Organic Syntheses

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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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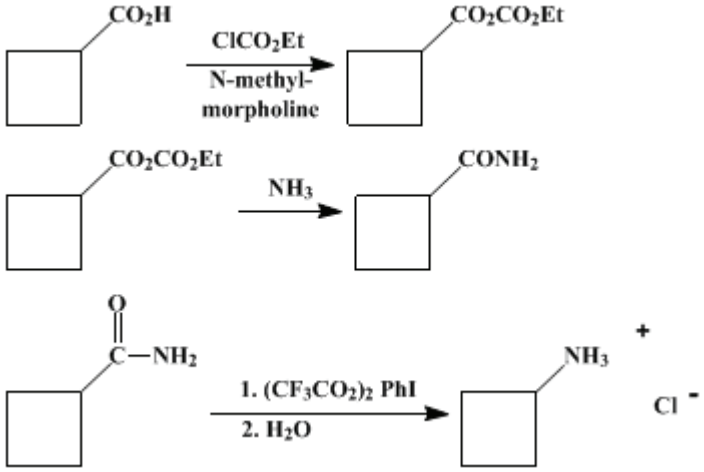
HOFMANN REARRANGEMENT UNDER MILDLY ACIDIC CONDITIONS USING [I,I-BIS(TRIFLUOROACETOXY)] IODOBENZENE: CYCLOBUTYLAMINE HYDROCHLORIDE FROM CYCLOBUTANECARBOXAMIDE

[Cyclobutanamine hydrochloride]



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Checked by C. Eric Schwarta and Edwin Vedejs.

1. Procedure

A. *Cyclobutanecarboxamide*. (See (Note 1).) A 250-mL, round-bottomed flask, equipped with a mechanical stirrer and a drying tube (Drierite), is flame-dried and allowed to cool to room temperature. The flask is equipped with a punctured rubber septum, through which is inserted a −90° thermometer. The flask is subjected to a nitrogen atmosphere by inserting a syringe needle connected to a nitrogen bubbler through the septum along with a second syringe needle used as an outlet. Under a flow of nitrogen the flask is charged via syringe with cyclobutanecarboxylic acid (6.0 g, 59.9 mmol, (Note 2)), 60 mL of dry tetrahydrofuran (Note 2), and *N*-methylmorpholine (6.6 mL, 59.9 mmol, (Note 2)). Stirring is commenced, and the solution is cooled to an internal temperature of −15°C using a dry ice–isopropyl alcohol bath at −20° to −25°C. Ethyl chloroformate (5.7 mL, 59.9 mmol; (Note 2) and (Note 3)) is added and the solution is stirred for 5 min. The addition of ethyl chloroformate results in an internal temperature rise to +8 to +10°C and the precipitation of a white solid. Following the precipitation the continuously stirred mixture, still in the dry ice–isopropyl alcohol bath, is allowed to reach an internal temperature of −14°C. Anhydrous ammonia (Note 2), introduced into the flask via a syringe needle, is vigorously bubbled through the solution for 10 min with manual stirring; the internal temperature rises abruptly to 25°C. With the flask still in the cooling bath, stirring is continued for an additional 30 min, and the reaction mixture is stored in the freezer at −15°C overnight (Note 4).

The slurry is stirred with tetrahydrofuran (100 mL) at room temperature for 5 min and ammonium salts are removed by suction filtration through a Büchner funnel. After the solids are rinsed with tetrahydrofuran (20 mL), the filtrate is passed through a plug of silica gel (65 g Merck 60 230-400 mesh) in a coarse porosity sintered-glass filter funnel with aspirator suction. The funnel is further washed with acetonitrile (750 mL) and the combined filtrates are evaporated (rotary evaporator) to give a white solid. This material is recrystallized by heating (steam bath) with 8 : 1 ether : ethanol (70 mL); if necessary, ethanol is added dropwise to obtain a homogeneous solution. Cooling to room temperature results in white flakes that are collected by filtration (ether wash), 2.93 g. Two more crops (1.3 g total) are obtained by repeating the process for a total of 4.23 g (71%), mp 152–153°C (lit.[2] 155°C). In several

similar runs, the yield of amide was 4.23–4.49 g (71–76%).

