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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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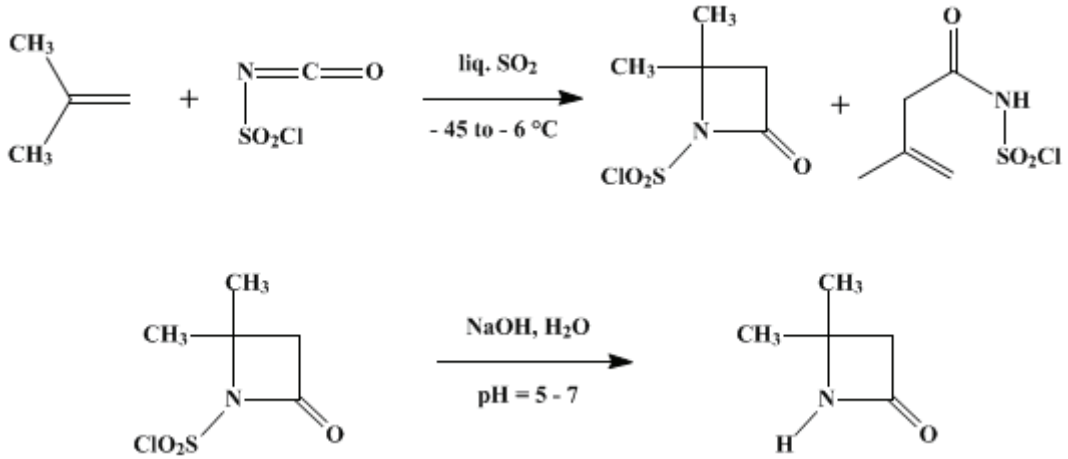
β-ISOVALEROLACTAM-N-SULFONYL CHLORIDE AND β-ISOVALEROLACTAM

[2-Azetidinone-4,4-dimethyl-1-sulfonyl chloride and 2-azetidinone-4,4-dimethyl]



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1. Procedure

Caution! Chlorosulfonyl isocyanate is highly corrosive and may be contaminated with cyanogen chloride. This preparation should be carried out in a good hood, and rubber gloves should be worn.

A. *β-Isovalerolactam-N-sulfonyl chloride*. A 200-ml. four-necked flask fitted with a mechanical stirrer, a dry ice-jacketed dropping funnel (Note 1), and a thermometer is cooled with a dry ice-methylene chloride slush bath while 67 ml. of sulfur dioxide (Note 2) is condensed into the flask. Both the dry ice condenser and the dropping funnel are protected with drying tubes containing anhydrous calcium sulfate. With the liquid sulfur dioxide at −20°, the flask is charged with 0.3 g. of finely powdered potassium chloride (Note 3) and 47.1 g. (0.33 mole) of chlorosulfonyl isocyanate.[2] Then 19.5 g. (0.35 mole) of isobutylene, previously condensed in a cold trap, is added to the dropping funnel. The temperature of the flask is lowered to −40° to −50°, and isobutylene is added dropwise over a 20-minute period (Note 4), (Note 5). After the isobutylene addition is completed, the cooling bath under the flask is removed, and the reaction mixture is allowed to warm up until the solvent begins to reflux (approximately −6°). The colorless contents of the flask are then poured into 125 ml. of water contained in a 400-ml. beaker over a period of 1 minute with vigorous agitation provided by a mechanically driven paddle stirrer. Sulfur dioxide is evolved while β-isovalerolactam-N-sulfonyl chloride precipitates as a gritty, crystalline, white solid (Note 6). The major portion of dissolved sulfur dioxide is removed by impinging a vigorous stream of air on the surface of the liquid in the beaker until the temperature of the mixture rises again after falling to 0–4°. The precipitate is removed by suction filtration and is washed three times with 33-ml. portions of ice water. The yield of moist product containing 10–20% water is 52–56 g. (Note 7). The product in this form is more suitable for subsequent conversion to the free β-lactam than if it is anhydrous or in a more coarsely crystalline form.

To prepare the anhydrous compound, the solid is dissolved in methylene chloride, whereupon the water separates as the upper phase. The organic layer is dried over anhydrous sodium sulfate, and the solvent is removed under reduced pressure at room temperature to give a colorless, crystalline mass, m.p. 75–77°. Small amounts of the pure compound may be obtained in the form of long needles by recrystallization from ether, m.p. 77–78°. The yield is 43–46 g. (65–70%) in anhydrous form (Note 8).

