Organic Syntheses

A Publication
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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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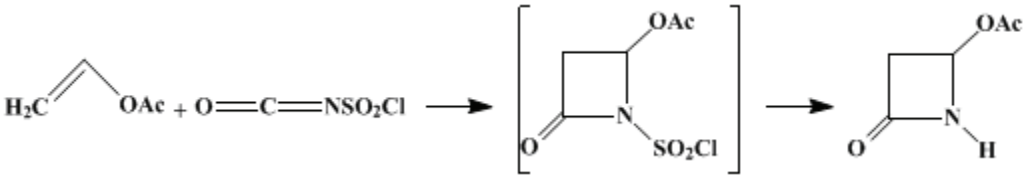
# SYNTHESIS OF A KEY β-LACTAM INTERMEDIATE BY A [2 + 2] CYCLOADDITION ROUTE: 4-ACETOXYAZETIDIN-2-ONE

## [2-Azetidinone, 4-(acetyloxy)-]

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## 1. Procedure

A 500-mL, four-necked, round-bottomed flask equipped with a mechanical stirrer, rubber septum with a nitrogen source, a thermometer, and a pressure-equalized dropping funnel is charged with 150 mL (140 g, 1.63 mol) of vinyl acetate (Note 1) and (Note 2). Stirring is initiated and the flask content is cooled in an ice–water bath to 3°C. Chlorosulfonyl isocyanate (25 mL, 40 g, 0.28 mol) (Note 2) and (Note 3) is added as rapidly as possible from the addition funnel while maintaining the temperature at less than 5°C. The cooling bath is removed and the temperature is allowed to rise to 10°C. At this point an exothermic reaction begins. Intermittent cooling is required as the temperature is kept at 10–15°C for 40 min. The dark-red mixture is then cooled to −40°C in a dry ice–acetone bath.

A 1.0-L, three-necked flask equipped with a thermometer, a mechanical stirrer, and a septum cap is charged with a mixture of 67 g (0.80 mol) of sodium bicarbonate, 71.5 g (0.69 mol) of sodium bisulfite, and 200 mL of water. This mixture is cooled in a dry ice–acetone bath to −20°C with vigorous stirring. Immediately (Note 4) the reaction mixture is added dropwise via cannula at a rate such that the temperature remains at −10°C. This addition takes 30–40 min. When approximately half of the reaction solution has been added, an additional 35.7 g (0.34 mol) of sodium bisulfite is added to the aqueous quench mixture. After the addition is complete, the mixture is stirred for an additional 40 min at −10°C. The light-yellow mixture (pH 7) is extracted with three 500-mL portions of chloroform (Note 5). The combined extracts are dried over magnesium sulfate and concentrated on a rotary evaporator at 40°C at 70 mm (Note 6). Final solvent removal with a vacuum pump gives a two-phase, oily mixture. The mixture is stirred with three 100-mL portions of hexane, and the hexane extracts are decanted (Note 7) and discarded. Removal of the final traces of solvent with a vacuum pump gives 16.1–22.8 g (44–62% yield based on chlorosulfonyl isocyanate) of a light-orange oil that slowly solidifies on standing at −20° C. The resulting solid melts at 34°C (Note 8).

## 2. Notes

1. Commercial vinyl acetate (Aldrich Chemical Company, Inc.) was used directly without purification. The checkers observed that distilled vinyl acetate afforded slightly higher yields and improved product purity (Note 7).
2. The volume of reagents used was determined by cannulation into the graduated addition funnel before charging into the reaction flask.
3. Aldrich Chemical Company, Inc. chlorosulfonyl isocyanate was used directly without purification.
4. The mixture tended to freeze if allowed to stand at −20°C.
5. Filtration of the mixture through sintered glass aided in breaking emulsions.
6. Room temperature is even more satisfactory, although the concentration takes longer. Heat leads to decomposition of the product.
7. The hexane-soluble impurity is believed to originate in the vinyl acetate. This purification may not be necessary in all cases.

8. The material prepared by this route contains a trace of a yellow impurity (vinyl acetate polymer?). However, the impurity is not detected in the $^{1}H$ NMR, $^{13}C$ NMR, or mass spectrum of the product. Very careful column chromatography is required to remove the color and in the hands of the submitters 4-acetoxyazetidin-2-one,[3] prepared by the preceding method, is adequate for any further manipulation. High-vacuum distillation may be employed to obtain a colorless sample (bp 80–82°C at $10^{-3}$ mm); however, extensive losses occur. The spectra are as follows: IR ($CHCl_3$) $cm^{-1}$: 3350 (NH), 1790 (β-lactam C=O), 1730 (acetate C=O); $^{1}H$ NMR ($CDCl_3$) δ: 2.03 (s, 3 H, $OCOCH_3$), 3.00 (d of d, 1 H, $J_{3b\text{-}3}$ = 15.0, $J_{3b\text{-}4}$ = 1.5), 3.28 (d of d, 1 H, $J_{3a\text{-}3b}$ = 15.0, $J_{3a\text{-}4}$ = 4.6, $H_{3a}$), 5.81 (d of d, 1 H, $J_{4\text{-}3a}$ = 4.6, $J_{4\text{-}3b}$ = 1.6), 7.4–7.1 (br, 1 H, NH); $^{13}C$ NMR ($CDCl_3$) δ (off-resonance multiplicity, assignment): 45.0 (t, C3), 73.2 (d, C4), 166.4 (s, C2).

Thin-layer chromatographic analysis of 4-acetoxyazetidin-2-one was carried out on E. Merck Silica gel F254 plates by elution with ethyl acetate. The hexanesoluble impurity ($R_f$ 0.67) was detected by shortwave UV. 4-Acetoxyazetidin-2-one ($R_f$ 0.38) was detected by exposure of the plate for 5 min to chlorine gas followed by spraying with TDM solution (Note 9) and heating with a hot air gun.

9. TDM spray solution was prepared as follows. Solution A: 2.5 g of 4,4'-tetramethyldiaminodiphenylmethane (TDM) was dissolved in 10 mL of glacial acetic acid and diluted with 50 mL of $H_2O$. Solution B: 5 g of potassium iodide was dissolved in 100 mL of $H_2O$. Solution C: 0.3 g of ninhydrin was dissolved in 90 mL of $H_2O$ diluted with 10 mL of glacial acetic acid. Solutions A and B and 1.5 mL of solution C were mixed and stored in a brown bottle.

## 3. Discussion

Within the current synthetic effort in β-lactam chemistry, 4-acetoxyazetidin-2-one and its derivatives play an important role in the total synthesis of many conventional β-lactams and their analogs.[4,3,5,6] There is therefore a requirement for a simple large-scale preparative method for this key intermediate. This synthesis is a modification of that reported by Clauss et al.[7]

## References and Notes


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

acetic acid (64-19-7)

ethyl acetate (141-78-6)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

potassium iodide (7681-11-0)

sodium bisulfite (7631-90-5)

chlorine (7782-50-5)

magnesium sulfate (7487-88-9)

vinyl acetate (108-05-4)

hexane (110-54-3)

CHLOROSULFONYL ISOCYANATE (1189-71-5)

ninhydrin (938-24-9)

4-Acetoxyazetidin-2-one,
2-Azetidinone, 4-(acetyloxy)- (28562-53-0)

4,4'-tetramethyldiaminodiphenylmethane