Organic Process Research & Development **1999**, *3*, 232−234

Scale Up of a Ritter Reaction

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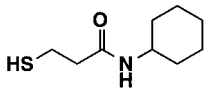
Abstract:

The Ritter reaction of secondary or tertiary alcohols with acrylonitrile provides easy access to acrylamides which would otherwise be difficult to prepare. A safe procedure for conducting this reaction is described.

Reaction between nitriles and alcohols or olefins to give carboxylic amides, the Ritter reaction, is well documented.[1] This reaction is a very efficient way to prepare amides with secondary or tertiary alkyl groups on the nitrogen. Modification[2] of the Ritter reaction allows primary alcohols to react with nitriles when activated by trifluoromethanesulfonic anhydride, complementing the traditional Ritter reactions. Activation of olefins by electrophilic palladium(II) salts[3] instead of strong acids was shown to be feasible, though less successful. More recently, the Ritter reaction was elegantly applied to the enantiospecific synthesis of 3-aza-bicyclic compounds using chiral terpenes[4] and to the chiral synthesis of *cis*-aminoindanol.[5] Surprisingly, Sohar et al.[6] observed a Ritter reaction with an unexpected retention of chirality at the carbonium ion center. Application of the Ritter reaction along with the sigmatropic rearrangement was also reviewed[7] for the synthesis of N-containing terpenes. These developments exemplified the significance of the Ritter reaction in the preparation of a variety of compounds.

As part of an effort to develop a practical process for preparing a mildewcide, *N*-cyclohexylisothiazolone, we needed to synthesize the starting *N*-cyclohexyl-3-mercaptopropionamide (**1**). Compound **1** can be prepared by the Ritter



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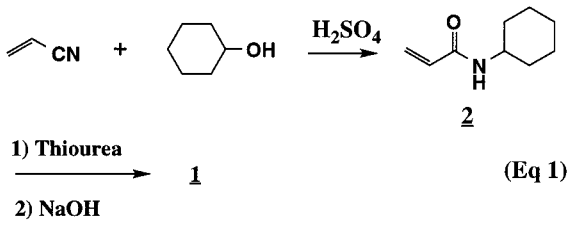
reaction of acrylonitrile with cyclohexanol, followed by thiolation with thiourea[8] (eq 1) according to the literature procedure. All literature references on the preparation of



N-cyclohexylacrylamide (**2**) as of 1984 involved adding concentrated sulfuric acid to a mixture of acrylonitrile and cyclohexanol. This worked reasonably well on a small laboratory scale. When we scaled up this procedure to 2 mol reactant scale, a violent reaction occurred several hours after all the reagents had been mixed at room temperature, ejecting most of the flask contents. Further search revealed an earlier patent[9] which described the violent nature of this particular reaction. However, no other paper mentioned the runaway or violent nature of the Ritter reaction, especially when acrylonitrile was the substrate.

Seeking a safer way to perform this reaction, we realized that there was a long induction period at room temperature in the literature procedure[9] due to the low instantaneous sulfuric acid-to-nitrile/alcohol ratio, until all the necessary sulfuric acid had been added. We believed that the formation of cyclohexyl carbonium ion was the rate-determining step. The concentration of the acid is too low with respect to that of the alcohol during acid addition. Therefore, generation of cyclohexyl carbonium ion intermediate is very slow until enough sulfuric acid is added. Presumably, the rate of formation of the cyclohexyl carbonium ion is first order in cyclohexanol and first order in sulfuric acid. We used two different approaches to address these issues. First, we kept the reaction temperature moderate throughout the course of reagent addition to prevent buildup of unreacted starting materials. Second, we maintained a high and constant sulfuric-to-cyclohexanol ratio throughout the addition. These two modifications ensured a reasonable rate of carbonium ion formation and its reaction with acrylonitrile.

Cyclohexanol was also successfully replaced with cyclohexene to give acrylamide **2** with comparable yield. This eliminated the need to thaw the cyclohexanol, which had been stored outside in cold weather. The following methods illustrate our improvements to this Ritter reaction.