B. *β-Isovalerolactam*. A 200-ml. beaker is provided with a combination pH electrode, a mechanically driven paddle stirrer, a thermometer, and a syringe or dropping funnel (Note 9). An amount of water just sufficient for immersion of the pH electrode (20 ml.) is introduced, and with vigorous stirring the first portion (about one quarter) of the 52–56 g. (about 0.20–0.22 mole) of moist β-isovalerolactam-N-sulfonyl chloride is added. The liberated acid is neutralized by dropwise addition of approximately 10*N* sodium hydroxide solution (Note 10) to maintain the pH of the mixture between 2 and 8, and preferably in the range 5–7 (Note 11). The temperature is kept at 20–25° with cooling supplied by an ice bath as necessary. More lactam-N-sulfonyl chloride is added as the hydrolysis proceeds.

Hydrolysis is very sluggish at first, especially if anhydrous or coarsely crystalline sulfonyl chloride is used. Hydrolysis of the first one quarter to one half of the sulfonyl chloride requires 1–3 hours, and by that time the increasing salt concentration of the solution will cause the separation of the β-lactam as a second liquid phase. The sulfonyl chloride is significantly more soluble in this water-containing lactam phase, and as a result the rate of hydrolysis increases markedly (Note 12). Hydrolysis of the remainder of the sulfonyl chloride can be completed in about 30 minutes to 1 hour. The pH is adjusted finally to 7, and the mixture is cooled to 10° while being repeatedly seeded with sodium sulfate decahydrate. This converts all the precipitated sodium sulfate to the decahydrate (Note 13), and the β-lactam which originally separated in oily form is dissolved. The sodium sulfate decahydrate is removed by suction filtration and is washed with 90 ml. of chloroform. Small portions of the chloroform washings are then used for repeated extraction of the lactam from the salt solution. The extracts are combined, dried over anhydrous potassium carbonate, and distilled through an 8-in. Vigreux column. Most of the chloroform is removed by distillation at atmospheric pressure, and the product is distilled under reduced pressure, b.p. 70° (1.0 mm.), n^{25}D 1.4475, freezing point 14.7° (Note 14), weight 16.7–17.3 g. (51–53% overall from chlorosulfonyl isocyanate). The product is 99.8% pure by vapor phase chromatographic analysis.

2. Notes

1. A jacket which is suitable for holding dry ice may be made easily for use with a cylindrical dropping funnel. The neck and bottom of a narrow-mouthed polyethylene bottle are cut off, and two or three vertical slits are made at the narrow end to allow it to slip over the body of the dropping funnel and rest on the stop-cock barrel. The size of the dropping funnel will determine the size of polyethylene container to be used.
2. The checkers used anhydrous sulfur dioxide supplied in cylinders by the Matheson Co., Inc., East Rutherford, New Jersey, without further purification. Traces of moisture will not interfere with the reaction, and it is sufficient if the liquid sulfur dioxide is clear and colorless. If necessary, however, the gaseous sulfur dioxide may be dried with anhydrous calcium chloride before condensing it.
3. Addition of potassium chloride may be omitted if the chlorosulfonyl isocyanate is free of sulfur trioxide. Otherwise, traces of sulfur trioxide will give rise to a yellow or brown coloration of the reaction mixture and to formation of small amounts of by-products which, because of their emulsifying activity, may interfere with further processing.
4. The reaction may also be carried out at higher temperatures, *e.g.*, at −10°, with simultaneous addition of gaseous isobutylene over a prolonged period of time. This, however, results in a reaction product of lower purity than is obtained by the present procedure.
5. The reaction is exothermic, and the rate of addition should be controlled to keep the temperature within the limits indicated.
6. The cycloaddition reaction is accompanied by another reaction giving about 30% of 3-methyl-3-butenamide-N-sulfonyl chloride which is readily hydrolyzed during the aqueous work-up. The β-lactam-N-sulfonyl chloride which is the major product of the reaction is relatively stable to hydrolysis under the conditions of its isolation.
7. The product may be stored for several days before its conversion to the free β-lactam in a polyethylene bag placed in a refrigerator or preferably under dry ice in a Dewar flask.
8. The cycloaddition reaction can also be carried out with ether as solvent, especially in small batches.[3]
9. For hydrolysis of a much larger quantity of material, a four-necked flask may be employed instead of a beaker.
10. Three moles of sodium hydroxide solution is used per mole of sulfonyl chloride. The use of base of known concentration provides a means of following the hydrolysis as well as determining the true

