Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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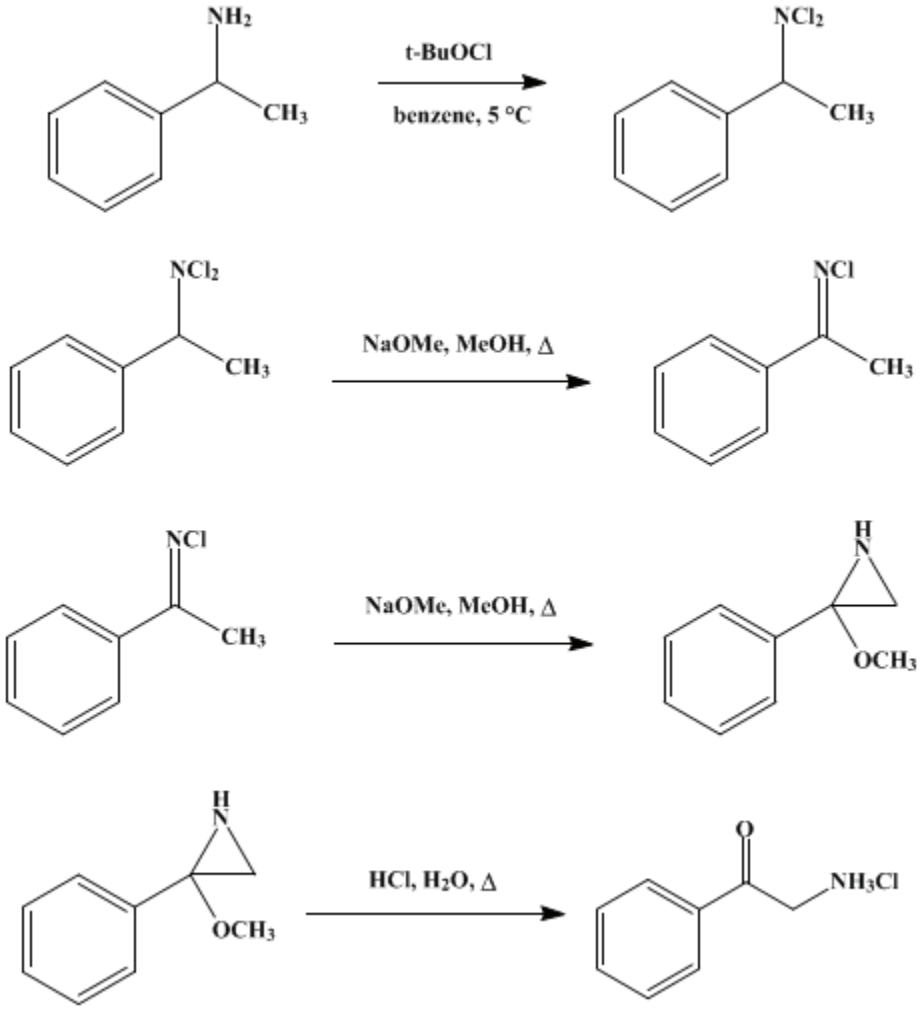
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.041.0082

Organic Syntheses, Coll. Vol. 5, p.909 (1973); Vol. 41, p.82 (1961).

PHENACYLAMINE HYDROCHLORIDE

[Acetophenone, 2-amino-, hydrochloride]



Submitted by Henry E. Baumgarten and James M. Petersen[1].
Checked by William E. Parham, Norman Newman, and R. M. Dodson..

1. Procedure

In a thoroughly dry 500-ml., three-necked, round-bottomed flask fitted with a mechanical stirrer, dropping funnel, and a Y-tube containing a calcium chloride drying tube and a thermometer (Note 1) are placed 24.2 g. (26 ml., 0.20 mole) of α-phenylethylamine (Note 2) and 50 ml. of dry benzene (Note 3). The solution is cooled in an ice-salt bath to 5°, and a solution of 44.5 g. (50 ml., 0.41 mole) of *tert*-butyl hypochlorite[2] (Note 4) in 50 ml. of dry benzene (Note 3) is added at such a rate as to maintain the temperature below 10° (Note 5). After the addition of the *tert*-butyl hypochlorite solution is complete, the reaction mixture is stirred at room temperature 1–4 hours (Note 6).

