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of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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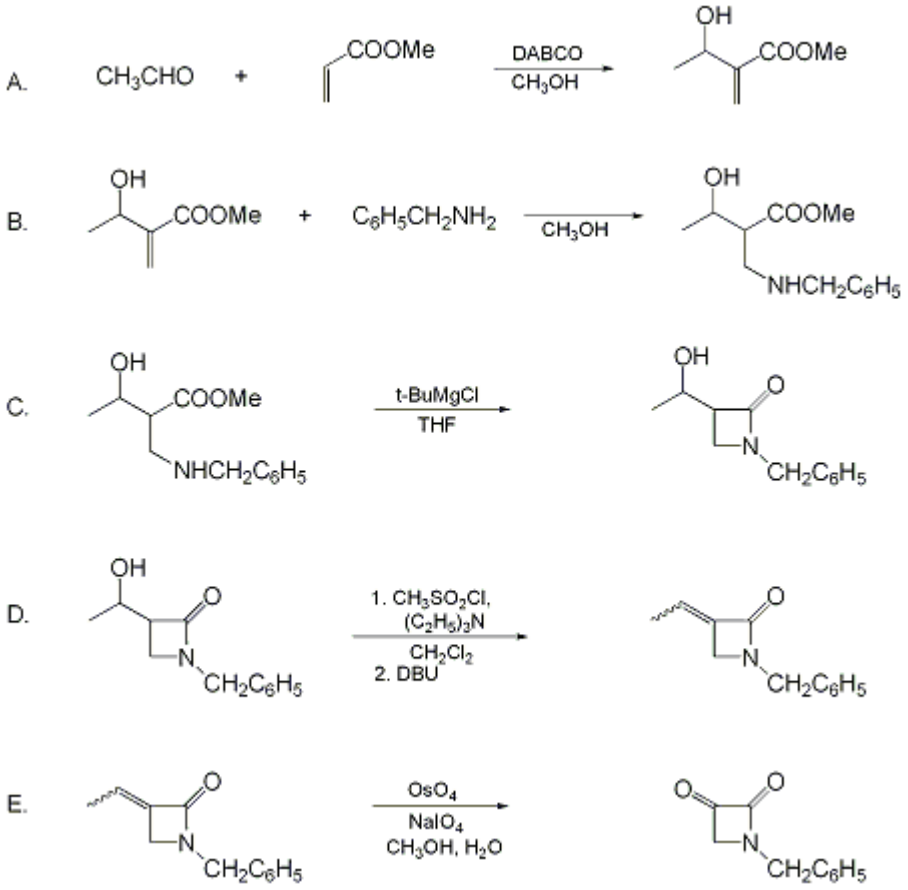
N-BENZYL-2,3-AZETIDINEDIONE

[2,3-Azetidinedione, 1-(phenylmethyl)-]



Submitted by Carsten Behrens and Leo A. Paquette[1] .
Checked by Kei Manabe and Kenji Koga.

1. Procedure

A. Methyl 3-hydroxy-2-methylenebutanoate . A 500-mL, one-necked, round-bottomed flask, equipped with a magnetic stirring bar, is charged with 90.05 mL (1.0 mol) of methyl acrylate , 80 mL (1.43 mol) of acetaldehyde , 11.22 g (0.1 mol) of 1,4-diazabicyclo[2.2.2]octane and 4.0 mL (0.1 mol) of methanol (Note 1). The flask is sealed with a rubber septum and stirred at room temperature for 48 hr. The resulting oil is taken up in ethyl acetate (300 mL) and washed once with water (200 mL). The aqueous layer is back-extracted with ethyl acetate (200 mL) and the combined organic phases are dried over anhydrous magnesium sulfate . After concentration under reduced pressure, the resulting clear oil is fractionally distilled to give 102.1 g (79%) of methyl 3-hydroxy-2-methylenebutanoate as a colorless liquid, bp 62-63°C (1 mm) (Note 2).

B. Methyl 2-(benzylamino)methyl-3-hydroxybutanoate . A dried, 2-L, one-necked, round-bottomed flask, equipped with a magnetic stirring bar, is charged with 68.7 g (0.53 mol) of methyl 3-hydroxy-2-methylenebutanoate and 800 mL of anhydrous methanol . After the addition of 57.7 mL (0.53 mol) of benzylamine (Note 1), the mixture is stirred at room temperature for 48 hr (Note 3). The methanol is removed under reduced pressure to leave 125.6 g (100%) of the amino ester as a clear oil, essentially pure by ^{1}H NMR analysis (Note 4).

