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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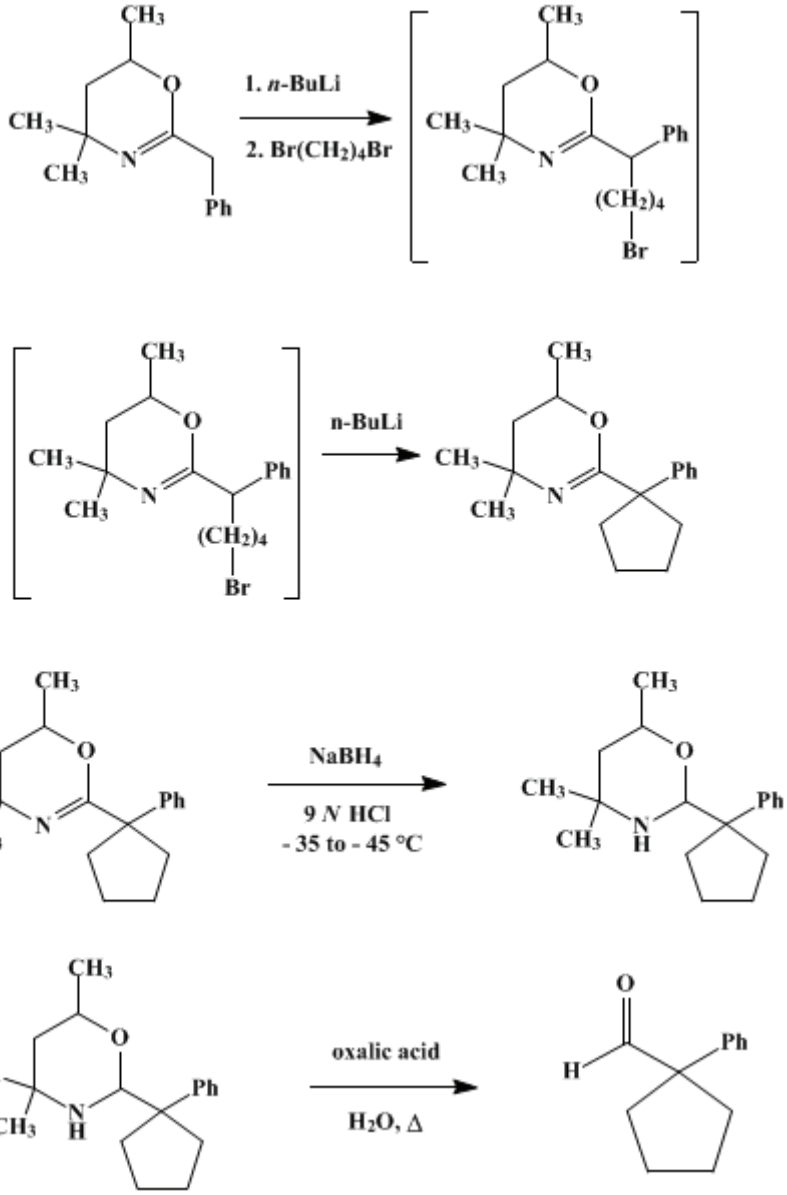
Organic Syntheses, Coll. Vol. 6, p.905 (1988); Vol. 51, p.24 (1971).

ALDEHYDES FROM 2-BENZYL-4,4,6-TRIMETHYL-5,6-DIHYDRO-1,3(4*H*)-OXAZINE: 1-PHENYLCYCLOPENTANECARBOXALDEHYDE

[Cyclopentanecarboxaldehyde, 1-phenyl-]



Submitted by Ieva R. Politzer and A. I. Meyers[1].
Checked by Dennis R. Rayner and Richard E. Benson.

1. Procedure

A. 2-(1-*Phenylcyclopentyl*)-4,4,6-*trimethyl*-5,6-*dihydro*-1,3(4H)-*oxazine*. A 1-l., three-necked flask is equipped with a magnetic stirring bar, a 125-ml. pressure-equalizing funnel fitted with a rubber septum, and a nitrogen inlet tube. The system is flushed with nitrogen, and 500 ml. of dry tetrahydrofuran (Note 1) and 21.7 g. (0.100 mole) of 2-benzyl-4,4,6-trimethyl-5,6-dihydro-1,3(4*H*)-oxazine (Note 2) are added to the flask. The stirred solution is cooled to −78° with an acetone–dry ice

bath, and 49 ml. (0.11 mole) of a 2.25 *M* solution of *n*-butyllithium in *n*-hexane (Note 3) is injected into the addition funnel. The *n*-butyllithium solution is added over a period of 15 minutes, and the funnel is rinsed by injecting 5 ml. of dry tetrahydrofuran. The yellow to orange solution is allowed to stir at −78° for 30 minutes (Note 4).

