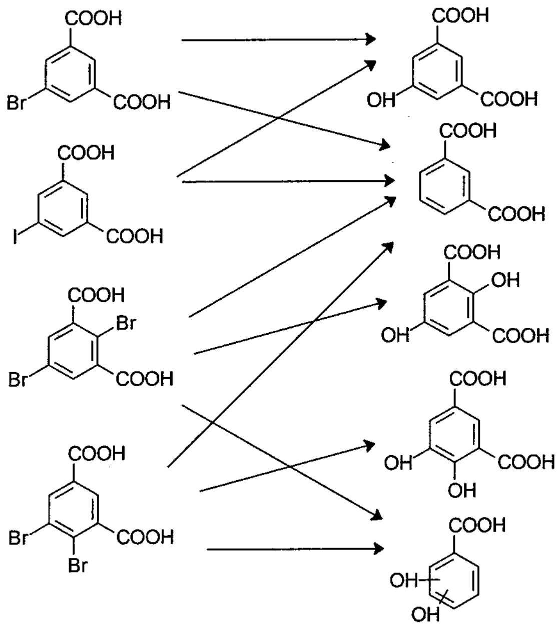
Precipitation by Feeding the Reaction Mixture into Water Followed by Neutralization. A few experiments were carried out to neutralize the reaction mixture after precipitation. This was to reduce the potential corrosion of the equipment. Aqueous solutions of NaOH were used. After the usual precipitation procedure, aqueous 40% NaOH was added to the reaction mixture at 80−90 °C to pH = 2.4. The product was filtered at 80 °C and washed with hot water (at 80−90 °C). The dry, crude product contained ca. 83.2% 5-BIPA, 1.0% IPA, 6.0% Na_2SO_4, 8.5% DBIPA, and 1.4% IIPA.

Filtration of the Precipitated Crude 5-BIPA from Cooled Oleum Solution and Use of Recovered Filtrate in the Next Bromination (Procedure Proposed by Y. Bercovici, IMI). After the bromination, the reaction mixture was cooled to 20−30 °C, and the crude 5-BIPA which precipitated was filtered. The obtained cake contained ca. 50% crude 5-BIPA (ca. 91.2% 5-BIPA, 0.7% IPA, 5.5% DBIPA, 1.4% IIPA) and 50% oleum. The cake may be used directly in the next hydrolysis stage without further treatment. The filtrate, containing ca. 82% oleum (<8% free SO_3) and 18% crude 5-BIPA (ca. 69.2% 5-BIPA, 3.6% IPA, 25.4% DBIPA, 1.3% IIPA), may be used in the next bromination experiment. The main advantages of this work-up method are the reduction of the amount of oleum required for the production of a unit of 5-BIPA and a considerable reduction in the quantity of waste.

Preparation of Crude 5-HIPA. 5-HIPA was prepared by the hydrolysis of crude 5-BIPA with aqueous NaOH, in an autoclave, in the presence of a copper catalyst. The starting material, crude 5-BIPA, as shown above, is a composition of main product, 5-BIPA (85−94%), together with several by-products, IPA (0.3−1.0%), IIPA (1.5−2.0%), and DBIPA (4−12%).

Different copper compound catalysts, such as Cu, CuCl, CuO, $CuBr_2$, $CuSO_4$, Cu_2O, and so forth, may be used. After full conversion was achieved, the autoclave was cooled to room temperature and opened, and the reaction mixture was filtered to remove the catalyst. The filtrate was acidified to

Scheme 4. **Hydrolysis of crude 5-HIPA**



pH = 1 with H_2SO_4 or HCl at 60−80 °C and cooled to 20 °C, and the crude 5-HIPA precipitate was filtered.

At full conversion, the main product of the hydrolysis was 5-HIPA. By-products of the reaction were IPA (some present in the starting material and some formed by hydrogenolysis of 5-BIPA and DBIPA), two isomers of dihydroxybenzoic acid, formed by the decarboxylation of dihydroxyisophthalic acid, and two isomers of dihydroxyisophthalic acid (DHIPA), formed by the hydrolysis of DBIPA (Scheme 4). The structure of the impurities was determined on the basis of GC/MS analysis.

Most of the DHIPA formed from DBIPA decomposes into benzoic acid derivatives and further into fractions nondetected in crude 5-HIPA.