B. *Cyclobutylamine hydrochloride*. A 500-mL, round-bottomed flask is equipped with a magnetic stirring bar and covered with aluminum foil. To the flask is added a solution of [I,I-bis(trifluoroacetoxy) iodo]benzene (16.13 g, 37.5 mmol; (Note 5)) in 37.5 mL of acetonitrile, and the resulting solution is diluted with 37.5 mL of distilled deionized water. Cyclobutanecarboxamide (2.48 g, 25 mmol) is added; the amide quickly dissolves. Stirring is continued for 4 hr, and the acetonitrile is removed with a rotary evaporator. The aqueous layer is stirred with 250 mL of diethyl ether; to the stirring mixture is added 50 mL of concd hydrochloric acid (Note 6). The mixture is transferred to a separatory funnel and the layers are separated. The aqueous layer is extracted with two 125-mL portions of ether. The organic fractions are combined and extracted with 75 mL of 2 *N* hydrochloric acid. The aqueous fractions are combined and concentrated with a rotary evaporator using a vacuum pump. Benzene (50 mL, (Note 2)) is added to the residue and the solution is concentrated with the rotary evaporator, again using a vacuum pump. Addition of benzene and concentration is repeated five more times. The crude solid is dried under reduced pressure over sulfuric acid overnight. To the product is added 5 mL of absolute ethanol and 35 mL of anhydrous ether, and the solution is heated at reflux on a steam bath. Ethanol is added slowly to the mixture, with swirling, until all the material is dissolved; the solution is cooled to room temperature. Anhydrous ether is added slowly until crystallization just begins. The flask is placed in the freezer and the product is allowed to crystallize. Filtration of the product and drying overnight under reduced pressure over phosphorus pentoxide yields 1.86–2.06 g of cyclobutylamine hydrochloride (69–77%), mp 183–185°C (lit.[3] [4] 183–184°C).

2. Notes

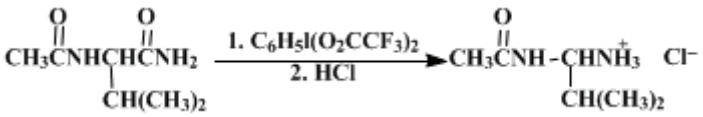
1. The method used here for preparing the amide gives superior yields to two literature methods that employ the acid chloride as an intermediate.[3,4]
2. Sources and purification of reagents are as follows. Cyclobutanecarboxylic acid, 98%, is from Aldrich Chemical Company, Inc., and is vacuum-distilled before use. Tetrahydrofuran is freshly distilled from sodium–benzophenone under nitrogen. *N*-Methylmorpholine, 99%, is from Aldrich Chemical Company, Inc., and is predried over barium oxide, distilled from ninhydrin, and stored over sodium hydroxide pellets. Ethyl chloroformate, 97%, is from Aldrich Chemical Company, Inc., and is freshly distilled prior to use under a nitrogen atmosphere. Anhydrous ammonia (99.99% min) is from a Matheson lecture bottle. The silica gel used for flash chromatography is Davidson grade 62, 60–200 mesh. Acetonitrile is from Fisher Scientific Company, HPLC grade. Benzene, spectral grade, is from J. T. Baker.
3. The submitters have repeated this preparation with isobutyl chloroformate substituted for ethyl chloroformate with no increase in yield.
4. The submitters purified the product by flash chromatography as follows. Tetrahydrofuran is removed on a rotary evaporator. Silica gel (20 g) and 80 mL of acetonitrile (Note 2) are added to the flask. The resulting slurry is concentrated with a rotary evaporator to a dry solid. The material is scraped from the flask and loaded onto a flash-chromatography column (50-mm diameter) containing 250 g of silica gel, prepared according to the method of Still.[7] The column is eluted with acetonitrile (Note 2) at a flow rate of 0.5 in./min (Note 7). The first 500 mL of eluent is measured with a graduated cylinder and discarded, and then fractions (80 × 23 mL) are collected in test tubes. A small aliquot (5 μL) is taken from every other tube and these aliquots are spotted in successive lanes on a silica gel TLC plate (E. Merck No. 5735), which is developed with acetonitrile. The plate is dried and the product detected by the chlorine/starch-potassium iodide procedure (Note 8). This thin-layer analysis reveals that early fractions from the flash chromatography column contain a small amount of ethyl carbamate impurity at $R_f = 0.53$; another unidentified impurity ($R_f = 0.37$) follows. The product cyclobutanecarboxamide emerges next, beginning at about fraction 14 ($R_f = 0.26$). The product appears as a blue-black spot on a faint blue background. There is some overlap between the second impurity and the product. The fractions containing only product are pooled and concentrated in a 1-L, round-bottomed flask with a rotary evaporator to a white crystalline solid. This product is dried under reduced pressure overnight to yield cyclobutanecarboxamide (4.52 g, 76.1%), mp 156–157.5°C (lit.[2] 155°C).
5. [I,I-Bis(trifluoroacetoxy)iodo]benzene is prepared by dissolving, with heating, a given number of grams of (I,I-diacetoxyiodo)benzene(iodobenzene diacetate, Aldrich Chemical Company, Inc.; see also *Org. Synth., Coll. Vol. V*, **1973**, 660) in twice that number of milliliters of trifluoroacetic acid that has

