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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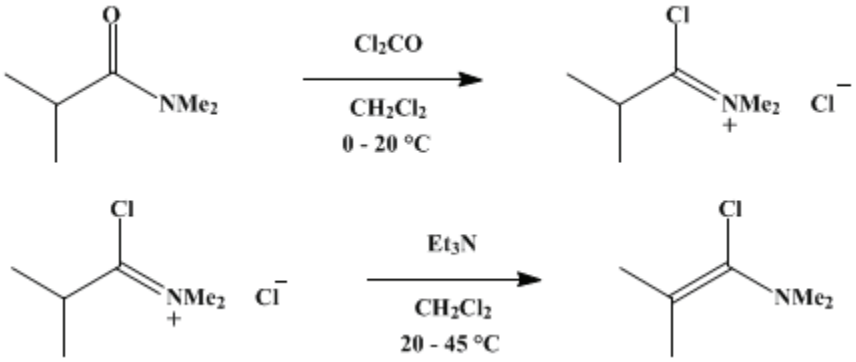
α-CHLORO ENAMINES, REACTIVE INTERMEDIATES FOR SYNTHESIS: 1-CHLORO-*N*,*N*,2-TRIMETHYLPROPENYLAMINE

[Propenylamine, 1-chloro-*N*,*N*,2-trimethyl-]



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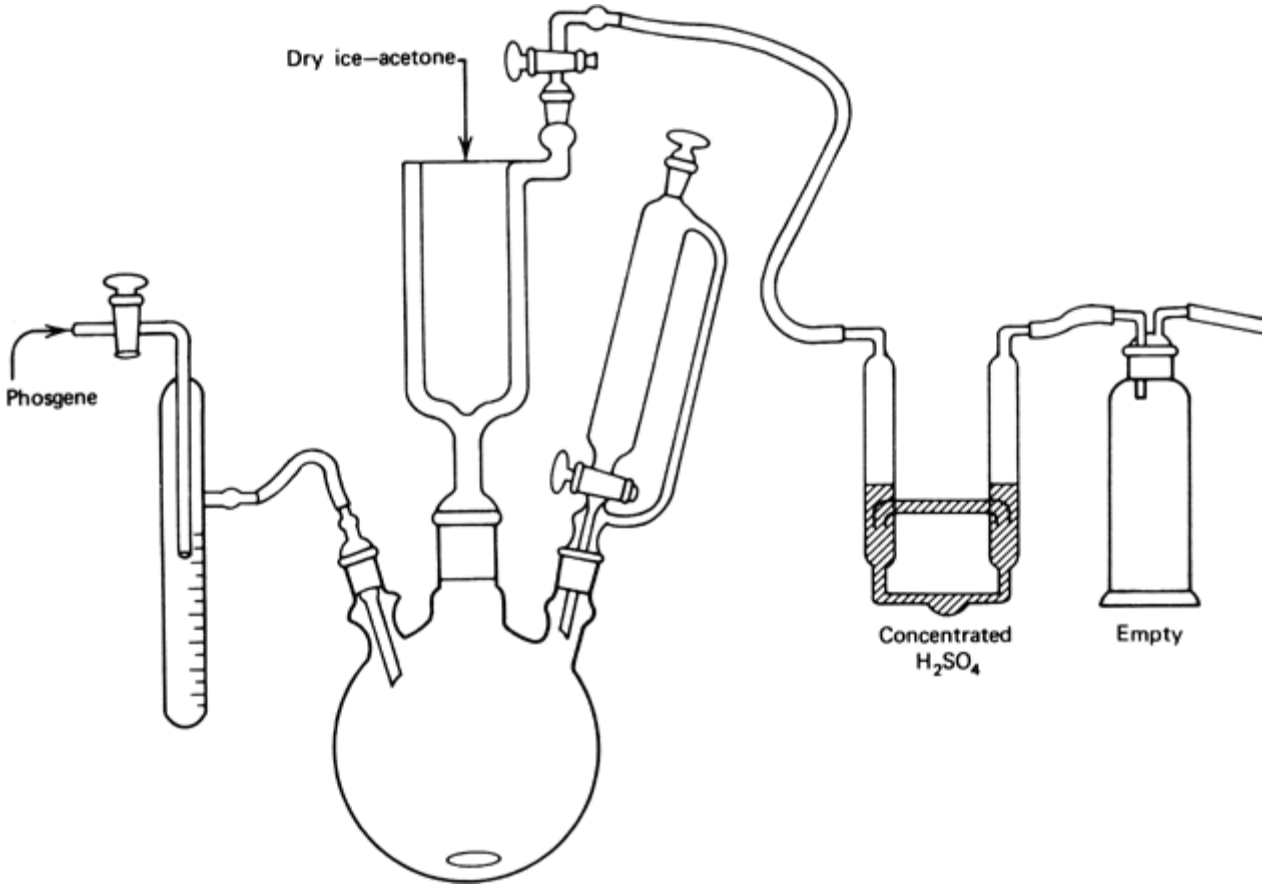
Checked by Masayuki Murakami, Mitsuru Yoshioka, and Wataru Nagata.

