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A Publication
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for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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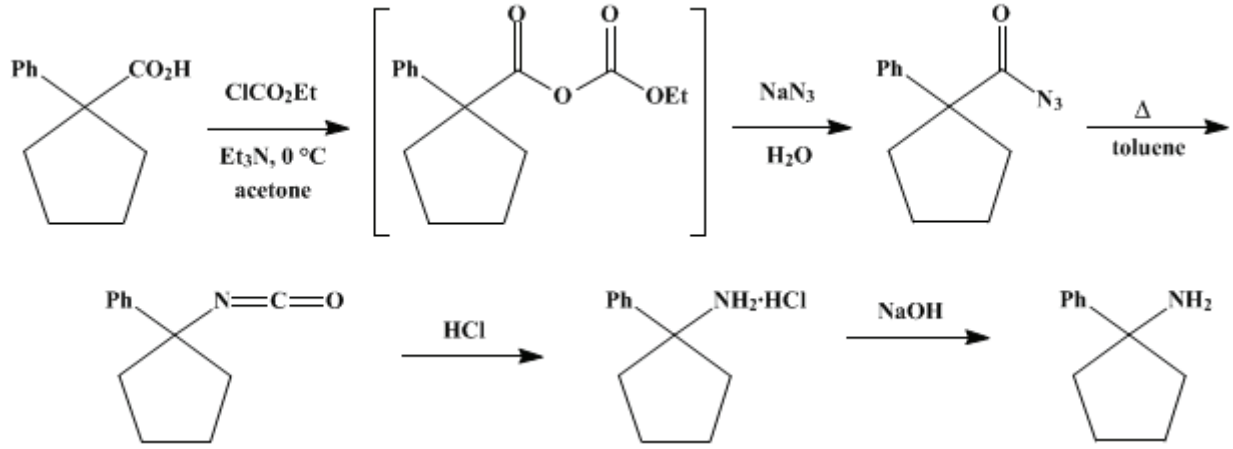
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.051.0048

Organic Syntheses, Coll. Vol. 6, p.910 (1988); Vol. 51, p.48 (1971).

AMINES FROM MIXED CARBOXYLIC-CARBONIC ANHYDRIDES: 1-PHENYLCYCLOPENTYLAMINE

[Cyclopentanamine, 1-phenyl-]



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1. Procedure

A 1-l., three-necked, round-bottomed flask equipped with an air stirrer, dropping funnel, and low-temperature thermometer is charged with 38.0 g. (0.200 mole) (Note 1) of 1-phenylcyclopentanecarboxylic acid and 150 ml. of acetone. The mixture is stirred, and 22.3 g. (30.6 ml., 0.221 mole) of triethylamine is added over 5 minutes (a 2° rise in temperature is observed). The solution is chilled to −5 to 0° in an ice-salt bath, and 24.0 g. (21.1 ml., 0.221 mole) of ethyl chlorocarbonate (Note 2) in 50 ml. of acetone is added slowly (25 minutes), maintaining the temperature between −5 to 0°. After the addition is complete, the cold mixture is stirred for an additional 15 minutes. A solution of 26.0 g. (0.400 mole) of sodium azide in 75 ml. of water is added over a 25-minute period while the temperature is kept at −5 to 0°. The mixture is stirred for 30 minutes longer at this temperature, poured into 750 ml. of ice water, and shaken with four 250-ml. portions of toluene (Note 3). The combined toluene extracts are dried over anhydrous magnesium sulfate and transferred to a 2-l., three-necked, round-bottomed flask equipped with a two-necked, Claisen-type adapter, stirrer, and reflux condenser. The stirred solution is heated cautiously (Note 4) under reflux for 1 hour on a steam bath (nitrogen evolution is observed initially). The toluene is then removed at 50° with a rotary evaporator (aspirator pressure). The flask containing the residual, oily isocyanate is again fitted with the Claisen-type adapter, stirrer, and reflux condenser. The oil is stirred, cooled in an ice bath, and 300 ml. of 8 *N* hydrochloric acid (Note 5) is added. The cooling bath is removed, the stirred mixture is gradually heated on a steam bath (Note 6) until carbon dioxide evolution has subsided (30 minutes), and the solution is heated under reflux for 10 minutes. The flask is evacuated with a water aspirator and warmed in a bath at 50° for about 10 minutes. About 10–20 ml. of distillate is collected before a crystalline product separates (Note 7). Ice water (200 ml.) is added to the flask with cooling in an ice bath, and 1 l. of 2.5 *N* sodium hydroxide is added slowly to pH 12. The mixture is shaken with three 200-ml. portions of diethyl ether, the combined extracts are dried over anhydrous magnesium sulfate, and the ether is removed by distillation at 50° with a water aspirator, yielding 29.7 g. of an oil. Distillation of the crude product gives 24.5–26.1 g. (76–81%) of 1-phenylcyclopentylamine, b.p. 112–114° (9 mm.), $n_D^{20.5}$ 1.5439 (Note 8).

