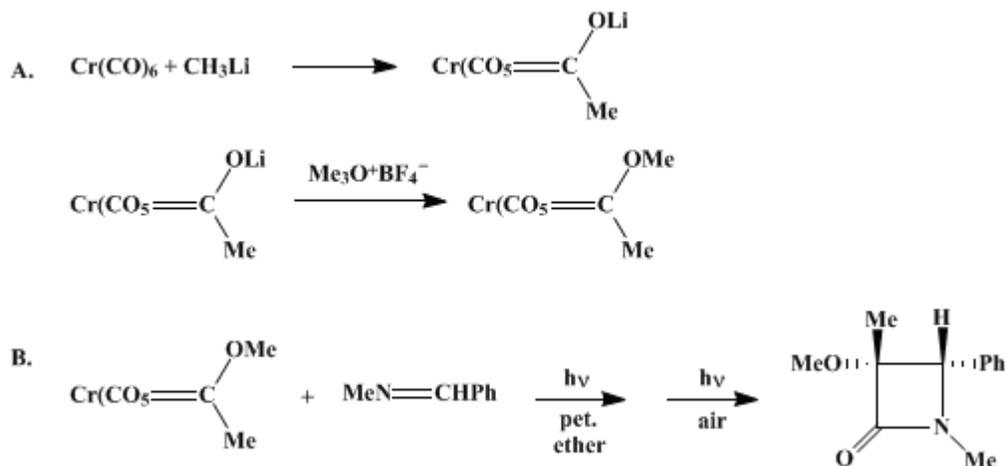


1,3-DIMETHYL-3-METHOXY-4-PHENYLAZETIDINONE

[2-Azetidinone, 3-methoxy-1,3-dimethyl-4-phenyl-]



Submitted by Lous S. Hegedus, Michael A. McGuire, and Lisa M. Schultze¹.

Checked by Ming Chang P. Yeh and Martin F. Semmelhack.

1. Procedure

A. [(Methyl)(methoxy)carbene]pentacarbonyl chromium(0).² A 1-L, two-necked, round-bottomed flask equipped with magnetic stirring bar, 100-mL addition funnel, reflux condenser, and gas inlet is charged with 17.8 g (0.085 mol) of chromium hexacarbonyl (Note 1). The apparatus is evacuated (oil pump) and filled with argon (four cycles), and a positive pressure is maintained with an argon-filled balloon on a T-tube. Dry diethyl ether (500 mL) is transferred via cannula into the flask and stirring is commenced. The addition funnel is charged with 60 mL (1.42 M in ether, 0.085 mol) of methyllithium via cannula and rapid dropwise addition is begun. The methyllithium is added over a 15-min period, during which time the solution turns from bright yellow to dark brown. The solution is heated at reflux for approximately 1.5 hr. After the solution is cooled, the solvent is removed by rotary evaporation. The dark-brown residual solid is taken up in 80 mL of water (in air), and 13.0 g (0.088 mol) of trimethyloxonium tetrafluoroborate (Note 2) is added over a 30-min period with stirring (Note 3). The mixture is extracted several times with 200-mL portions of cold pentane (Note 4). The combined pentane layers are dried over anhydrous magnesium sulfate and filtered through a bed of Celite. The solution is concentrated by rotary evaporation to approximately 60 mL and is cooled to -20°C under argon. After 1 hr the resulting bright-yellow crystals (17.6 g, 83%) are collected and dried at 25°C under reduced pressure for 10 min (Note 5).

B. 1,3-Dimethyl-3-methoxy-4-phenylazetidinone. A 250-mL Pyrex Erlenmeyer flask is charged with 1.25 g (5.0 mmol) of [(methyl)(methoxy)carbene]pentacarbonyl chromium(0). The flask is fitted with a rubber septum, evacuated, and filled with argon (four cycles). Dry petroleum ether (175 mL) is transferred via cannula into the flask to produce a dark-yellow solution. The solution is charged with 0.59 g (5.0 mmol) of *N*-methylbenzylidenimine (Note 6). The flask is irradiated with six 20-W Vitalites (Note 7). The solution turns brown and heterogeneous within an hour. After 3 days (Note 8) the solution is filtered through a bed of Celite, the precipitate is washed with dry petroleum ether, and the now lighter-yellow solution is sealed in a flask, degassed, and irradiated as before. After 5 days of further irradiation, the mixture is filtered and the filtrate is exposed to air and irradiated again until a colorless solution is obtained (ca. 1 day). Filtration through a bed of Celite and removal of solvent by rotary evaporation affords colorless crystals of essentially pure β -lactam 2. Recrystallization from hexane gives 0.67–0.76 g (65–74% yield), mp $76\text{--}77^\circ\text{C}$ (Note 9).