1. Procedure

Caution! Phosgene is highly toxic. This preparation should be carried out in a well-ventilated hood.

A. 1-*Chloro*-N,N,2-*trimethylpropylideniminium chloride*. A 1-l., three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a pressure-equalizing dropping funnel, an inlet tube connected to a graduated trap with a flexible polyethylene tube, and a dry-ice condenser connected to a series of three traps. The first and last traps in the series contain sulfuric acid and 10% potassium hydroxide, respectively, and the middle trap is left empty, as shown in Figure 1. Phosgene (85–100 ml., 1.2–1.4 moles) (Note 1) is condensed in the graduated trap which is cooled in an acetone–dry ice bath. The flask is charged with 200 ml. of anhydrous dichloromethane (Note 2) and cooled in an ice–salt bath. The liquid phosgene is slowly poured into the flask (Note 3), the inlet tube is replaced with a thermometer, and a solution of 115 g. (1.00 mole) of freshly distilled *N*,*N*-dimethylisobutyramide (Note 4) in 150 ml. of anhydrous dichloromethane is added dropwise from the dropping funnel over 20 minutes. The temperature is maintained at 0° during this time and gradually raised to room temperature within *ca.* 1 hour. The gas evolution becomes vigorous, and the phosgene begins to boil. The reaction mixture, containing a white precipitate, is left overnight at room temperature. The flask is prepared for distillation and connected to a water pump (Note 5), maintaining a slightly reduced pressure in the system. The excess phosgene and most of the solvent are removed by warming the flask in a water bath at *ca.* 50° and collected in an ice-cold receiver (Note 6). The white or pale-yellow solid remaining, 1-chloro-*N*,*N*,2-trimethylpropylideniminium chloride, is used directly in Part B.

Figure 1.



B. 1-*Chloro*-N,N,2-*trimethylpropenylamine*. The flask is equipped with a dropping funnel, a mechanical stirrer, and a reflux condenser protected from moisture with a sulfuric acid trap. The iminium chloride is suspended in 200 ml. of anhydrous dichloromethane, and 140 g. (1.39 moles) of triethylamine (Note 7) is slowly added to the mixture from the dropping funnel, with vigorous stirring, over 1 hour (Note 8). The temperature rises to 45°, and the solvent begins to reflux. The resulting suspension is stirred at room temperature for an additional 2 hours, after which 150 ml. of dry, low-boiling petroleum ether (Note 9) is added to complete the precipitation of triethylamine hydrochloride (Note 10). The mixture is quickly filtered under nitrogen (Note 11) into a 1-l., round-bottomed flask through an Iena sintered-glass filter. A 300-ml. portion of petroleum ether is used to wash the flask and the triethylamine hydrochloride on the filter. The solvent is removed by distillation under nitrogen. Further distillation through a Vigreux column under nitrogen gives 93–103 g. (69–77%) of 1-chloro-*N,N*,2-trimethylpropenylamine, b.p. 125–130° (760 mm.) (Note 12) and (Note 13). The compound is very sensitive to humidity and should be immediately stored in ampoules (Note 14).

2. Notes

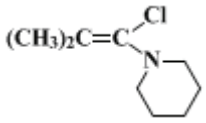
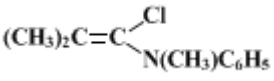
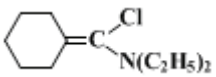
1. The submitters used technical grade phosgene purchased from Gardner Cryogenics Europe N. V., 1800 Vilvoorde, Belgium.
2. Technical grade dichloromethane was dried by refluxing over phosphorus pentoxide for 24 hours and distilled.
3. Alternatively phosgene may be allowed to distill into the flask cooled in an acetone–dry ice bath. For this operation the inlet tube should extend to the bottom of the flask.
4. Following a procedure reported in the literature,[2] the checkers prepared *N,N*-dimethylisobutyramide, b.p. 67–68° (15 mm.), in 85% yield by treating reagent grade isobutyryl chloride with 2 molar equivalents of reagent grade dimethylamine in anhydrous ethyl ether at 0°. The reported boiling point for *N,N*-dimethylisobutyramide is 175–176° (744 mm.).[2] Isobutyryl chloride and dimethylamine were both purchased from Tokyo Kasei Kogyo Company Ltd., Tokyo, Japan. These two reagents are also