2. Notes

1. 1-Phenylcyclopentanecarboxylic acid,[2,3] m.p. 157–159°, was obtained from Aldrich Chemical Company, Inc.
2. A commercial grade of ethyl chlorocarbonate, stabilized with calcium carbonate, was employed without purification.
3. Approximately 3.6–3.9 g. of 1-phenylcyclopentanecarboxylic acid (m.p. 158–159.5°) can be recovered by acidification of the aqueous solution which remains after washing with toluene.
4. Rearrangement of the azide must be carried out carefully as the reaction is exothermic, and a large volume of nitrogen is evolved. The submitters have encountered no difficulties if the described dilution (0.2 mole of azide in 1 l. of toluene) is employed. The steam bath should be replaced by a cooling bath if the solution refluxes vigorously.
5. Approximately 8 *N* hydrochloric acid was prepared by addition of 100 ml. of water to 200 ml. of 37.5% hydrochloric acid.
6. Heating should be gradual and in a large reaction vessel as hydrolysis of isocyanate is accompanied by evolution of carbon dioxide and considerable foaming may occur. If excessive foaming occurs, the steam bath should be removed.
7. The checkers carried the synthesis through to this point without interruption. Since this required about 8 hours on the scale described, the equipment and chemicals were made ready the preceding day.
8. ^{1}H NMR spectrum ($CDCl_3$) δ 1.30 (s, 2H, NH_2), 1.83 (broad s, 8H, $4CH_2$), and 7.33 (m, 5H, C_6H_5). The distilled product was of high purity, as determined by GC analysis. A 122 cm. × 6.4 mm. O.D. stainless-steel column containing 3% SE-30 on Diatoport S (80–100 mesh) and programmed from 100–200° at 10°/minute was used. The retention time is about 5 minutes.

3. Discussion

1-Phenylcyclopentylamine has also been prepared from 1-phenylcyclopentanecarboxylic acid by the Hofmann degradation of the intermediate amide[4,5] and from the intermediate carboxylic acid chloride by the Curtius reaction.[6] In the method described, using the mixed carboxylic-carbonic anhydride,[7] improved yields of the amine are obtained.

The usual procedure of preparing acid azides, which involves treating an acid chloride with sodium azide,[8,9] suffers from the disadvantage that it is often difficult to obtain pure acid chlorides in good yields from acids which either decompose or undergo isomerization in the presence of mineral acids.[7] Synthesis of the azide by way of the ester and hydrazide[10] has been used to circumvent this difficulty, but is much less convenient. The present procedure permits ready formation of acid azides in excellent yields from mixed carboxylic–carbonic anhydrides and sodium azide under very mild conditions.

A possible limitation to this procedure, however, is that it is dependent upon the relative reactivity of the two carbonyl groups of the mixed carboxylic–carbonic anhydride toward the azide anion. Although either carbonyl group may be attacked by the azide ion, an attack on the more electrophilic carbonyl group is usually strongly favored and high yields of the acid azides generally result. Steric considerations may be important, but preference for azide attack on even a somewhat hindered carboxylic carbonyl is illustrated by the present example in which this group is proximal to phenyl and cyclopentyl groups.

This modification of the Curtius reaction has been used extensively in many laboratories and has been found to be generally applicable. Some examples from the literature include the stereoselective synthesis of a wide variety of cyclopropylamine derivatives from the corresponding acids,[11,12,13] the stereoselective preparation of some substituted norbornylamines from easily isomerized acids,[14] the preparation of some 1-aminocyclobutanecarboxylic acids from the corresponding acid esters,[15] the preparation of a substituted cyclobutanone from the corresponding cyclobutane-1,1-dicarboxylic acid *via* the 1,1-diamine,[16] and the preparation of a variety of heterocyclic amines from the corresponding acids.[17,18,19]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 433

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

hydrochloric acid (7647-01-0)

ether,
diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

calcium carbonate (471-34-1)

acetone (67-64-1)

toluene (108-88-3)

sodium azide (26628-22-8)

ethyl chlorocarbonate (541-41-3)

magnesium sulfate (7487-88-9)

triethylamine (121-44-8)

1-phenylcyclopentanecarboxylic acid (77-55-4)

1-Phenylcyclopentylamine,
Cyclopentanamine, 1-phenyl- (17380-74-4)