To find the optimum reaction conditions, the influence of the temperature, NaOH/5-BIPA molar ratio, and amount of catalyst on the reaction rate and selectivity was studied. The crude 5-BIPA used in these experiments consisted of 5-BIPA, 92.1%; IPA, 0.4%; IIPA, 2.2%; DBIPA1/DBIPA2, 0.9/4.4.

Examples 1−6 illustrate the effect of the temperature on the hydrolysis of crude 5-BIPA in the presence of a copper catalyst (Cu_2O), at a constant NaOH/5-BIPA molar ratio (Table 4).

The results presented in Table 4 show the following: (a) A certain amount of IPA is formed during the hydrolysis, perhaps as a result of the debromination of 5-BIPA and DBIPA. (b) An increase in the temperature leads to an increase in the hydrolysis rate of 5-BIPA and to decomposition of the DHIPA but also to an increase in the amount of IPA formed.

Examples 7−10 illustrate the effect of changing the ratio of base to crude 5-BIPA, at a constant temperature and catalyst concentration (Table 5).

As can be seen from the results, the selectivity of the hydrolysis depends on the molar ratio of NaOH/5-BIPA. The best results were obtained at a molar ratio of 5. Examples 11−15 illustrate the effect of using different amounts of Cu_2O catalyst on the hydrolysis of crude 5-BIPA, at constant temperature and catalyst concentration (Table 6).

Table 4. **Influence of the temperature on the hydrolysis of crude 5-BIPA (crude BIPA 55 g; H_2O 175 g; NaOH/5-BIPA molar ratio = 5; Cu_2O 2% w/w of the crude 5-BIPA)**

expt	temp °C	time h	composition, GC, % 5-BIPA	5-HIPA	DHBA	DHIPA	IPA
1	120	1.5	23.8	71.1	–	4.4	0.4
		3.0	3.8	93.0	–	2.8	0.6
2	140	1.5	N.D.	96.0	0.2	3.1	0.7
3	160	1.5	N.D.	98.6	0.3	0.2	0.9
4	170	1.5	N.D.	98.6	0.3	–	1.1
5	180	1.0	N.D.	98.3	0.3	–	1.4
6	210	1.0	N.D.	98.3	–	–	1.7

Table 5. **Influence of the NaOH/5-BIPA molar ratio on the hydrolysis of crude 5-BIPA (crude BIPA − 55 g; H_2O − 175 g; Time − 1.5 h; Temp. − 170 °C; Cu_2O − 2% w/w of the crude 5-BIPA)**

expt	molar ratio NaOH/5-BIPA	composition, GC, % 5-BIPA	5-HIPA	DHBA	DHIPA	IPA
7	3	4.2	86.5	–	5.2	3.8
8	4	N.D.	97.5	–	1.2	1.3
9	5	N.D.	99.0	0.1	–	0.9
10	6	N.D.	98.3	0.4	–	1.3

Table 6. **Influence of the quantity of catalyst on the reaction (crude BIPA 55 g; H_2O 175 g; time 1.5 h; temp 170 °C; NaOH/5-BIPA molar ratio 5)**

expt	Cu_2O w/w 5-BIPA	composition,GC, % 5-BIPA	5-HIPA	DHBA	DHIPA	IPA
11	0.001	13.2	83.7	–	1.3	1.8
12	0.2	N.D.	97.1	0.2	1.3	1.4
13	1.0	N.D.	98.3	0.3	0.2	1.2
14	2.0	N.D.	98.4	0.3	0.3	1.0
15	3.0	N.D.	98.5	0.3	0.2	1.0

As seen from the data in Table 6, full conversion of the 5-BIPA was achieved in all the experiments, except in expt no. 11, when only 0.001% Cu_2O was used. The problem in using a small quantity of Cu_2O is that the DHIPA remains in the crude 5-HIPA. In addition, when <2% catalyst is used, more IPA is present in the crude 5-HIPA.

Purification of Crude 5-HIPA. A single crystallization of crude 5-HIPA from H_2O gives a product with a purity of >99%. The yield of the crystallization stage is 93%.

Summary

A method was developed by which 5-HIPA was prepared with a purity of >99% and an overall yield of 65−70%, using two chemical steps and one crystallization.