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(1) For review of Ritter reactions, see: Krimen, L. I.; Cota, D. J. *Org. React.* **1969**, *17*, 213.
(2) Martinez, A. G.; Alvarez, R. M.; Vilar, E. T.; Fraile, A. G.; Hanack, M.; Subramanian, L. R. *Tetrahedron Lett.* **1989**, *30* (5), 581.
(3) Hegedus, L. S.; Mulhern, T. A.; Asada, H. *J. Am. Chem. Soc*. **1986**, *108*, 6224.
(4) Samaniego, W. N.; Baldessari, A.; Ponce, M. A.; Rodriguez, J. B.; Gros, E. G.; Caram, J. A.; Marschoff, C. M. *Tetrahedron Lett.* **1994**, *35* (38), 6967.
(5) Senanayake, C. H.; Roberts, F. E.; DiMichele, L. M.; Ryan, K. M.; Liu, J.; Fredenburgh, L. E.; Foster, B. S.; Douglas, A. W.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36* (23), 3993.
(6) Sohar, P.; Mathre, D. J.; Blacklock, T. J. European Patent EP 0617037A1, 1994.
(7) Ichikawa, Y. *Yuki Gosei Kagaku Kyokaishi* **1997**, *55* (4), 281.
(8) Bauer, L.; Welsh, T. L. *J. Org. Chem*. **1961**, *26*, 1443.
(9) Fugate, W. O.; D'Errico, M. J. U.S. Patent 3,151,157, 1964.

10.1021/op980211c CCC: $18.00
Published on Web 04/30/1999

Improved Ritter Reaction

Method A. An inert solvent (e.g., monochlorobenzene) was charged to the reactor and heated to 45−50 °C. Concentrated sulfuric acid and a premixed mixture of acrylonitrile and cyclohexanol were simultaneously added to the flask via two separate addition funnels at such a rate that addition times for both reagents were the same. After the addition, the mixture was warmed to complete the reaction. In this method, the product mixture may be taken directly to the thiolation step to give mercaptopropionamide **1** in the same solvent. This mercaptoamide solution may, in turn, be used in the chlorination step to prepare the desired isothiazolone biocide.[10]

Method B (Solvent-Free Process). All or part of the requisite concentrated sulfuric acid was charged to the reactor and heated to 45−50 °C. A premixed mixture of acrylonitrile and cyclohexanol along with any remaining sulfuric acid was added via two separate addition funnels at such a rate as to maintain the reaction temperature at 45−50 °C. After the addition(s), the mixture was warmed to reaction completion. The mixture can be quenched with water, and the acrylamide product can be filtered and dried, or it can be directly treated with thiourea to give the mercaptopropionamide **1**.

Both methods provide a higher starting temperature for facile generation of the cyclohexyl carbonium ion and its trapping with acrylonitrile. A stoichiometric or an excess amount of the sulfuric acid is also present at all times during the addition to ensure reactant consumption. There is no buildup of unreacted starting materials which might lead to violent eruption after all the reactants are mixed in either method. Both methods scaled up smoothly in the pilot plant and successfully provided the *N*-cyclohexyl-3-mercaptopropionamide for the manufacture of an isothiazolone biocide.[10] Method B provides a solvent-free process, an attractive feature when the starting nitrile/alcohol (or alkene) is a liquid.

Experimental Section

All starting materials were either commercial grades or purchased from Aldrich Chemical Co. and used without further purification. Commercial grade sulfuric acid of 95−98% concentration was equally suitable for the reactions. All melting points were uncorrected.

Method A: Preparation of *N*-Cyclohexyl-3-mercaptopropionamide (1). A premixed solution of acrylonitrile/cyclohexanol (13.3 g, 0.25 mol/25.1 g, 0.25 mol) and concentrated sulfuric acid (51.1 g, 95.8%, 0.5 mol) were added through two addition funnels into a flask containing chlorobenzene (60 g) at 45−55 °C. The mixture was then heated to 60−70 °C for 3−5 h and cooled to 20 °C. After the mixture was cooled, water (150 g) was added slowly. After the mixture was stirred for 30 min, thiourea (19 g, 0.25 mol) was added, and the mixture was warmed to 60 °C for 1 h. Upon cooling of the mixture to 20 °C, aqueous sodium hydroxide solution (50%, 80 g, 1 mol) was added between 20 and 60 °C under nitrogen, and the mixture was held at 60 °C for 1 h. The organic layer was separated and washed with warm water to yield 33.9 g of *N*-cyclohexyl-3-mercaptopropionamide in chorobenzene (72.4% yield by potency assay).