The Y-tube is replaced by a reflux condenser fitted with a calcium chloride drying tube, and a freshly prepared solution of 13.8 g. (0.60 g. atom) of sodium in 140 ml. of anhydrous methanol (Note 7) is added to the benzene solution of N,N-dichloro-α-phenylethylamine at such a rate as to maintain gentle reflux (Note 8). After addition of the sodium methoxide is complete, the reaction mixture is heated under reflux until a test with acidified starch-iodide paper is negative (about 45–70 minutes)

(Note 9). The reaction mixture is cooled in an ice-water bath, and the precipitated sodium chloride is removed by filtration through a Büchner funnel. The filter cake is washed with three 25-ml. portions of dry benzene. The combined filtrates are added very slowly with shaking or stirring *to* 150 ml. of 2*N* hydrochloric acid contained in a 1-l. beaker (Note 10). The layers are separated, and the benzene layer is extracted with three 50-ml. portions of 2*N* hydrochloric acid. The combined acid extracts are washed twice with 50-ml. portions of ether (Note 11). The ether extracts are discarded. The pale amber to yellow aqueous solution is evaporated to dryness at a temperature not greater than 40° (Note 12). The residue is transferred to a 1-l. round-bottomed flask fitted with a reflux condenser to which is added 400 ml. of isopropyl alcohol-hydrochloric acid solution (Note 13). The mixture is heated under reflux for at least 30 minutes and is filtered hot through a Büchner funnel. The residual solid is returned to the flask and extracted in the same manner with a 150-ml. portion of the isopropyl alcohol-hydrochloric acid solution. The solid residue (sodium chloride) is discarded (Note 14). The two extracts are cooled separately in the refrigerator overnight and then filtered on a Büchner funnel (Note 15). The nearly colorless crystals are washed on the filter with two 50-ml. portions of dry ether. Each of the filtrates is diluted with an equal volume of dry ether (400 ml. and 150 ml., respectively) and is allowed to stand in the refrigerator overnight. From these diluted filtrates additional crops of crystals are collected (Note 16). The combined yield of the three to four crops is 18.9–24.8 g. (55–72%), m.p. 185–186° dec. (Note 17) and (Note 18). Normally the product is sufficiently pure for use without further purification: however, the product may be recrystallized from isopropyl alcohol-hydrochloric acid solution (Note 12), using 100 ml. of the solution for each 6 g. of compound. The recovery is about 5.5 g. per 6.0 g. of crude product.