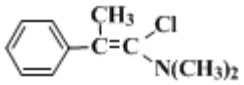
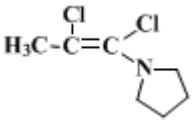
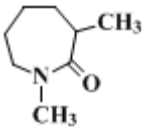
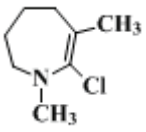
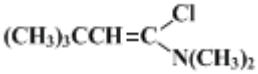
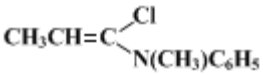
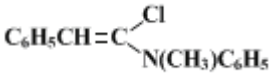
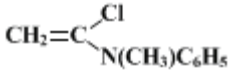
available from Aldrich Chemical Company, Inc., and the Specialty Gas Division, J. T. Baker Chemical Company, respectively.
5. A phosphorus pentoxide tube is placed between the water pump and the distillation apparatus.
6. The submitters found that filling the flask with argon helped to reduce exposure to moisture in the air.
7. The submitters used Baker-grade triethylamine purchased from J. T. Baker Chemicals N.V., P.O. Box 1, Deventer, Holland, after distillation from potassium hydroxide.
8. The reaction is exothermic. The checkers found that the yield of the final product was raised from 57% in the first run to 71% in the second and third runs when the triethylamine was added at 30–34° with slight cooling. Another procedural change made by the checkers in Part A in these last two runs was that the dry ice condenser was kept in place for more than 8 hours after the addition of *N,N*-dimethylisobutyramide was completed. In the first run the condenser was removed after 20 minutes.
9. The submitters used technical petroleum ether, b.p. <70°, which was distilled from sodium wire.
10. Leaving the reaction mixture overnight before filtration did not affect the yield.
11. A slow stream of dry nitrogen was passed through an inverted funnel placed over the filtration apparatus.
12. The checkers collected several fractions during the distillation. Early fractions boiling at 100–125° (760 mm.) were shown to be a mixture of the product and triethylamine. The product from two runs carried out at one-half scale was collected in two main fractions amounting to 2.2–5.8 g., b.p. 125–130° (760 mm.), and 41.7–45.4 g., 130–134° (760 mm.). The total yield was 47.5–47.6 g. (71%), b.p. 125–134°. The submitters obtained 105–110 g. (78–82%), b.p. 129–130° (760 mm.).
13. The checkers obtained an analysis on the distilled product. Analysis calculated for $C_6H_{12}NCl$: C, 53.93; H, 9.05; N, 10.48; Cl, 26.54. Found: C, 54.51; H, 9.21; N, 10.69; Cl, 26.49. The spectral properties of the product are as follows: IR (CCl_4) cm.$^{-1}$: 1653, 1470, 1451, 1295, 1124, 1013; ^{1}H NMR (*ca.* 15% w/v in CCl_4), δ (multiplicity, number of protons, assignment): 1.73 (s, 3H, allylic C*H*$_3$), 1.79 (s, 3H, allylic C*H*$_3$), 2.37 (s, 6H, 2NC*H*$_3$); ^{1}H NMR (about 15% w/v in $CDCl_3$), δ (multiplicity, number of protons, assignment): 1.77 (s, 6H, two allylic C*H*$_3$) and 2.38 (s, 6H, 2NC*H*$_3$); mass spectrum (225°, 70 e.v.) *m/e* (relative intensity): 135 (M + 2, 24), 133 (M, 77), 98 (100), 83 (56), 82 (23), 72 (31), 44 (36), 42 (60).
14. The tubes should be sealed immediately to avoid hydrolysis. In spite of this precaution, a light precipitate is always formed.

3. Discussion

1-Chloro-*N,N*,2-trimethylpropenylamine has been prepared by reaction of 2-methylpropenylidenebis(dimethylamine) with phosphorous trichloride or dichlorophenylphosphine.[3] The present method[4] is far more convenient and general. The reagents are inexpensive, the amide reactants are readily available, and the procedure is applicable to the synthesis of various α-chloro enamines on a large scale with only minor modifications (Table I).[5]

TABLE I
SYNTHESIS OF α-CHLORO ENAMINES FROM AMIDES

Entry	Amide	α-Chloro Enamine	Yield(%)
1			85
2	$(CH_3)_2CHCON(CH_3)C_6H_5$		55–79
3			40