Method A: Preparation of *N*-Cyclohexylacrylamide (2) Using Cyclohexene. A homogeneous mixture of acrylonitrile (50 g, 0.94 mol) and cyclohexene (77.4 g, 0.94 mol) was added to a stirred volume of monochlorobenzene (220 mL) at 45 °C while concentrated sulfuric acid (192 g, 98%) was added from another addition funnel. The rate of the addition was adjusted such that the pot temperature was kept at 45−55 °C. The addition time was kept at about 30 min for both reagents. After the addition, the mixture was heated at 60 °C for an additional 3 h. The mixture was cooled to ambient temperature, and the chlorobenzene was removed under reduced pressure. The resulting brown liquid was poured into stirred ice water (2 L) and mixed for 2 h at room temperature. The white precipitate was filtered and washed with cold water until the filtrate was no longer acidic. The wet product cake was dried in a vacuum oven at 55 °C to yield the desired *N*-cyclohexylacrylamide (**2**). Yield was 131.2 g (90.9%). This material was used directly for the next step without further purification.

Method B: Preparation of *N*-Cyclohexylacrylamide (2). Sulfuric acid (95.8%, 46.0 g, 0.45 mol) was placed in a jacketed 3-L, three-neck flask and heated to 45 °C. A mixture of acrylonitrile (94.5 g, 1.783 mol) and cyclohexanol (180.2 g, 1.802 mol) was prepared and added to the flask simultaneously with additional sulfuric acid (95.8%, 322.3 g, 3.151 mol) using two addition funnels, keeping the temperature at 45−55 °C during the addition. At the end of the addition, the brown solution was heated to 60 °C for 3 h to complete the reaction. The mixture was then poured into 3 L of ice water with constant stirring. The white precipitate that formed was filtered, washed with water until the filtrate was no longer acidic, and dried in a vacuum oven at 55 °C to yield *N*-cyclohexylacrylamide (**2**, 242.4 g, 88% yield) as white to off-white solids; mp 109−110 °C.

General Procedure for Preparing *N*-Cyclohexyl-3-mercaptopropionamide (1) from *N*-Cyclohexylacrylamide (2). A mixture of *N*-cyclohexylacrylamide (15.3 g, 0.1 mol), concentrated hydrochloric acid (19.4 g, 37.6%), thiourea (7.6 g, 0.1 mol), and water (10 g) was heated to 60 °C for 2 h. The mixture was cooled to 20 °C, and aqueous sodium hydroxide (50%, 16 g) was slowly added under nitrogen, keeping the temperature below 30 °C. The resulting mixture was heated to 60 °C for 1 h and extracted with methylene chloride (2 × 50 mL). Removal of methylene chloride afforded *N*-cyclohexyl-3-mercaptopropionamide (**1**, 16.9 g), which was purified by vacuum distillation at 0.095 mmHg/130 °C to yield pure *N*-cyclohexyl-3-mercaptopropionamide (13.7 g, yield 73.3%); mp 73.5−75.5 °C.

Note: Mercaptopropionamides are susceptible to air oxidation to give the corresponding disulfide. The thiolation reaction, during and after treatment with sodium hydroxide, should be carried out under a blanket of nitrogen.

Preparation of *N*-(2-Methyl-2-butyl)methacrylamide. A premixed solution of 2-methyl-2-butene (7.0 g, 0.1 mol) and methacrylonitrile (6.7 g, 0.1 mol) was added to a stirred solution of concentrated sulfuric acid (98%, 10.0 g) in acetic

(10) Chang, S. J. U.S. Patent 4,868,310, 1989.

acid (50 mL) at 10 °C. The addition rate was adjusted such that the pot temperature was maintained at 10−20 °C. After the addition, the mixture was allowed to stir overnight at room temperature. The brown thick liquid was poured into 200 g of ice water, and the product was extracted with 2 × 100 mL of methylene chloride. The methylene chloride solution was dried over sodium sulfate, filtered, and concentrated to an oil. Distillation of the crude product at 10 mmHg yielded *N*-(2-methyl-2-butyl)methacrylamide (10.1 g, 65%); bp 84 °C.

Received for review August 14, 1998.

OP980211C