Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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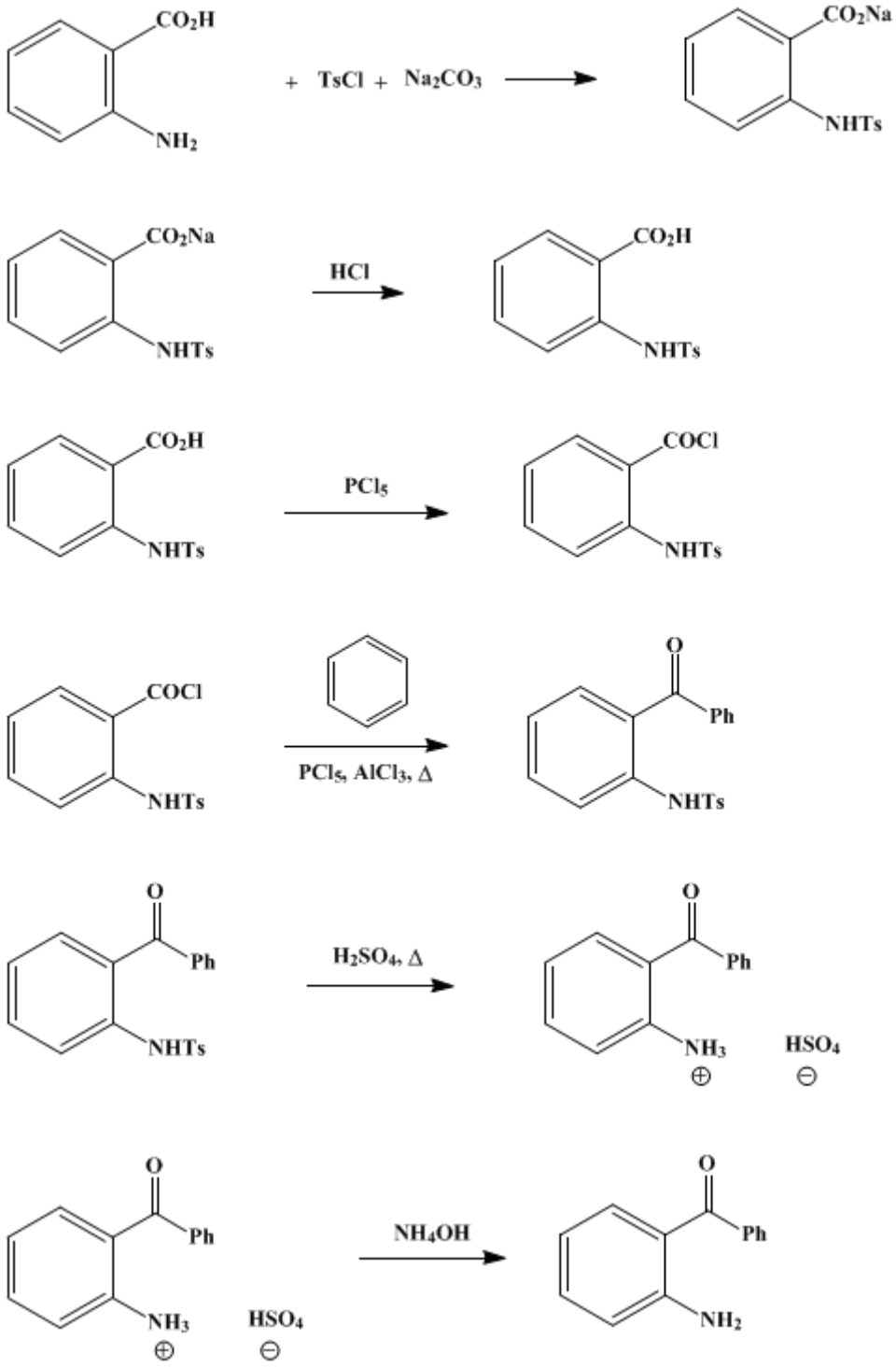
2-AMINOBENZOPHENONE

[Benzophenone, 2-amino-]



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1. Procedure

A. *p-Toluenesulfonylanthranilic acid.* In a 5-l. three-necked flask equipped with a stirrer and a thermometer extending to the bottom of the flask are placed 1.5 l. of water and 260 g. (2.4 moles) of technical grade dry sodium carbonate (Note 1). While the mixture is warmed, 137 g. (1 mole) of anthranilic acid is added in three portions, and the temperature is raised to 70° to effect complete solution. The solution is allowed to cool to about 60°, and 230 g. (1.2 moles) of technical *p*-toluenesulfonyl chloride is added in 5 portions over a period of about 20 minutes (Note 2). When all the *p*-toluenesulfonyl chloride has been added, the reaction mixture is maintained at 60–70° for an additional 20 minutes. The temperature is raised to about 85°, 10 g. of Norit is added cautiously, and the solution is filtered by suction through a previously heated Büchner funnel.