C. N-Benzyl-3-(1-hydroxyethyl)azetidin-2-one . Into a flame-dried, 1-L, three-necked, round-bottomed flask fitted with a condenser, addition funnel, and a large magnetic stirring bar, is placed 12.24 g (0.50 mol) of magnesium turnings and 400 mL of dry tetrahydrofuran (Note 5). tert-Butyl chloride (60.0 mL, 0.55 mol) (Note 6) is placed in the addition funnel and slowly added to the magnesium turnings as the reaction mixture spontaneously begins to reflux. When the addition is completed, heating is continued for 1 hr more (Note 7). A solution of 30.0 g (0.13 mol) of methyl 2-(benzylamino)methyl-3-hydroxybutanoate in 100 mL of anhydrous tetrahydrofuran is slowly added dropwise to the well stirred Grignard solution (Note 8) over a period of 3 hr at room temperature. The mixture is then carefully neutralized with 300 mL of saturated ammonium chloride solution (Note 8) and the separated aqueous phase is extracted with diethyl ether (2 × 300 mL). The combined organic layers are washed with brine (500 mL), dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The resulting orange oil is purified by passing it down a short silica gel column (elution with 5% methanol in dichloromethane). The appropriate fractions are pooled and freed of solvent under reduced pressure to give 19.45-21.85 g (73-82%) of N-benzyl-3-(1-hydroxyethyl) azetidin-2-one as a yellowish oil (Note 9).

D. N-Benzyl-3-(Z/E)-ethylideneazetidin-2-one . Into a dry, 250-mL, one-necked, round-bottomed flask, fitted with a magnetic stirring bar, is placed 9.60 g (0.047 mol) of N-benzyl-3-(1-hydroxyethyl) azetidin-2-one , 125 mL of dry dichloromethane (Note 10), and 13.0 mL (0.093 mol) of triethylamine . The solution is cooled in an ice bath before 4.0 mL (0.052 mol) of methanesulfonyl chloride (Note 11) is introduced. The mixture is stirred at 0°C for 1 hr, transferred to a separatory funnel, and washed with saturated sodium bicarbonate solution (2 × 150 mL) and brine (200 mL). The organic phase is dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to leave 14.3 of orange oil (Note 12).

The oil is immediately dissolved in 200 mL of dry benzene and transferred to a 500-mL, one-necked, round-bottomed flask to which is added 7.73 g (0.051 mol) of 1,8-diazabicyclo[5.4.0]undec-7-ene, DBU (Note 13). The flask is fitted with a condenser, heated at reflux for 8 hr, allowed to cool to room temperature, and washed with 200 mL of water and 200 mL of brine . The organic phase is dried over anhydrous magnesium sulfate, filtered, and evaporated to leave a dark brown oil. This material is chromatographed on silica gel (elution with 30% ethyl acetate in hexanes) (Note 14) and (Note 15) to give 7.02 g (79.9% for the two steps) as a very pale yellow oil.

E. N-Benzylazetidine-2,3-dione . N-Benzyl-3-(Z/E)-ethylideneazetidin-2-one (5.0 g, 26.7 mmol) is dissolved in 150 mL of methanol and 100 mL of water contained in a 500-mL, one-necked, round-bottomed flask. Sodium metaperiodate (14.3 g, 67.0 mmol) (Note 16) is introduced, followed by approximately 40 mg of osmium tetraoxide (Note 17). The reaction mixture is stirred vigorously for 12 hr under nitrogen, treated with Celite (6 g), and agitated for an additional hour prior to filtration. The filtrate is concentrated to 1/3 of its volume under reduced pressure, then extracted with ethyl acetate (2 × 200 mL). The combined organic phases are washed once with brine, dried, and concentrated to leave a dark brown oil. This oil is flushed through a short pad of silica gel (8 cm × 8 cm) using dichloromethane as eluant (900 mL). The pure fractions are pooled and evaporated to give a clear pale yellow oil, which crystallizes on prolonged standing at 5°C. The yield of N-benzylazetidine-2,3-dione is 3.12-3.64 g (66.7-77.9%) (Note 18).

2. Notes

1. Methyl acrylate, acetaldehyde, 1,4-diazabicyclo[2.2.2]octane, and benzylamine were purchased from the Aldrich Chemical Company, Inc. The first two reagents were distilled before use and the last two were used without further purification.
2. The product exhibits the following spectroscopic properties; IR ($CHCl_3$) cm^{-1}: 3500, 1720, 1635 ; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.33 (d, 3 H, J = 6.5), 2.80 (br s, 1 H), 3.74 (s, 3 H), 4.57 (q, 1 H, J = 6.5), 5.79 (s, 1 H), 6.16 (s, 1 H) .
3. The progress of this reaction can be conveniently monitored by ^1H NMR spectroscopy. A small aliquot is evaporated to dryness and the disappearance of the vinyl protons at δ 5.79 and 6.16 ($CDCl_3$ solution) is followed.
4. The spectroscopic properties of this diastereomeric mixture are as follows: ^1H NMR (300 MHz,

