Organic Process Research & Development **2002**, *6*, 74–77

An Improved Process for the Preparation of Benzyl-*N*-vinyl Carbamate[1]

Cheruthur K. Govindan

PPG Industries Inc., Chemicals Group Technical Center, Monroeville, Pennsylvania 15146, U.S.A.

Abstract:

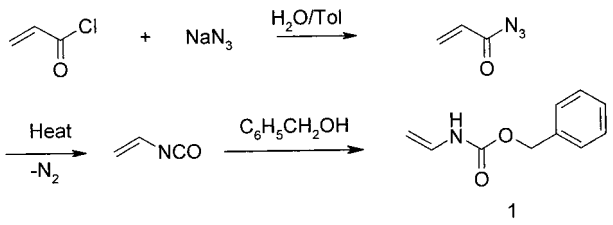
An improved method that can be easily scaled up has been developed for the preparation of benzyl-*N*-vinyl carbamate. In this method vinyl isocyanate formed by the Curtius rearrangement of acryloyl azide is codistilled with a solvent such as toluene into benzyl alcohol containing a catalyst and inhibitor. The product thus obtained can be purified by crystallization, avoiding purification by high-vacuum distillation or chromatography. Potential safety issues associated with the process are discussed.

Introduction

Benzyl-*N*-vinyl carbamate (*Z*-vinylamine, **1**) is a valuable synthetic intermediate. *Z*-Vinylamine undergoes alkylation readily on the carbon α to the nitrogen, a property that has been used in the synthesis of *β*-lactam antibiotics.[2] Compounds such as **1** can be readily polymerized to polyvinylamine derivatives.[3−6] Recently, a major pharmaceutical company has expressed interest in **1** as an intermediate for a new drug candidate.[8]

There are several methods described in the literature[3−7] for the synthesis of compounds like **1**, but none that can be adapted easily to a commercial process. The most studied method is shown in Scheme 1. Acryloyl azide, prepared by

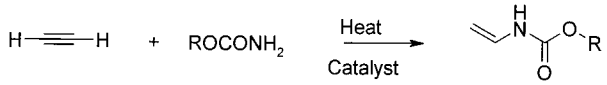
Scheme 1



the reaction of acryloyl chloride with sodium azide, was allowed to decompose to vinyl isocyanate (Curtius rearrangement[9]) in the presence of benzyl alcohol-containing pyridine. The product was then isolated in 60% yield by vacuum distillation. The yield of the product was extremely sensitive to reaction conditions. Even trace amounts of acid (from unreacted acryloyl chloride) were found to reduce the yield drastically.[5] The yield loss was attributed to the formation of dibenzylethyledenedicarbamate ($CH_3CH-(NHCOOCH_2C_5H_5)_2$, **2**) in the presence of acid. It was also reported that attempts to isolate vinyl isocyanate by distillation resulted in low yields since it polymerized readily, even on the walls of the equipment used. The polymer formed was highly cross-linked and soluble only in concentrated sulfuric acid.

The reaction of acetylene with alkyl carbamates in the presence of catalysts under high temperature and pressure yields[3] N-substituted vinyl carbamates such as ethyl-*N*-vinyl carbamate (Scheme 2). The product was isolated by high-

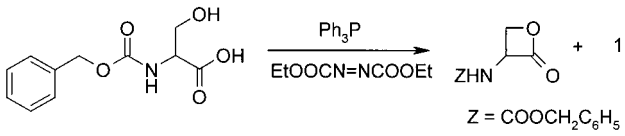
Scheme 2



vacuum distillation, but the yield was not reported. This reaction can probably be adapted to make **1**, but the process would require specialized high-pressure equipment that is beyond the capability of most fine chemical plants, and therefore this method is not a candidate for scale-up.

Vederas and co-workers have reported[7] that **1** is the major byproduct formed during the preparation of α-amino-*β*-lactones from serine by modified Mitsunobu procedures (Scheme 3). It has been mentioned that **1** is the major product

Scheme 3



if the reaction is done at room temperature. The starting materials involved in the Mitsinobu reaction are expensive, and atom economy is very poor. Products in Mitsunobu reactions are contaminated with stoichiometric amounts of triphenylphosphine oxide and dialkylhydrazine dicarboxylate that are hard to remove by distillation or crystallization. Column chromatography followed by vacuum distillation is often required to isolate the product in pure form.