2. Notes

1. The submitters used apparatus with ground-glass joints and dried the various pieces in the oven at 120–140° overnight before use. The Y-tube was constructed from a 24/40 male joint by joining a short length of 8-mm. i.d. glass tubing to the unground end of the joint in such a fashion as to permit insertion of a thermometer through the joint into the flask and then joining a second short piece of 8-mm. i.d. glass tubing in such a fashion as to permit attachment of a calcium chloride tube without interfering with the thermometer opening. If desired, a four-necked flask may be substituted for the Y-tube and three-necked flask.
2. The submitters used *dl*-α-phenylethylamine obtained either from the Eastman Kodak Company or Matheson, Coleman and Bell without further purification. The preparation of *dl*-α-phenylethylamine has been described previously in *Organic Syntheses*.[3,4]
3. Reagent grade dry benzene is dried by simple distillation, the first 10% of the distillate being discarded.
4. The submitters did not redistil the *tert*-butyl hypochlorite. If it is desired to avoid the use of *tert*-butyl hypochlorite, an equivalent quantity of dichloramine B (N,N-dichlorobenzenesulfonamide, Arapahoe Chemical Co., Boulder, Colorado) may be substituted. This material is soluble in benzene but the benzenesulfonamide is not; therefore the reaction mixture must be filtered just before the addition of the sodium methoxide solution. Using this technique, the submitters obtained 44–52% of phenacylamine hydrochloride.
5. The rate of addition is not critical, for the reaction is not especially exothermic. However, at even slightly elevated temperatures the N,N-dichloroamines may begin to decompose with the formation of undesired products; therefore the addition can be carried out as rapidly as desired within the specified temperature range. With a reasonable cooling efficiency this will be well below 30 minutes, but no harm will be done if a longer period is required.
6. The halogenation reaction appears to be quite rapid; therefore the time of stirring is not critical but probably should not be prolonged beyond 4 hours. The submitters used this time interval to prepare the sodium methoxide solution, and the actual time lapse depended upon the time required to prepare this solution. The solution of N,N-dichloro-α-phenylethylamine should be clear yellow after the stirring period. A turbid solution or one containing a precipitate usually indicates a poor sample of *tert*-butyl hypochlorite.
7. Commercial absolute methanol is dried by heating the material under reflux over magnesium turnings for 4 hours, followed by distillation into a dried receiver. Normally 1 g. of magnesium turnings per 100 ml. of absolute methanol will be sufficient. To allow for losses during the drying and distillation, the charge of methanol should be at least twice the amount required for the preparation.

It is advantageous to dry the methanol the day before the preparation is to be carried out and to store the dried methanol in a carefully sealed, *dry* flask or to allow the methanol-magnesium mixture to reflux overnight followed by distillation just prior to use.
The submitters used the inverse addition procedure for preparing the methanolic sodium methoxide, as follows. In a thoroughly dry 500-ml., three-necked, round-bottomed flask fitted with a mechanical stirrer, dropping funnel, and a reflux condenser carrying a calcium chloride drying tube is placed 13.8 g. (0.60 g. atom) of sodium freshly cut into small pieces. To this is added slowly 140 ml. of anhydrous methanol at such a rate as to maintain vigorous reflux. If all the sodium does not dissolve during the addition of the methanol, the mixture may be heated on the steam bath until solution is effected or additional methanol (up to 25 ml.) may be added. The preparation of the solution of sodium methoxide requires about 30 minutes.
It may be advantageous to allow a slow stream of dry nitrogen to pass through the apparatus during the addition of the methanol. The submitters routinely omit this precaution and, as yet, have experienced no accidents or fires. For other precautions see Note 1, *Org. Syntheses*, Coll. Vol. **3**, 215 (1955).
8. The rate of addition probably is not critical but should not be allowed to proceed uncontrolled. The submitters added the sodium methoxide solution at such a rate as to cause vapors of the refluxing methanol to condense in the first 2–3 in. of the reflux condenser without application of external heating.
9. A positive test is the immediate formation of a dark violet or brown spot on starch-iodide paper moistened with 2*N* hydrochloric acid. A negative test may consist of a very faint beige color or complete absence of color.
10. The reverse mode of addition may lower the yield and introduce unwanted condensation products of the amino ketone, which is not stable in neutral or alkaline solution.
11. The procedure should be continued up to at least this point without stopping. After this operation the sequence may be interrupted at any time.
If the *tert*-butyl hypochlorite has been prepared in advance and if the methanol to be used has been allowed to reflux over magnesium overnight, the solvents can be distilled and the reaction carried to this point in an 8-hour day. However, it may be preferable to prepare the dry solvents the day before the reaction is to be run. The latter procedure appears to have little effect on the final yield provided that the solvents are stored in tightly sealed containers and transferred with due care.
12. The submitters strongly recommend the use of a rotating evaporator (such as the Flash-Evaporator, Laboratory Glass Supply Co., New York 31, N. Y.). with which the solution can be reduced to a syrup in about 4 hours. The further evaporation is facilitated by adding 100 ml. of commercial absolute ethanol at this point and continuing the evaporation. Total time for evaporation will be about 6 hours, and the product will be a crystalline mass. The extraction step may be carried out in the 2-l. flask normally used with the evaporator.
If a rotating evaporator is not available, the solution is poured into a large porcelain evaporating dish and is allowed to stand protected in the hood for several days. Toward the end of this time, the evaporation may be accelerated by the addition of 100 ml. of ethanol as described above. The checkers removed water by blowing air over the solution.
13. The isopropyl alcohol-hydrochloric acid solution contains 1 ml. of concentrated hydrochloric acid per 100 ml. of isopropyl alcohol. If the hydrochloric acid is omitted, the product will be impure and the yield greatly reduced. Sodium chloride is not appreciably soluble in this solution.
14. The yield of sodium chloride is usually 33–35 g. (94–100%). It is often helpful to recover and weigh the sodium chloride before discarding it. An excess over the theoretical amount indicates incomplete extraction.
15. If the reflux period has been sufficiently long, little or no precipitate will be formed at this stage in the second extracting solution, which is used to ensure efficient extraction.
16. At this stage, crops of crystals may be formed in each solution.
17. Further treatment of the filtrate normally will yield little crystalline material.
18. The submitters report that, on the basis of experience in student preparation courses, the usual percentage yields for fairly capable technicians on their first trial are in the low fifties, and on subsequent trials in the sixties. Persons with exceptionally good laboratory technique may get even greater yields than those specified (up to 78%).
This procedure may be used for the preparation of a variety of α-amino ketones as is indicated in Table I, which summarizes most of the submitters' experience with this reaction. Principal deviations from the procedure will be in the time required for a negative starch-iodide test and the nature and amount of