1,4-Dibromobutane (23.8 g., 0.110 mole) (Note 5) is injected into the addition funnel and added to the solution with stirring over a period of about 15 minutes. The funnel is rinsed by injection of 5 ml. of dry tetrahydrofuran, and the reaction is stirred at −78° for 45 minutes. *n*-Butyllithium (55 ml., 0.12 mole) in *n*-hexane is injected into the addition funnel and added to the solution over a period of 15 minutes. The reaction is stirred at −78° for 1 hour and stored at −20° overnight (Note 6). The mixture is poured into about 300 ml. of ice water and acidified to pH 2–3 with 9 *N* hydrochloric acid. The acidic solution is shaken with three 200-ml. portions of diethyl ether, and the ether extracts are discarded. The aqueous layer is made basic by careful addition of 40% sodium hydroxide (Note 7). The resulting mixture is shaken with four 200-ml. portions of ether, and the ether extracts are dried over anhydrous potassium carbonate. The ether is removed with a rotary evaporator, giving 24.4–25.8 g. (90–95%) of crude 2-(1-phenylcyclopentyl)-4,4,6-trimethyl-5,6-dihydro-1,3(4*H*)-oxazine, which is sufficiently pure for use in the following step.

B. 2-(1-*Phenylcyclopentyl*)-4,4,6-*trimethyltetrahydro*-1,3-*oxazine*. A 600-ml. beaker containing a magnetic stirring bar is charged with 200 ml. of tetrahydrofuran, 200 ml. of 95% ethanol, and 25.0 g. (0.0922 mole) of the oxazine obtained in Part A. The mixture is stirred and cooled to −35 to −40° with an acetone bath to which dry ice is added as needed. A 9 *N* hydrochloric acid solution is added dropwise to the stirred solution until an approximate pH of 7 is obtained as determined by pH paper. A solution of sodium borohydride is prepared by dissolving 5.0 g. (0.13 mole) in a minimum amount of water (5–8 ml.) to which 1 drop of 40% sodium hydroxide is added (Note 8). The sodium borohydride solution and 9 *N* hydrochloric acid solution are alternately added dropwise to the stirred solution so that a pH 6–8 is maintained (Note 9). During the addition care is taken to maintain a temperature between −35 and −45°. After addition of the borohydride solution is complete, the reaction mixture is stirred at −35° for 1 hour. A pH of 7 is maintained by occasional addition of 9 *N* hydrochloric acid (Note 10). The reaction mixture is then stored at −20° overnight.

The reaction mixture is poured into 300 ml. of water, and the resulting mixture is made basic with 40% sodium hydroxide. The mixture is shaken three times with 200-ml. portions of ether, and the combined ether extracts are washed with 10 ml. of saturated sodium chloride. After drying over potassium carbonate, the ether is removed with a rotary evaporator, giving 22.9–25.0 g. (91–99%) of product, which is used without purification in the next step (Note 11).

C. 1-*Phenylcyclopentanecarboxyaldehyde*. The crude tetrahydroöxazine (25.0 g., 0.0916 mole) from Part B is heated at reflux with 300 ml. of water containing 37.8 g. (0.300 mole) of oxalic acid dihydrate for 3 hours. The solution is cooled, and the aldehyde is extracted with four 150-ml. portions of petroleum ether (b.p. 40–60°). The organic extracts are combined, washed with 10 ml. of saturated sodium hydrogen carbonate, and dried with anhydrous powdered magnesium sulfate. The petroleum ether is removed with a rotary evaporator, and the product is distilled through a Vigreux column, giving 7.8–8.7 g. (50–55%) of 1-phenylcyclopentanecarboxaldehyde, b.p. 70–73° (0.1 mm.) $n_D^{26.5}$ 1.5350, IR spectrum (neat) 1720 cm.$^{-1}$ (C=O) (Note 12).

2. Notes

1. Tetrahydrofuran is dried by distillation from lithium aluminum hydride. [See *Org. Synth.*, **Coll. Vol. 5**, 976 (1973) for warning regarding the purification of tetrahydrofuran.]