An analysis of the above methods indicates that the Curtius rearrangement route is the best candidate for scale-up if certain difficulties associated with materials handling and product isolation are overcome. Raw materials involved in the synthesis according to Scheme 1 are relatively

(1) Part of this work has been described before. Govindan, C.; Pascone, J. U.S. Patent. 6,140,531, 2000.
(2) Wieber, G. M.; Hegedus, L. S.; Akermark, B.; Michalson, E. T. *J. Org. Chem.* **1989**, *54*, 4649−4653.
(3) Dickey, J. B. U.S. Patent 2,592,254, 1952.
(4) Hart, R. *Bull. Soc. Chim. Belg.* **1956**, *65*, 291−296.
(5) Wolfrom, M. L.; Mc. Fadden, G. H.; Chaney, A. *J. Org. Chem.* **1961**, *26*, 2597−2599.
(6) (a) Hughes, A. R.; Pierre, T. *Macromol. Synth.* **1977**, *6*, 31−37. (b) Onerberger, C. G.; Podsiadly, C. J. *Macromol. Synth.* **1072**, *4*, 87−90.
(7) Arnold, L. D.; Drover, J. C. G.; Vederas, J. C. *J. Am. Chem. Soc.* **1987**, *109*, 4649−4659.
(8) am Ende, D. J.; DeVries, K. M.; Clifford, P. J.; Brenek, S. J. *Org. Process Res. Dev.* **1998**, *2*, 382−392.
(9) Smith, P. A. *Org. React.* **1946**, *3*, 337.

 10.1021/op0102316 CCC: $22.00
Published on Web 12/13/2001

inexpensive and easily prepared. However, the thermal stability, reactivity, and toxicity of raw materials and intermediates are of major concern. Acryloyl azide is a low-molecular weight organic azide that contains 43% nitrogen and that can potentially be an explosive. Acryloyl chloride and azide can polymerize readily when heated. Recently (after the work described here was completed), a group from Pfizer[8] has published a detailed account on the safety aspects of this synthesis.

The high-vacuum distillation conditions employed for the isolation of **1** in previously reported methods are not easily attainable in a commercial plant. Isolation of the product by crystallization would be highly beneficial in a commercial process. We here report the results of a study that was undertaken to determine if an improved process to make **1** could be developed via the Curtius rearrangement route.

Results and Discussion

Preparation of Acryloyl Azide. Acryloyl azide was synthesized from acryloyl chloride and sodium azide under Schotten−Bauman conditions. Earlier workers have recommended repeated washings of the toluene solution obtained by base to remove unreacted acryloyl chloride. We have found that in the presence of quaternary ammonium compounds[10] this reaction rapidly goes to completion using only 5% excess of sodium azide compared to 20−25% excess sodium azide that was used in the literature procedure.[5] Toluene solutions of acryloyl azide obtained can be used directly without further treatments.

Stability of Acryloyl Azide Solutions. One of our major concerns regarding the preparation of **1** as shown in Scheme 1 was the stability of acryloyl azide. Safety issues involved in the handling of acryloyl azide have been thoroughly addressed in the paper by the Pfizer group.[8] However, before this paper was published, we had done a significant amount of work to determine the stability of solutions of acryloyl azide in toluene under normal handling and reaction conditions.

Most acyl azides decompose between 20 and 100 °C[9] with evolution of nitrogen. Low-molecular weight acyl azides, because of their high nitrogen content, are extremely unstable in neat form and likely to be explosive. Their decomposition in solution can easily get out of control. The potential of acryloyl azide to undergo rapid exothermic polymerization makes it even more hazardous. Therefore, we studied the thermal stability of acryloyl azide in toluene at various temperatures. Our results can be summarized as follows: (1) Solutions of acryloyl azide in toluene are stable for periods of up to 24 h when stored at 0−5 °C in the presence of phenothiazine. Gas evolution, formation of solid polymers, or weight loss does not occur during this time. (2) When stored at room temperature overnight, formation of light yellow crystals occurs. These crystals are unstable when dry and undergo deflagration when subjected to friction. We suspect that the crystals are of polyacryloyl azide and that this material is friction-sensitive. (3) Slow decomposition with nitrogen evolution occurs up to 65−70 °C. Above this temperature, reaction can become rapid and self-sustained. (4) The refluxing mixture of vinyl isocyanate and toluene moderates the reaction, and the temperature does not rise above 90−95 °C. However, gas evolution is brisk, and proper venting of nitrogen evolved is required to avoid the buildup of pressure in the reactor.