$CDCl_3$) δ: 1.14-1.20 (two sets of doublets, 3 H, J = 6.3), 2.43-2.49 (m, 2 H), 2.98-3.04 (m, 2 H), 3.66 (s, 3 H), 3.74 (s, 2 H), 4.15-4.19 (m, 1 H), 7.25 (m, 5 H) .
5. Tetrahydrofuran was dried by distillation from sodium benzophenone ketyl.
6. tert-Butyl chloride was purchased from J. T. Baker Inc. and distilled prior to use.
7. If unreacted magnesium remains at this time, more tert-butyl chloride is introduced in order to achieve complete conversion to the Grignard reagent.
8. It is essential to have good stirring during this step. If the reaction mixture becomes significantly turbid, a change to mechanical stirring is advisable.
9. This compound has the following properties: R_f = 0.3 (5% ethanol in dichloromethane; IR ($CHCl_3$) cm^{-1}: 3500-3300, 1740 ; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.24 (d, 3 H, J = 6.3), 2.65 (br s, 1 H), 3.14-3.22 (m, 3 H), 4.17 (m, 1 H), 4.37 (m, 2 H), 7.22-7.36 (m, 5 H) .
10. Dichloromethane was distilled from calcium hydride.
11. Methanesulfonyl chloride was obtained from the Mallinckrodt Company and distilled under reduced pressure before use.
12. This product is unstable and should be used without delay. It exhibits the following ^1H NMR spectrum: (80 MHz, $CDCl_3$) δ: 1.5 (m, 3 H), 3.0 (s, 3 H), 3.3 (m, 3 H), 4.4 (s, 2 H), 5.0 (m, 1 H), 7.3 (s, 5 H) .
13. DBU (96%) was obtained from the Aldrich Chemical Company, Inc. , and distilled under reduced pressure before use.
14. The Z- and E-isomers have quite different R_f values in 3:1 hexane-ethyl acetate (0.25 and 0.10, respectively) and can easily be separated if desired. ^1H NMR for the Z-isomer (300 MHz, $CDCl_3$) δ is as follows: 2.03 (d, 3 H, J = 7.1), 3.52 (s, 2 H), 4.46 (s, 2 H), 5.58 (q, 1 H, J = 7.1), 7.53 (s, 5 H); for the E-isomer (300 MHz, $CDCl_3$) δ: 1.66 (d, 3 H, J = 7.0), 3.59 (s, 2 H), 4.45 (s, 2 H), 6.13 (q, 1 H, J = 7.0), 7.20-7.34 (m, 5 H) .
15. The product can alternatively be purified by Kugelrohr distillation (165°C, 0.5-1.0 mm). However, the yield is significantly lower (52%).
16. Sodium metaperiodate was obtained from GFS Chemicals Inc., Columbus, OH .
17. Osmium tetraoxide was purchased from the Strem Chemicals Inc.
18. The spectral data are as follows: IR ($CHCl_3$) cm^{-1}: 1830, 1768 ; ^1H NMR (300 MHz, CD_3COCD_3) δ: 3.93 (s, 2 H), 4.79 (s, 2 H), 7.30-7.39 (m, 5 H) ; ^{13}C NMR (75 MHz, CD_3COCD_3) δ: 47.0, 59.9, 128.7, 129.1, 129.7, 135.8, 164.4, 195.6 . The dione is stable for several weeks when kept in the dark at 5°C.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