been distilled from a small amount of phosphorus pentoxide. For example, 40 g of (I,I-diacetoxyiodo) benzene is dissolved in 80 mL of trifluoroacetic acid in an Erlenmeyer flask, which is allowed to stand in a dark drawer. The [I,I-bis(trifluoroacetoxy)iodo]benzene crystallizes and is isolated by suction filtration within 2 hr (53–70% yield). If crystallization does not occur, it can be induced by scratching or seeding. It has been the submitters' experience that if a dark-yellow trifluoroacetic acid supernatant is obtained, the yield of the rearrangement reaction carried out with the resulting reagent is invariably poor; the supernatant solution is normally very lightly colored. If the proportion of trifluoroacetic acid is reduced, a greater weight of crystals is obtained; however, this material gives considerably lower yields in the rearrangement. Upon standing, particularly in the light, [I,I-bis(trifluoroacetoxy)iodo]benzene turns yellow; this reagent also gives poor yields in the rearrangement and yellow reaction mixtures; the reaction mixtures of satisfactory rearrangements are water-white. The reagent should be stored in a dark bottle under nitrogen or argon. The submitters have also found that the rearrangement can be effected with (I,I-diacetoxyiodo)benzene or iodobenzene and two equivalents of trifluoroacetic acid.
6. Hydrochloric acid not only provides the chloride counterion for the final product, but also effects the removal of any uncreated (I,I-bis(trifluoroacetoxy)iodo)benzene as the ether-soluble (I,I-dichloroiodo) benzene (iodobenzene dichloride).
7. A nitrogen regulator has to be set at 8 psi to achieve a pressure sufficient to maintain a flow rate of 0.5 in./min. A slower flow rate results in poor resolution.
8. The thin-layer plate is chlorinated for 1 min by placing it in a chamber with potassium chlorate to which a few drops of hydrochloric acid are added. The plate is dried in air for 10 min and then sprayed with aqueous 1% starch-1% potassium iodide solution.

3. Discussion

Hypervalent iodine reagents have been used recently for a variety of organic transformations,[8] including α-hydroxylation of ketones.[5,6] (I,I-Dicarboxyiodo)benzene derivatives have also found a variety of uses.[9] The use of (I,I-diacetoxyiodo)benzene for the conversion of amides to carbamates in alcohol solvents was studied by Smith and Baumgarten,[10] and the "acidic Hofmann rearrangement" utilized in this preparation, in which amides are converted directly into the corresponding amines in partially aqueous solution, was developed by Loudon et al.[11 12] and applied to a variety of amides; the mechanism of the rearrangement has also been studied.[13] The rearrangement occurs with retention of stereochemical configuration at the migrating alkyl group,[10,12,14] and the relative rates of rearrangement generally follow the migratory preferences observed in the Lossen rearrangement, Baeyer–Villiger reaction, and similar migrations to electron-deficient centers.

A particularly interesting application of this reagent is the preparation of "geminal amino amides," a novel class of compounds that have surprising stability in aqueous solution.[15 16 17] These derivatives have found application in the construction of *retro-inverso*-peptides,[18 19] in the design of a novel class of prodrugs,[20 21] and as intermediates in a carboxyl-terminal peptide degradation.[22 23]



Although iodine(III) reagents attack double bonds, the rearrangement of the amide group is, at least in some cases, more rapid than electrophilic attack on alkenes. Thus 3-cyclohexene-1-carboxamide rearranges smoothly to the corresponding amine as long as only one equivalent of [I,I-bis (trifluoroacetoxy)iodo]benzene is used.

The acidic nature of the reagent is important; the trifluoracetic acid liberated in the reaction catalyzes hydrolysis of the intermediate isocyanate, and also ensures that the amine which is formed is protonated and cannot react with the isocyanate to give urea by-products. The reaction can be accelerated by addition of pyridine to an observed pH of about 3.5, and is retarded by added acid or trifluoroacetate ion.[12,13] In the present procedure pyridine was not employed, since the reaction in its absence proceeds with a satisfactory rate.

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

starch

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

ether,
diethyl ether (60-29-7)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

barium oxide

potassium iodide (7681-11-0)

nitrogen (7727-37-9)

pyridine (110-86-1)

chlorine (7782-50-5)

Benzophenone (119-61-9)

sodium (13966-32-0)

potassium chlorate (3811-04-9)

urea (57-13-6)

Iodobenzene (591-50-4)

ethyl chloroformate (541-41-3)

ethyl carbamate (51-79-6)

Tetrahydrofuran (109-99-9)

iodobenzene dichloride (2401-21-0)

Cyclobutanecarboxylic acid (3721-95-7)

argon (7440-37-1)

trifluoroacetic acid,
Trifluoracetic acid (76-05-1)

Cyclobutanecarboxamide (1503-98-6)

ninhydrin (938-24-9)

isobutyl chloroformate (543-27-1)

phosphorus pentoxide (1314-56-3)

Cyclobutylamine hydrochloride,
Cyclobutanamine hydrochloride (6291-01-6)

iodobenzene diacetate (3240-34-4)

N-methylmorpholine (109-02-4)

[I,I-BIS(TRIFLUOROACETOXY)]IODOBENZENE,
[I,I-bis(trifluoroacetoxy)iodo]benzene,
(I,I-bis(trifluoroacetoxy)iodo)benzene (2712-78-9)

(I,I-diacetoxyiodo)benzene (3240-34-4)

(I,I-dichloroiodo)benzene