In a 4-l. beaker equipped with a stirrer which can be operated above the liquid level to break the foam are placed 250 ml. of 12*N* hydrochloric acid and 250 ml. of water. The filtrate obtained above is cooled to about 50° and is added to the hydrochloric acid in small portions and at such a rate that the mixture does not foam over. If efficient stirring is used in the foam layer, this addition can be carried out in 5 minutes. The product is isolated by filtration through a Büchner funnel and is washed on the filter, first with a 250-ml. portion of dilute hydrochloric acid (prepared by diluting 50 ml. of 12*N* hydrochloric acid to about 250 ml.) to remove anthranilic acid, and then with 500 ml. of water. The product is sucked as dry as possible and is then spread in a thin layer and allowed to air dry for about 15 hours. When easily pulverizable, the material is transferred to an oven and dried for 3 hours at 100–120°.

There is obtained 257–265 g. (88–91%) of *p*-toluenesulfonylanthranilic acid as a pale lavender powder with a neutral equivalent of 294–300, which indicates a purity of 97–99% (Note 3). This product is suitable for conversion to 2-aminobenzophenone, but it may be recrystallized by dissolving in hot 95% ethanol (10 ml. per g.) and then adding water (4 ml. per g.). The recovery in the first crop is about 75% of material melting at 229–230° and having a neutral equivalent of 295.

B. 2-*Aminobenzophenone*. In a dry 3-l. three-necked flask equipped with a stirrer, a reflux condenser connected to a hydrogen chloride trap, and a thermometer extending to the bottom of the flask are placed 146 g. (0.5 mole) of dry *p*-toluenesulfonylanthranilic acid, 1.5 l. of thiophene-free benzene, and 119 g. (0.57 mole) of phosphorus pentachloride. The mixture is stirred and heated at about 50° for 30 minutes. The murky solution (Note 4) is then cooled to 20–25°, and 290 g. (2.2 moles) of anhydrous aluminum chloride is added in 4 portions. When addition is complete, the dark mixture is heated with stirring at about 80–90° for 4 hours. The mixture is cooled to room temperature and poured onto a mixture of 500 g. of ice and 40 ml. of 12*N* hydrochloric acid in a 5-l. round-bottomed flask. The benzene is best removed by vacuum distillation using a water aspirator (Note 5). The grainy, brown, crude product is separated by filtration on a Büchner funnel and washed thoroughly with dilute hydrochloric acid, with water, then with two 500-ml. portions of 5% sodium carbonate (to remove anthranilic acid and starting material), and finally with three 500-ml. portions of water (Note 6). The filter cake is sucked reasonably dry.

The crude, moist sulfonamide is dissolved in 1.6 l. of concentrated sulfuric acid by warming on the steam bath for 15 minutes. The sulfuric acid solution is divided into two equal parts, each of which is placed in a 4-l. beaker. The beakers are cooled in ice baths while 1.6 kg. of ice is added slowly and with stirring to the contents of each beaker. During the addition of the ice, phenyl *p*-tolyl sulfone separates. A total of 50 g. of Norit is added, and the solution is filtered (Note 7) and (Note 8).

The filtrates are best neutralized separately. Two 5-gal. crocks are half filled with crushed ice, and one-half of the total filtrate is poured into each. For neutralization, commercial 12*N* ammonium hydroxide is added slowly with stirring; a total of 4.8 l. is required. The solid is collected on a Büchner funnel, washed with water, and air-dried.

The product is obtained in the form of bright yellow crystals, m.p. 103–105°. The yield is 68–71 g. (69–72% based on *p*-toluenesulfonylanthranilic acid). This material is dissolved in 1 l. of hot 95% ethanol, treated with 15 g. of Norit, and filtered. The hot solution is diluted with 700 ml. of hot water and cooled. After a second recrystallization, the yield of hexagonal yellow plates is 47 g.; m.p. 105–106°. Another 6 g. of pure aminoketone can be recovered from the filtrate. The total yield of recrystallized 2-aminobenzophenone is 53 g. (54%) (Note 9).