amount of product present for calculating the yield in Part A.
11. At high pH (>10–11) saponification of the sulfonyl chloride to the sodium salt of 3-amino-3-methylbutyric acid-N-sulfonic acid will predominate, and at too low a pH (*e.g.*, pH of 0) hydrolysis to 3-hydroxy-3-methylbutyramide will prevail.
12. Care should be taken that the sulfonyl chloride is not added too rapidly, as the increased hydrolysis rate at this point will not permit adequate control of temperature and pH if a large amount of sulfonyl chloride is present. For repeat preparations a portion of the reaction mixture from a preceding batch may be introduced to achieve a more rapid hydrolysis rate sooner in the reaction. For the first preparation there are ways of increasing the initial rate of hydrolysis, or shortening the time interval before the transition from low to higher hydrolysis rate occurs. These are use of sodium sulfate solution instead of pure water, addition of a few tenths of a gram of potassium iodide, or addition of a small amount (1 ml.) of methylene chloride. However, these steps are not necessary if a reasonable amount of patience is exercised.
13. If seeding with sodium sulfate decahydrate is omitted, the unstable heptahydrate may crystallize.
14. The freezing point given was determined by the checkers as the temperature of a solid-melt equilibrium for a sample of 99.8% purity. The submitter reports the melting point at 15.3° after recrystallization from isopropyl ether and redistillation.

3. Discussion

The only methods reported[3] for the preparation of 4,4-dimethyl-2-azetidinone-1-sulfonyl chloride and 4,4-dimethyl-2-azetidinone are those described here.

Conversion of β-lactam-N-sulfonyl chlorides to the free lactams may also be accomplished by means of reducing agents,[3,4] and for β-lactam-N-sulfonyl chlorides which are hydrolytically more stable than the one in the present example this represents a method to be preferred over pH-controlled hydrolysis.[3] The N-sulfonyl chlorides are reduced to N-sulfinic acids which spontaneously decompose to β-lactams and sulfur dioxide. Among the reducing agents which may be used are thiophenol, hydrogen sulfide, zinc dust, iron power, iodide ion, and sodium sulfite.[4] Iodide ion need be used only in catalytic amounts, as the liberated iodine is reduced again to iodide ion by the sulfur dioxide split off.

4. Merits of the Preparation

This procedure illustrates a general method for preparing aliphatic and, in certain cases, aromatic β-lactams containing a free NH group and substituted in either the 4 position or in both the 3 and 4 positions of the 2-azetidinone ring. The major byproduct of the cycloaddition step is a β,γ-unsaturated carboxamide-N-sulfonyl chloride which, in the case of certain aromatic olefins, may predominate. Reactions of both β-lactam-N-sulfonyl chlorides and the β,γ-unsaturated carboxamide-N-sulfonyl chlorides have been tabulated.[3]

Recently additional examples of the synthesis of 3,4-disubstituted 2-azetidinones have been reported[5,6] as well as a kinetic study of the reaction of chlorosulfonyl isocyanate with olefins.[7]

β-Lactams substituted only in the 3 position cannot be prepared by the present procedure, since the lactam formed has the nitrogen of the chlorosulfonyl isocyanate attached to the more highly substituted carbon atom of the olefinic double bond in Markownikoff fashion. 2-Azetidinones substituted in the 3 position only have been prepared by Grignard reagent-catalyzed cyclizations of esters of appropriately substituted β-amino acids.[8,9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 226
- Org. Syn. Coll. Vol. 5, 598

References and Notes

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

2-azetidinone-4,4-dimethyl

calcium chloride (10043-52-4)

potassium carbonate (584-08-7)

ether (60-29-7)

sodium sulfite (7757-83-7)

sodium hydroxide (1310-73-2)

sulfur trioxide (7446-11-9)

chloroform (67-66-3)

iron (7439-89-6)

hydrogen sulfide (7783-06-4)

sulfur dioxide (7446-09-5)

sodium sulfate (7757-82-6)

potassium iodide (7681-11-0)

nitrogen (7727-37-9)

iodine (7553-56-2)

carbon (7782-42-5)

zinc (7440-66-6)

methylene chloride (75-09-2)

Thiophenol (108-98-5)

potassium chloride (7447-40-7)

cyanogen chloride (506-77-4)

isobutylene (9003-27-4)

isopropyl ether (108-20-3)

sodium sulfate decahydrate (7727-73-3)

CHLOROSULFONYL ISOCYANATE (1189-71-5)

β-Isovalerolactam-N-sulfonyl chloride,
4,4-dimethyl-2-azetidinone-1-sulfonyl chloride (17174-96-8)

β-Isovalerolactam,
4,4-dimethyl-2-azetidinone (4879-95-2)

2-Azetidinone-4,4-dimethyl-1-sulfonyl chloride

3-methyl-3-butenamide-N-sulfonyl chloride

3-hydroxy-3-methylbutyramide

2-azetidinone (930-21-2)

sodium salt of 3-amino-3-methylbutyric acid-N-sulfonic acid