The recommended conditions for the first bromination step are as follows: bromine/IPA molar ratio, 0.55−0.65; oleum, 20−40% free SO_3. The quantity used depends on the oleum concentration: 4.3 kg of oleum/kg of IPA for oleum with 20% free SO_3, and 2.7 kg of oleum/kg of IPA for oleum with 40% free SO_3. I_2 (2−3%) catalyst is used. The reaction is carried out at 102−107 °C for 6 h. Three options for the reaction mixture work-up were investigated: (1) the precipitation of brominated organics from the reaction mixture by adding to H_2O, followed by filtration; (2) the precipitation of the brominated organics from the reaction mixture by adding to H_2O, followed by neutralization of the formed H_2SO_4 solution with NaOH and filtration; and (3) filtration of the precipitated crude 5-BIPA from the cooled oleum solution and recycling the filtrate to the next bromination. All these work-up methods give crude material containing 0.3−1.0% IPA, 85−94% 5-BIPA, 1.5−2.0% 5-IIPA, and 4−12% dibrominated products. The crude 5-BIPA was used for the hydrolysis stage without additional treatment.

Two different schemes may be used for the hydrolysis step. The first one, which makes it possible to increase the loading of the pressure reactor, is based on hydrolysis with 35% NaOH, followed by transfer of the reaction mixture to an additional reactor, dilution to dissolve precipitated salts, and then filtration from the catalyst. According to the second route, the hydrolysis is performed with 20% NaOH. Under this condition, most of the salts obtained during the reaction are dissolved, and the reaction mixture may be filtered without prior dilution; thus, the additional reactor is not necessary. The disadvantage of this route is the lower loading of the pressure reactor. The duration of the hydrolysis is affected by the DBIPA content in the crude 5-BIPA. When the crude 5-BIPA contains a large quantity of DBIPA (>10%), the reaction time must be increased. The work-up comprises catalyst filtration, precipitation by acidification with H_2SO_4 to pH 1.0−1.5 at ~80 °C, filtration of the crude product at 20 °C, and washing at 20 °C. The filtration temperature, the washing temperature, and the quantity of washing H_2O may be changed within a small range, depending on the quantity of DBIPA in the crude 5-BIPA. The recommended conditions for the hydrolysis stage are 20−35% aqueous NaOH solution; NaOH/5-BIPA molar ratio, 4.5−5.0; Cu_2O catalyst, 2−3% w/w of the crude 5-BIPA; temperature/time, 160 °C/6−8 h.

A single crystallization of the crude 5-HIPA from H_2O gives a product with a purity of >99%. The yield of the crystallization stage is 93%.

In conclusion, a practical process, with industrial potential, was developed, which may compete with existing industrial processes.

Experimental Section

GC analyses were conducted on a Hewlett-Packard 5890 series II apparatus. A 30 m capillary column, Rtx-20, was used for analysis of the 5-BIPA. A 30 m capillary column, DB-5, was used for analysis of the 5-HIPA. GC/MS analyses were conducted on a Hewlett-Packard 5890 series II apparatus equipped with a 5970 series mass selective detector, using a 10 m capillary column (i.d. = 0.25 mm), Rtx-1, for analysis of 5-BIPA and a 20 m capillary column (i.d. = 0.18 mm), Rtx-1, for analysis of 5-HIPA. For GC and GC/MS analyses the products were silylated by reacting a sample (20 mg) with an excess of the silylating agent (1 mL) bis-(trimethylsilyl)trifluoroacetamide (Aldrich) for 1 min at 70−90 °C. ^{1}H NMR spectra were measured with a Bruker WP200 spectrometer using TMS as an internal standard.

Bromination of IPA with Work-Up Comprising Precipitation by Feeding Brominated Reaction Mixture into Water. Into a 3-L flask were introduced 199.7 g of (1.2 mol) IPA, 4 g of I_2, and 450 mL of 20% oleum. The mixture was stirred without heating to dissolve the IPA in the oleum. The reaction mixture was then heated to 103−106 °C and stirred vigorously; then 121 g (0.756 mol) of Br_2 was added dropwise over 4 h. Heating and stirring were continued for an additional 2 h, and a sample was removed to check the reaction conversion (if the product contains >0.8−1.0% IPA, an additional quantity of Br_2 must be added). The reaction mixture was transferred, by means of a peristaltic pump, into a 3-L flask containing 1500 mL of H_2O at 70 °C. The product precipitated. The speed of the transfer was restricted due to the temperature of the contents of the flask rising to boiling point. The precipitation was carried out with vigorous stirring. The product was filtered at 80−90 °C and washed with 500 mL of hot H_2O (at 80−90 °C). The crude product was placed in 1500 mL of of H_2O, and the mixture was stirred at 90−100 °C for 1 h. The product was filtered at 80−90 °C and washed with 500 mL of hot H_2O (at 80−90 °C) to give, after drying, 255 g of an off-white powder. The 5-BIPA content, by GC, was 86−90%. The yield was about 80%.