2. 2-Benzyl-4,4,6-trimethyl-5,6-dihydro-1,3(4*H*)-oxazine is available from Columbia Organic Chemicals Company, Inc. The product was distilled, b.p. 80–82° (0.25 mm.). It may be prepared according to a modification of the method of Ritter and Tillmanns.[2] A 2-l. flask equipped with a thermometer, a stirrer, and a 250-ml. addition funnel is charged with 200 ml. of concentrated sulfuric acid (95–98%). Stirring is begun, the acid is cooled to 0–5° with an ice bath, and 128.7 g. (1.100 moles) of phenylacetonitrile is added from the funnel at such a rate that the temperature is maintained at 0–5°. After the addition is complete, 118 g. (1.00 mole) of 2-methyl-2,4-pentanediol is added at a rate to maintain a reaction temperature of 0–5°. The mixture is stirred for an additional hour and poured onto

700 g. of crushed ice. The aqueous solution is washed with two 75-ml. portions of chloroform, and the extracts discarded. The aqueous solution is made alkaline with 40% sodium hydroxide, with ice being added periodically during the neutralization to keep the solution temperature below 35°. The yellow oil is separated, and the aqueous solution is washed three times with 75-ml. portions of ether. The oil and ether extracts are combined, and the solution is dried over anhydrous potassium carbonate. The ether is removed with a rotary evaporator, and the product is distilled through a 25-cm. Vigreux column, yielding 107–115 g. (49–53%) of 2-benzyl-4,4,6-trimethyl-5,6-dihydro-1,3(4*H*)-oxazine as a straw-yellow liquid, b.p. 78–80° (0.25 mm.); n_D^{27} 1.5085; IR spectrum (neat) 1660 and 1600 cm.$^{-1}$, ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 6H), 3.32 (s, 2H), 4.04 (m, 1H) and 7.08 (m, 5H).

3. *n*-Butyllithium in *n*-hexane is available from Lithium Corporation of America, Inc.

4. If less solvent is used, the anion may appear as a yellow precipitate, but it is also usable in this form.

5. 1,4-Dibromobutane was distilled, b.p. 40–45° (0.5 mm.).

6. Alternatively, the reaction mixture may be allowed to reach room temperature over a period of 2–3 hours.

7. Ice may be added to keep the mixture cool during the neutralization.

8. The aqueous borohydride suspension is warmed, and the borohydride lumps crushed to achieve a homogeneous solution. The product available from Alfa Inorganics, Inc., was used by the checkers.

9. It is convenient to introduce the acid and hydride solutions from two burets or dropping funnels placed above the beaker. A total volume of about 15 ml. of 9 *N* hydrochloric acid is required.

10. The reaction can be conveniently monitored by IR spectroscopy, observing the intensity of the band at 1650 cm.$^{-1}$ (C=N). The submitters observed almost complete disappearance of this band, whereas the checkers found it still present in medium intensity in their product. In those instances where the α-carbon bears three alkyl substituents, steric effects retard the rate of addition, and in some cases (i.e., α,α,α-triethyl or larger groups) the C=N bond is resistant to reduction.

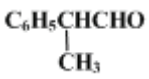
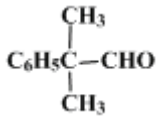
11. The intensity of the IR band at 1650 cm.$^{-1}$ should be weak.

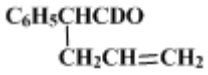
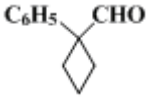
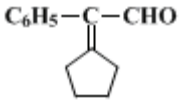
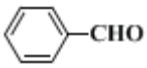
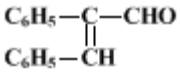
12. The ^{1}H NMR spectrum (CCl_4) shows peaks at δ 1.5–2.7 (m, 8H, 4CH_2), 7.2 (s, 5H, C_6H_5), and 9.3 (s, 1H, C*H*O). GC on a 240 cm. × 6 mm. column packed with 10% SE-30 on Chromosorb P at 120° gives a single peak with a retention time of 1.3 minutes.

3. Discussion

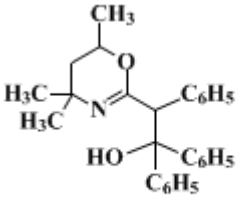
This procedure illustrates a general method for preparing α-phenyl aldehydes.[3] Additional examples are given in Table I.