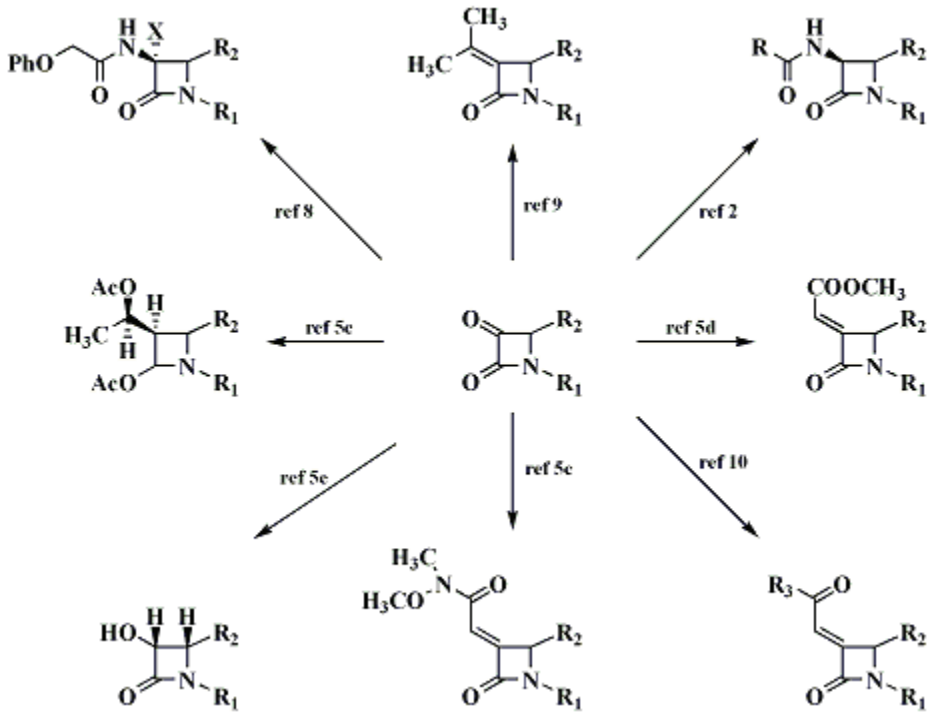
3. Discussion

The previously reported preparations of N-benzyl-2,3-azetidinedione involve either high-pressure lactamization with carbon monoxide and lead(II) acetate, $Pd(OAc)_2$, in the presence of triphenylphosphine,[2] or construction of the β-lactam from an isoxazolidine precursor.[3] The present approach uses the readily available methyl 2-(benzylamino)methyl-3-hydroxybutanoate [4] [5] [6] to synthesize the lactam. Significantly, cyclization proceeds readily without prior protection of the hydroxyl group. Oxidative cleavage of the double bond in N-benzyl-3-ethylideneazetidin-2-one has previously been accomplished via ozonolysis.[3] However, this process results in concomitant competitive attack on the benzyl group when performed on a reasonable scale. The reaction mixture is very difficult to purify when this occurs. The osmium tetraoxide-mediated bond cleavage, on the other hand, is a clean reaction with an easy workup.

The method detailed here uses cheap starting materials and the sequence proceeds in high-yielding steps. Finally, it is noted that the title compound can exhibit high enol content depending on solvent.[2]

N-Benzyl-2,3-azetidinedione may be regarded as the most readily available of the unadorned α-keto-β-lactams. More complex analogs are of course known,[7] [8] [9] [10] [11] [12] [13] particularly derivatives of the penicillin[14] [15] [16] and cephalosporin antibiotics.[17] [18] All members feature a high density of functionality in a small ring and consequently hold considerable synthetic potential. The transformations shown below

have already been recorded.



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

N-Benzyl-2,3-azetidinedione:
2,3-Azetidinedione, 1-(phenylmethyl)- (10); (75986-07-1)

Methyl 3-hydroxy-2-methylenebutanoate:
Butyric acid, 3-hydroxy-2-methylene-, methyl ester (8):
Butanoic acid, 3-hydroxy-2-methylene-, methyl ester (9); (18020-65-0)

Methyl acrylate:
Acrylic acid, methyl ester (8);
2-Propenoic acid, methyl ester (9); (96-33-3)

Acetaldehyde (8,9); (75-07-0)

1,4-Diazabicyclo[2.2.2]octane [DABCO] (8,9); (280-57-9)

Benzylamine (8);
Benzenemethanamine (9); (100-46-9)

Magnesium (8,9); (7439-95-4)

tert-Butyl chloride:
Propane, 2-chloro-2-methyl- (8,9); (507-20-0)

N-Benzyl-3-(Z/E)-ethylideneazetidin-2-one:
2-Azetidinone, 3-ethylidene-1-(phenylmethyl)- (12); (115870-02-5)

Triethylamine (8);
Ethanamine, N,N-diethyl- (9); (121-44-8)

Methanesulfonyl chloride (8,9); (124-63-0)

1,8-Diazabicyclo[5.4.0]undec-7-ene [DBU]:
Pyrimido[1,2-a]azepine, 2,3,4,6,7,8,9,10-octahydro- (8,9); (6674-22-2)

Sodium metaperiodate:
Periodic acid, sodium salt (8,9); (7790-28-5)

Osmium tetroxide:
Osmium oxide (8);

Osmium oxide, (T-4)- (9); (20816-12-0)

Methyl 2-(benzylamino)methyl-3-hydroxybutanoate:
Butanoic acid, 3-hydroxy-2-[[(phenylmethyl)amino]methyl]-, methyl ester (12); (R^*,R^*)- (118559-03-8);

(R^*,S^*)- (118558-99-9)

N-Benzyl-3-(1-hyrdoxyethyl)azetidin-2-one:
2-Azetidinone, 3-(1-hydroxyethyl)-1-(phenylmethyl)-, (11); (R^*,R^*)- (89368-08-1); (R^*,S^*)- (89368-09-2)