It can be concluded from our studies that solutions of acryloyl azide in toluene containing phenothiazine as an inhibitor are fairly stable at low temperatures towards thermal decomposition. This conclusion is supported by ARC studies reported previously[8] that have shown that the self-heat onset temperature for acryloyl azide is 27 °C. It is possible to store toluene solutions of acryloyl azide at 0−5 °C for up to 24 h without significant decomposition. However, it is strongly recommended that these solutions be used as soon as prepared.

Synthesis of 1. According to literature procedures [2,5] for the synthesis of **1**, acryloyl azide is added gradually to a mixture of benzyl alcohol, toluene, pyridine, and BHT at 110 °C. The product is then isolated by vacuum distillation but requires a very high vacuum (<0.5 Torr) source. Prolonged heating of the product can lead to decomposition in the pot and reduce yields.[8] Conditions required for the distillation of **1** are not easily attainable in most chemical plants. We therefore concentrated our efforts on isolating the product by crystallization.

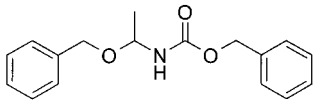
In initial experiments, the decomposition of acryloyl azide was carried out in the presence of benzyl alcohol according to the literature procedure[5] but using phenothiazine instead of BHT as an inhibitor. Analyses of the reaction mixture by NMR and HPLC revealed that 70−75% of the product mixture was **1**, 10−15% of the mixture was an impurity, and another 10−15% was a polymer. There was also unreacted benzyl alcohol present. The formation of impurities was noticed in all cases irrespective of the reaction temperature, the type of inhibitor (phenothiazine and MEHQ), and the amount or type of base used. In addition to pyridine, *N*-methylmorpholine and triethylamine were tried as the base during the decomposition of acryloyl azide.

All our efforts to isolate **1** in good yield and purity by the crystallization of the crude product failed. We were able to remove most of the high-molecular weight polymers by fractional precipitation. However, crystals obtained from the remaining product were always oily and impure. HPLC analyses showed the product to be 85−90% **1** with one major impurity being present.

Initially we believed that the impurity was **2** on the basis of suggestions in an earlier report.[5] However, HPLC retention time of this compound did not match that of an authentic sample of **2** prepared by the treatment of **1** with hydrogen chloride in ethanol. NMR spectrum of this compound was also different from that of **2**. It was observed that the decomposition of acryloyl azide in the presence of benzyl alcohol and triethylamine produced this compound in large amounts (30−40% of the product mixture) and that it crystallized readily from the crude reaction mixture on removal of the solvent under vacuum. The compound was identified by NMR spectroscopy to be **3**. Compound **3** is

(10) Pfister, J. R.; Wymann, W. E. *Synthesis* **1983**, 38−40.

formed by the addition of benzyl alcohol to **1** under reaction conditions. The Pfizer group[8] also has identified **3** as a major impurity formed during the preparation of **1**.



3

Compound **3** and the low-molecular weight polymers formed during the reaction are not easily removed by crystallization. Therefore, we eliminated the decomposition of acryloyl azide in benzyl alcohol followed by the isolation of **1** by crystallization as a potential route for scale-up.

It has been reported that **1** prepared by the reaction of vinyl isocyanate with benzyl alcohol crystallizes readily.[5] The isolation of vinyl isocyanate, however, is no easy task. It is a low-boiling, low-molecular weight isocyanate, and its toxicity has to be considered similar to that of methyl isocyanate. Its high propensity for polymerization is also of major concern. However, it occurred to us that if vinyl isocyanate is allowed to codistill with a solvent during the decomposition of acryloyl azide and the distillate is collected directly in benzyl alcohol, the above drawbacks could be overcome. Such a procedure would minimize the handling of vinyl isocyanate and remove most of the polymers formed during the decomposition of the azide from **1**.