2. Notes

1. [Chromium hexacarbonyl](#) was obtained by the checkers from Pressure Chemical Company, Pittsburgh, PA. and used without purification. It can be weighed in air as it is relatively nonvolatile and air-stable. The usual precautions appropriate for a potentially toxic metal carbonyl should be employed, but the low volatility makes handling relatively easy.
2. The checkers obtained [trimethyloxonium tetrafluoroborate](#) from Alfa Products, Morton/Thiokol, Inc.
3. Meerwein's reagent was added until the pH of the solution was slightly acidic.
4. The carbene complex is slightly air-sensitive in solution. The [pentane](#) was cooled to 0°C and [nitrogen](#) was bubbled through the solvent before use.
5. Longer drying resulted in loss of carbene complex by sublimation. The carbene complex was stored under [argon](#) at -20°C. The pure product shows ¹H NMR (CDCl₃) δ: 4.60 (s, 3 H, OCH₃) and 2.90 (s, 3 H, CH₃).
6. The checkers obtained [N-methylbenzylidenimine](#) from Aldrich Chemical Company, Inc. and used it without purification. It was added as a neat liquid, via syringe.
7. Vitalites were obtained by the checkers from a local hardware store. They were arranged horizontally, in banks of two in a way to provide maximum illumination of the flask. Aluminum foil was used generously around the outside of the lights in order to minimize light loss.
8. Precipitate forms and reduces light intensity in the solution. The complete conversion of reactants can be accelerated by more frequent filtration and by using sunlight in place of the Vitalites. The submitters were successful using the Vitalites with five filtrations over a 72-hr period. The checkers found that the reaction was incomplete under these conditions and the β-lactam must be purified by chromatography (silica gel column, elution with 1 : 1 [ethyl acetate](#) : [hexane](#)) in order to remove residual [benzaldehyde](#) and other minor impurities.
9. The product has the following spectral properties: ¹H NMR (CDCl₃) δ: 1.60 (s, 3 H, CH₃); 2.80 (s, 3 H, NCH₃); 3.03 (s, 3 H, OCH₃); 4.35 (s, 1 H, CH); 7.28 (s, 5 H, ArH); IR (CHCl₃) cm⁻¹: 1750.

3. Discussion

The procedure described is an efficient conversion of imines to β-lactams.³ It is very general, and imines such as thiazolines, benzothiazines, [dihydroisoquinoline](#), and [quinoline](#) itself, as well as simple aldehyde and ketone imines, are converted to β-lactams in fair to good yield. The reaction is stereospecific, producing only one diastereoisomer of the β-lactam. The chromium carbene complex is easy to prepare on a large scale, to store, and to handle, since it is air-stable as a solid. The β-lactam forming reaction proceeds under very mild conditions and requires only the most simple glassware and either sunlight or commercially available fluorescent tubes that duplicate the spectrum of sunlight (e.g., Vitalite). Product isolation consists of simple filtration and solvent removal. The procedure produces β-lactams containing heteroatom substituents at the 3-position. It is complementary or superior to existing methods for the conversion of imines to β-lactams involving ketenes,^{4 5 6} acid chlorides and base,^{7 8 9 10} or ketene silyl acetals.^{12 13}

This preparation is referenced from:

- [Org. Syn. Coll. Vol. 9, 1](#)

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

petroleum ether

[(Methyl)(methoxy)carbene]pentacarbonyl chromium(0)

[(methyl)(methoxy)carbene]pentacarbonyl chromium(0)]

thiazolines

benzothiazines

ethyl acetate (141-78-6)

ether,
diethyl ether (60-29-7)

nitrogen (7727-37-9)

benzaldehyde (100-52-7)

Quinoline (91-22-5)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

hexane (110-54-3)

Methylithium (917-54-4)

argon (7440-37-1)

N-methylbenzylidenimine (622-29-7)

Trimethyloxonium tetrafluoroborate (420-37-1)

dihydroisoquinoline

1,3-Dimethyl-3-methoxy-4-phenylazetidinone,
2-Azetidinone, 3-methoxy-1,3-dimethyl-4-phenyl- (82918-98-7)

chromium hexacarbonyl (13007-92-6)

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