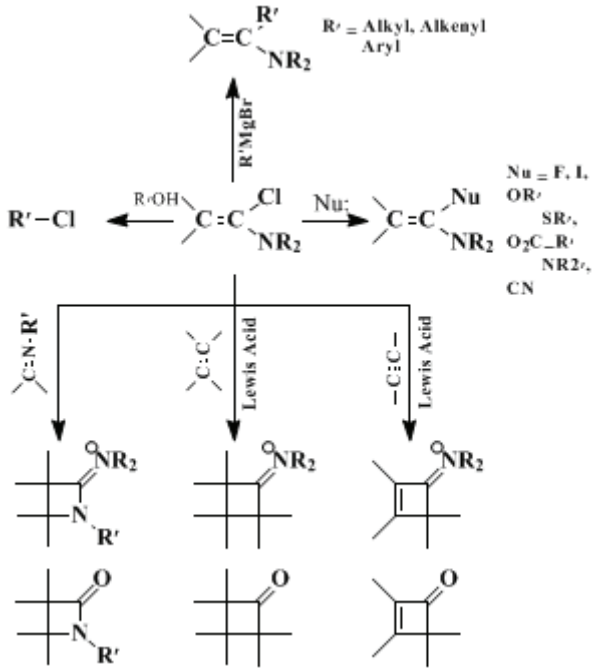
4	$C_6H_5CH(CH_3)CON(CH_3)_2$		76[a]
5			60–70[a]
6			75
7	$(CH_3)_3CCH_2CON(CH_3)_2$		65[a]
8	$CH_3CH_2CON(CH_3)C_6H_5$		45–62[a]
9	$C_6H_5CH_2CON(CH_3)C_6H_5$		45
10	$CH_3CON(CH_3)C_6H_5$		42

[a]The product is a mixture of *cis* and *trans* isomers.

The reaction of the more basic amides with phosgene is exothermic *(Caution!);* consequently the reaction mixture must be cooled in an ice bath. With the less reactive amides (*e.g.*, entries 2, 4, 5, and 8–10), however, the reaction often requires several days. It can be accelerated by the addition of catalytic amounts of *N,N*-dimethylformamide. With the monosubstituted acetamides or acetanilides, the solution must be saturated with gaseous hydrogen chloride before adding phosgene to avoid the formation of β-chlorocarbonyl α-chloro enamines resulting from elimination of hydrogen chloride and acylation of the α-chloro enamine with phosgene. The subsequent elimination reaction must be conducted with an excess of triethylamine in ethyl ether, carbon tetrachloride, or petroleum ether. Dichloromethane and chloroform are not suitable since these solvents promote the formation of condensation products to a considerable extent. With the exceptions of entries 7–10, α-chloroenamines derived from monosubstituted acetamides are unstable and should be kept in solution at concentrations below 1 *M*.

Most α-chloro enamines can be readily converted into the corresponding α-fluoro enamines by reaction with potassium or cesium fluoride.[6] The less stable α-iodo enamines are more conveniently prepared *in situ* from α-chloro enamines and potassium iodide. 1-Bromo-*N,N*,2-trimethylpropenylamine is easily obtained from the corresponding chloro compound and refluxing dibromomethane.[7] All α-haloenamines are highly hygroscopic and must be stored in sealed tubes.

α-Halo enamines are useful organic reagents that show versatile chemical behavior and have great synthetic potential.[5] As enamines derived from carboxylic acid halides, they react with a variety of electrophilic reagents on C-2 to give, after hydrolysis, a carboxamide substituted at the α-position. Moreover, spontaneous or catalyzed ionization leads to keteniminium ions that are strongly electrophilic and add various nucleophilic reagents at C-1.[5,8,9,10] Keteniminium ions are also capable of undergoing [2 + 2]-cycloaddition reactions with olefins,[11] acetylenes,[12] and imines[13] extremely readily. 1-Halo-*N,N*,2-trimethylpropenylamines are also highly effective reagents for the replacement of hydroxyl groups by chlorine, bromine, and iodine under neutral conditions.[5,7] A summary of some of the reactions of α-chloro enamines follows.



This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 441

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

petroleum ether

iminium chloride

2-methylpropenylidenebis(dimethylamine)

sulfuric acid (7664-93-9)

hydrogen chloride (7647-01-0)

ethyl ether (60-29-7)

chloroform (67-66-3)

carbon tetrachloride (56-23-5)

potassium iodide (7681-11-0)

nitrogen (7727-37-9)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

phosgene (75-44-5)

phosphorous trichloride (7719-12-2)

potassium (7440-09-7)

dimethylamine (124-40-3)

Triethylamine hydrochloride (554-68-7)

dibromomethane (74-95-3)

dichloromethane (75-09-2)

isobutyryl chloride (79-30-1)

N,N-dimethylformamide (68-12-2)

triethylamine (121-44-8)

dichlorophenylphosphine (644-97-3)

cesium fluoride (13400-13-0)

phosphorus pentoxide (1314-56-3)

1-Chloro-N,N,2-trimethylpropenylamine,
Propenylamine, 1-chloro-N,N,2-trimethyl- (26189-59-3)

N,N-dimethylisobutyramide (21678-37-5)

1-Bromo-N,N,2-trimethylpropenylamine (73630-93-0)

1-Chloro-N,N,2-trimethylpropylideniminium chloride (52851-35-1)