extraction and recrystallization solvent. *It is strongly recommended that any one using the reaction for the first time carry out the preparation on α-phenylethylamine before attempting to use it on other more valuable amines.*

TABLE I PREPARATION OF α-AMINO KETONES

Product	Approx. Reaction Time,[a] min.	Yields, %	Recryst. Solvent	M.P., °C.[b]
Hydrochloride of				
2-Aminocyclopentanone	180	34–36	*i*-PrOH	146–147
2-Aminocyclohexanone	25–45	49–73	*i*-PrOH	156
3-Amino-2-heptanone	210	50–75	*i*-PrOH	134–135
p-Bromophenacylamine	70	58–73	2*N* HCl	275
p-Chlorophenacylamine	80–90	49–60	EtOH	270–271
p-Methoxyphenacylamine	270	62–74	EtOH	200
p-Nitrophenacylamine	60	50–56	MeOH	243
p-Methylphenacylamine	80–90	70–72	*i*-PrOH	206–207
p-Phenylphenacylamine	80	54–71	2*N* HCL	185–186
α-Aminovalerophenone	30	65–66	*i*-PrOH-Et_2O	156.5–158
2-Amino-1-tetralone	100	63–70	*i*-PrOH	201–202
2-Amino-4,4-dimethyl-1-tetralone	300	61–65	*i*-PrOH	212–213
Desylamine (2-amino-2-phenylacetophenone)	30	45–46	*i*-PrOH	233–234
Phenacylamine	45–70	55–78	*i*-PrOH	185–186

*a*Time for negative starch-iodide test.
*b*Usually with decompsition.

3. Discussion

Phenacylamine hydrochloride has been prepared by (1) the hydrolysis of the quaternary salt obtained from phenacyl bromide and hexamethylenetetramine (the Delepine reaction),[5,6,7,8,9,10,11] (2) the hydrolysis of N-phenacylphthalimide (the Gabriel reaction),[12,13,14] (3) the reduction or catalytic hydrogenation of α-oximinoacetophenone,[10,15,16,17,18,19] (4) the reduction of α-nitroacetophenone,[20,21] (5) the catalytic hydrogenation of α-azidoacetophenone,[22] (6) the catalytic hydrogenation of α-benzylaminoacetophenone,[23] (7) the base-catalyzed rearrangement of the tosylate of acetophenone oxime (the Neber rearrangement),[24,25] (8) the base-catalyzed rearrangement of acetophenone dimethylhydrazone methiodide,[26] (9) the Friedel-Crafts acylation of benzene with glycyl chloride hydrochloride,[27] as well as by other procedures of uncertain preparative value. The present procedure is adapted from those of Baumgarten and Bower[19] and Baumgarten and Petersen.[28]