2. Notes

1. If sodium hydroxide is used, the main product is the *p*-toluenesulfonic acid salt of anthranilic acid. This salt has properties quite similar to those of the desired *p*-toluenesulfonylanthranilic acid but is useless for the preparation of 2-aminobenzophenone.
2. It is advisable to have sodium hydroxide solution available in case carbon dioxide is evolved indicating that the amount of sodium carbonate used was insufficient.
There is a tendency for salts to precipitate from the mixture and for some foaming to occur if much less water is used.
3. The melting point of the *p*-toluenesulfonylanthranilic acid is not a good criterion of purity because the *p*-toluenesulfonic acid salt of anthranilic acid has about the same value. The neutral equivalents are widely different: 154 for the salt and 291 for *p*-toluenesulfonylanthranilic acid. The compound obtained in this preparation gives a negative test for anthranilic acid on diazotization and treatment with alkaline β-naphthol solution. The probable impurity is the sodium salt of *p*-toluenesulfonylanthranilic acid.
4. When recrystallized *p*-toluenesulfonylanthranilic acid is used, the solution is clear at this point. The crude acid gives rise to a dark solution containing a small amount of suspended solid. The yield of 2-aminobenzophenone is the same in either case.
5. Steam distillation may also be used but should not be prolonged. If the contents of the flask are kept below 80°, the crude product is obtained as a fine powder. If the temperature becomes too high, the material melts and anthranilic acid is not easily removed from the solid mass obtained on cooling.
6. It is convenient to keep the wash solutions at 75–80°, but the temperature should not exceed 85° or part of the organic material will melt and clog the filter. It is advisable to transfer the solid to a 2-l. beaker to permit thorough washing. Most of the wash solution can be separated by decantation.
7. Phenyl *p*-tolyl sulfone may be isolated at this point by filtering the acid solution before using Norit. It can be purified by recrystallization from 95% ethanol; m.p. 125°.
8. The temperature of the solution should be 30–35°. If too cold some of the product will be retained on the filter, and if too hot the filter paper will be attacked by the acidic solution. 2-Aminobenzophenone is a weak base and separates as the free base from sulfuric acid solutions below about 4*N*.
9. 4'-Methyl-2-aminobenzophenone can be prepared similarly by substituting toluene for benzene. The yield of crude material, m.p. 85–88°, is 70%. On recrystallization from 95% ethanol, using 5 ml. per g., there is obtained, in two crops, a 70% recovery of 4'-methyl-2-aminobenzophenone, m.p. 92–93°. Because of the higher temperature required in the steam distillation (Note 5), the sulfonamide is obtained in a form difficult to purify. As a result the crude aminoketone usually contains 1–2 g. of aluminum oxide.

3. Discussion

The above procedure is essentially that of Ullmann and Bleier.[2] 2-Aminobenzophenone has also been prepared by reduction of 2-nitrobenzophenone,[3] by the Hofmann reaction of the amide of *o*-benzoylbenzoic acid with sodium hypobromite,[4] by the action of an excess of benzoyl chloride on aniline at 220°,[5] and by hydrolysis of the acetyl derivative which is obtained by the action of phenylmagnesium bromide on 2-methyl-3,1,4-benzoxaz-4-one (from anthranilic acid and acetic anhydride).[6] Various methods for the preparation of 2-aminobenzophenones have been summarized critically by Simpson, Atkinson, Schofield, and Stephenson.[7]

References and Notes

1. Cornell University, Ithaca, New York.
2. Ullmann and Bleier, *Ber.*, **35**, 4273 (1902); Stoermer and Finche, *Ber.*, **42**, 3118 (1909).
3. Geigy and Koenigs, *Ber.*, **18**, 2400 (1885); Tatschaloff, *J. prakt. Chem.*, [2] **65**, 308 (1902); Gabriel and Stelzner, *Ber.*, **29**, 1300 (1896).
4. Graebe and Ullmann, *Ann.*, **291**, 8 (1896); Hewett, Lermit, Openshaw, Todd, Williams, and Woodward, *J. Chem. Soc.*, **1948**, 292. (The submitters have found that the Curtius procedure gives better results than the method of Hofmann; cf. P. A. S. Smith, in Adams, *Organic*

Reactions, Vol. 3, p. 337, John Wiley & Sons, New York, 1946.)
5. Chattaway, *J. Chem. Soc.*, **85**, 386 (1904).
6. Lothrop and Goodwin, *J. Am. Chem. Soc.*, **65**, 363 (1943).
7. Simpson, Atkinson, Schofield, and Stephenson, *J. Chem. Soc.*, **1945**, 646.

Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

p-toluenesulfonic acid salt of anthranilic acid

2-methyl-3,1,4-benzoxaz-4-one

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

acetic anhydride (108-24-7)

aniline (62-53-3)

sodium hydroxide (1310-73-2)

phosphorus pentachloride (10026-13-8)

sodium carbonate (497-19-8)

β-naphthol (135-19-3)

carbon dioxide (124-38-9)

Norit (7782-42-5)

benzoyl chloride (98-88-4)

aluminum chloride (3495-54-3)

toluene (108-88-3)

ammonium hydroxide (1336-21-6)

Anthranilic Acid (118-92-3)

Phenylmagnesium bromide (100-58-3)

sodium hypobromite

aluminum oxide (1344-28-1)

2-Aminobenzophenone,
Benzophenone, 2-amino- (2835-77-0)

2-nitrobenzophenone (2243-79-0)

p-Toluenesulfonyl chloride (98-59-9)

o-benzoylbenzoic acid (85-52-9)

p-Toluenesulfonylanthranilic acid (6311-23-5)

phenyl p-tolyl sulfone (640-57-3)

sodium salt of p-toluenesulfonylanthranilic acid

4'-Methyl-2-aminobenzophenone