TABLE I
ALDEHYDES FROM 2-BENZYL-4,4,6-TRIMETHYL-5,6-DIHYDRO-1,3(4*H*)-OXAZINE[4,5,6,7]

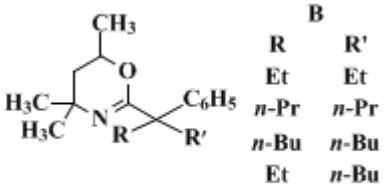
Alkylating Agent	Aldehyde	Yield, %
CH_3I		65
CH_3I (2,0 equiv.)		48
$CH_3CH_2CH_2Br$		64
CH_2=$CHCH_2Br$		70[a]

		
$BrCH_2CH_2Br$		57
$Br(CH_2)_3Br$		49
		54
		63

[a] Reduction was performed with $NaBD_4$.



(A)



B	
R	R'
Et	Et
n-Pr	*n*-Pr
n-Bu	*n*-Bu
Et	*n*-Bu

(B)

A limitation to this reaction sequence is that the reduction of the dihydroöxazine fails if bulky substituents are present. Thus, the alkylated oxazines A and B were not reduced under the reaction conditions specified in this procedure.

This technique may also be modified to prepare acetaldehyde derivatives, using 2,4,4,6-tetramethyl-5,6-dihydro-1,3(4*H*)-oxazine[3,4,5,6,7] and 2-carboethoxy acetaldehydes, using 2-(carboethoxymethyl)-4,4,6-trimethyl-5,6-dihydro-1,3(4*H*)-oxazine.[3] Functionalized aldehydes and dialdehydes may also be obtained by suitable modification.[8] Generally, the intermediates can be used without purification, and the overall yields of the aldehydes range from 50 to 70%.

In addition to the present method, 1-phenylcyclopentanecarboxaldehyde has been prepared by the reduction of *N*-acylaziridines obtained from 1-phenylcyclopentanecarboxylic acid.[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 17

References and Notes

1. Department of Chemistry, Wayne State University, Detroit, Michigan 48202. [Present address: Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523.]
2. E.-J. Tillmanns and J. J. Ritter, *J. Org. Chem.*, **22**, 839 (1957).
3. A. I. Meyers, H. W. Adickes, I. R. Politzer, and W. N. Beverung, *J. Am. Chem. Soc.*, **91**, 765 (1969); A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. C. Kovelesky, R. L. Nolen, and R. C. Portnoy, *J. Org. Chem.*, **38**, 36 (1973).
4. J. M. Fitzpatrick, G. R. Malone, I. R. Politzer, H. W. Adickes, and A. I. Meyers, *Org. Prep. Proced.*, **1**, 193 (1969).

5. A. I. Meyers, A. Nabeya, H. W. Adickes, and I. R. Politzer, *J. Am. Chem. Soc.*, **91**, 763 (1969).
6. A. I. Meyers, A. Nabeya, H. W. Adickes, J. M. Fitzpatrick, G. R. Malone, and I. R. Politzer. *J. Am. Chem. Soc.*, **91**, 764 (1969).
7. H. W. Adickes, I. R. Politzer, and A. I. Meyers, *J. Am. Chem. Soc.*, **91**, 2155 (1969).
8. A. I. Meyers, G. R. Malone, and H. W. Adickes, *Tetrahedron Lett.*, 3715 (1970).
9. J. W. Wilt, J. M. Kosturik, and R. C. Orlowski, *J. Org. Chem.*, **30**, 1052 (1965).

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

petroleum ether

ethanol (64-17-5)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether,
diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium hydrogen carbonate (144-55-8)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

phenylacetonitrile (140-29-4)

magnesium sulfate (7487-88-9)

n-butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

n-hexane (110-54-3)

oxalic acid dihydrate (6153-56-6)

sodium borohydride (16940-66-2)

1,4-dibromobutane (110-52-1)

1-Phenylcyclopentanecarboxaldehyde,
Cyclopentanecarboxaldehyde, 1-phenyl-,
1-Phenylcyclopentanecarboxyaldehyde (21573-69-3)

2-methyl-2,4-pentanediol (107-41-5)

1-phenylcyclopentanecarboxylic acid (77-55-4)

2-BENZYL-4,4,6-TRIMETHYL-5,6-DIHYDRO-1,3(4H)-OXAZINE (26939-22-0)

2-(1-Phenylcyclopentyl)-4,4,6-trimethyl-5,6-dihydro-1,3(4H)-oxazine

2,4,4,6-tetramethyl-5,6-dihydro-1,3(4H)-oxazine

2-(carboethoxymethyl)-4,4,6-trimethyl-5,6-dihydro-1,3(4H)-oxazine

2-(1-Phenylcyclopentyl)-4,4,6-trimethyltetrahydro-1,3-oxazine