Bromination of IPA with Work-Up Comprising Precipitation by Feeding the Brominated Reaction Mixture into Water, Followed by Neutralization with NaOH. Into a 1-L flask were introduced 100 g (0.6 mol) of IPA, 2 g of I_2 and 480 g of 20% oleum (Fertilizers & Chemicals Ltd.). The mixture was stirred without heating to dissolve the IPA in the oleum. The reaction mixture was then heated to 103−106 °C and stirred vigorously; then 61.4 g (0.38 mol) of Br_2 was added dropwise over 6 h. Heating and stirring were continued for an additional 2 h, and then a sample was removed to check the reaction conversion (if the product contains >0.8−1.0% IPA, an additional quantity of Br_2 must be added). The reaction mixture was transferred, by means of a peristaltic pump, into a 2-L flask containing 800 mL of H_2O at 70 °C. The product precipitated. The velocity of the transfer was restricted due to an increase in the temperature of the contents of the flask to boiling point. The precipitation was carried out with vigorous stirring. Aqueous 40% NaOH (ca. 1 kg) was added to the reaction mixture at 80−90 °C to pH = 2.4. The product was filtered at 80 °C and washed with 800 mL of hot H_2O (at 80−90 °C). The crude product after drying weighed about 135 g and contained: 83% 5-BIPA, 1.0% IPA, 6% Na_2SO_4, 8% DBIPA, and 1.5% IIPA. The overall yield was 77%.

Bromination of IPA with Work-Up Comprising Filtration of the Precipitated Crude 5-BIPA from Cooled Oleum Solution. Into a 1-L flask were introduced 100 g (0.6 mol) of IPA, 2 g of I_2 and 430 g of 20% oleum (Fertilizers & Chemicals Ltd.). The mixture was stirred without heating to dissolve the IPA in the oleum. The reaction mixture was then heated to 103−106 °C and stirred vigorously; then 61.4 g (0.38 mol) bromine was added dropwise over 6 h. Heating and stirring were continued for an additional 2 h, and a sample was removed to check the reaction conversion (if the product contains >0.8−1.0% IPA, an additional quantity of Br_2 must be added). The reaction mixture was cooled to 20 °C, and the precipitated product was filtered. The obtained cake (186 g) contained 50% crude 5-BIPA (91.2% BIPA, 0.7% IPA, 5.5% DBIPA, 1.4% IIPA) and 50% oleum (<8% free SO_3). The cake may be used directly in the hydrolysis stage without further treatment. The filtrate (336 g), containing 82% oleum (<8% free SO_3) and 18% crude 5-BIPA (72.2% 5-BIPA, 2.6% IPA, 23.4% DBIPA, 1.3% IIPA) may be used in the next bromination experiment.

Preparation of 5-HIPA. H_2O (640 g), NaOH (160 g), crude 5-BIPA (196 g, 0.8 mol), and Cu_2O (3.9 g, 0.027 mol) were placed into a 1-L autoclave. The autoclave was sealed and heated to 140 °C. Full conversion was achieved after 90 min. The autoclave was cooled to room temperature and opened, and the reaction mixture was filtered to remove the catalyst. The reaction mixture was transferred to a dropping funnel and added dropwise, with vigorous stirring, to 820 mL of 15% HCl (prepared from 332 mL of 37% HCl and 488 mL of water) placed in a 3-L flask at 60−70 °C. After cooling to 20 °C the product was filtered and washed with 100 mL of H_2O at 20 °C. After drying, 123 g of a cream-colored solid, with a purity of 98.2%, was obtained (93% yield, based on 5-BIPA).

Purification of crude 5-HIPA. 5-HIPA (100 g dry, crude, purity 98%) and 900 mL of H_2O were placed into a 2-L flask and heated to 100 °C, with stirring, for 1 h. The solution was then cooled to 20 °C with vigorous stirring, and the precipitated product was filtered and washed with 150 mL of H_2O at 20 °C. After drying, 93 g (93% yield, based on 5-HIPA) of an off-white solid was obtained.

The NMR, GC, and GC/MS spectra may be requested, if required.

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