4. Merits of the Preparation

The present procedure is a specific example of a synthetic method of some generality. The procedure describes an example which is of considerable interest *per se* but, perhaps more importantly, which also serves as a model for the use of this procedure for the preparation of other α-amino ketones. In the submitters' laboratory, this specific procedure is used routinely for the training of persons who will be using this general technique or related techniques.[29]

Of the procedures cited in Section 3, procedures (1), (3), and (4) have been examined by the submitters for comparison with the present procedure. Of these, the present procedure and that based on the Delepine reaction (1) appeared to be the most satisfactory for preparative purposes. Yields by the two procedures were comparable; however, the Delepine reaction could be run somewhat more conveniently on a larger scale (provided that one was willing to accept a tedious extraction of the product from the copious quantity of ammonium salts with which it is mixed). The Delepine reaction

also makes a lesser demand on the skill and technique of the operator. On the other hand, attempts in the submitters' laboratory to extend the Delepine reaction to *sec*-bromides have been unsuccessful; therefore the Delepine reaction appears to lack the generality of the present procedure, which shares such generality, apparantly, with procedures (2), (3), (7), and (8). Furthermore, the Delepine reaction gives a mixture of phenacylamine hydrochloride and hydrobromide[5,10] (although the submitters have found that by careful fractional crystallization from isopropyl alcohol-hydrochloric acid solution about 50% of the pure hydrochloride can be obtained).

Under appropriate conditions each of the intermediates shown in the equation may be prepared. Suitable conditions for the preparation of many N-chloroimines are described in this volume.[30] In the event that this procedure is found unsuitable, the use of slightly more than one equivalent of sodium methoxide *at room temperature* may be an acceptable alternative.[31] Solutions of the methoxy aziridine may be obtained by carrying out the present procedure up to the point where the starch-iodide test is negative. In favorable examples the methoxy aziridines may be isolated.[31]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 121
- Org. Syn. Coll. Vol. 5, 208

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

isopropyl alcohol-hydrochloric acid

dichloramine B

tosylate of acetophenone oxime

ethanol (64-17-5)

hydrochloric acid,
HCl (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

magnesium,
magnesium turnings (7439-95-4)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

sodium methoxide (124-41-4)

sodium (13966-32-0)

isopropyl alcohol (67-63-0)

hexamethylenetetramine (100-97-0)

Phenacyl bromide (70-11-1)

α-Phenylethylamine,
dl-α-phenylethylamine (3886-69-9)

α-oximinoacetophenone

α-nitroacetophenone (614-21-1)

Benzenesulfonamide (98-10-2)

phenacylamine

2-aminocyclohexanone

Phenacylamine hydrochloride,
Acetophenone, 2-amino-, hydrochloride (5468-37-1)

N,N-dichloro-α-phenylethylamine

N,N-dichlorobenzenesulfonamide (473-29-0)

methanol-magnesium

N-phenacylphthalimide

α-azidoacetophenone

α-benzylaminoacetophenone

acetophenone dimethylhydrazone methiodide

glycyl chloride hydrochloride

2-Aminocyclopentanone

3-Amino-2-heptanone

α-Aminovalerophenone

2-Amino-1-tetralone

2-Amino-4,4-dimethyl-1-tetralone

Desylamine,
2-amino-2-phenylacetophenone

methoxy aziridine

tert-Butyl hypochlorite (507-40-4)

p-Bromophenacylamine

p-Chlorophenacylamine

p-Methoxyphenacylamine

p-Nitrophenacylamine

p-Methylphenacylamine

p-Phenylphenacylamine