As described in the Experimental Section, the apparatus we used to translate the above idea into practice was a simple distillation assembly. The toluene solution of acryloyl azide was slowly pumped into the distillation flask containing preheated toluene. Vinyl isocyanate formed during the decomposition of acryloyl azide in the distillation flask was swept into the receiver flask containing benzyl alcohol, an inhibitor, and a catalyst. Nitrogen generated during the decomposition of the amide facilitated the transfer of distillate to the receiver flask. A small amount of acryloyl azide was found to codistill if the addition rate of the azide was too fast, but almost complete decomposition was accomplished by controlling the rate of addition of acryloyl azide and by incorporating a small column packed with ceramic saddles in the distillation assembly. It should be pointed out that residual acryloyl azide in the distillate can be a potential safety hazard, and care should be taken to avoid its accumulation in the distillate. Formation of a polymeric solid occurred during the decomposition in the distillation flask. On the basis of its weight, it accounted for 10−15% of acryloyl azide charged. This solid was not friction-sensitive and dissolved in dilute sodium hydroxide solution, thus facilitating easy cleanup.

The reaction between benzyl alcohol and vinyl isocyanate was slow at low temperatures, and significant amounts of benzyl alcohol and vinyl isocyanate remained unreacted even after several hours. An exothermic reaction occurred when the contents of the receiver were allowed to warm to room temperature, but the product was mainly a polymer. Addition of phenothiazine as an inhibitor and a tertiary amine as a catalyst avoided the polymerization reaction, and **1** was produced as the major product. The product thus obtained crystallized readily on addition of heptane to yield substantially pure **1** in yields comparable to literature procedures.

In our experiments, vinyl isocyanate did not polymerize on the walls of the distillation assembly. However, small droplets of vinyl isocyanate were found to accumulate in the cold parts of the condenser in some experiments. These droplets eventually polymerized to give a white solid. In addition to sulfuric acid, the polymer was soluble in either boiling benzyl alcohol or hot 2-(methylamino)ethanol.

Summary

An improved method to prepare **1** starting from acryloyl chloride in good yield and purity has been demonstrated in the laboratory. This method avoids most of the drawbacks of previously reported methods. The product can be isolated in good yield and acceptable purity by crystallization that makes the process more suitable for scale-up. The thermal stability of acryloyl azide has been studied in some detail. Solutions of this compound in toluene appear to be stable at subambient temperatures. However, it can undergo polymerization when stored for long periods of time, and the crystals formed can undergo rapid decomposition when dry. Care should be exercised to avoid the polymerization by storing the solutions below 5 °C. It is strongly recommended that solutions of acryloyl azide be used soon after their preparation. The explosive potential of acryloyl azide should be fully evaluated before it is handled on large-scale. Care should also be taken to avoid inadvertent accumulation of acryloyl azide and resulting unstable polymers in various parts of plant equipment.

Experimental Section

Important Safety Warning. *Some of the chemicals described in this paper can under go rapid decomposition and polymerization, with evolution of gaseous products. Acryloyl azide in neat form could be dangerously explosive, and vinyl isocyanate is probably very toxic. All experiments should be carried out behind a safety shield in a well-ventilated hood. Extreme care should be taken to avoid injury.*

Raw Materials. All raw materials used in this work were purchased from either Fisher Scientific or Aldrich Chemical Co. and used without further purification.

Analytical. HPLC analyses were performed on a Varian 9000 series HPLC system using a Zorbax C-8 or Capcel Pak ODS column. The latter column gave better separation of the components in reaction mixtures. A 6:4 mixture of acetonitrile and water (modified with 0.05% phosphoric acid) at a flow rate of 1 mL min^{-1} was used as the mobile phase. Detection wavelength was 210 nm. NMR spectra were recorded in $CDCl_3$ or CD_3CN on a Bruker-AM300 spectrometer.

Synthesis of Acryloyl Azide. A 1-L reactor was charged with 68.4 g (1.05 mol) of sodium azide, 200 mL of water, 200 mL of toluene, and 0.09 g of Adogen 464 (methyltrialkylammonium chloride). The mixture was cooled with stirring in ice−water bath, and 90 g (1 mol) of acryloyl chloride was added dropwise over a period of 1.5 h at 0−5

°C. After the addition, the mixture was stirred for 45 min. The organic phase was separated and stored at 0−5 °C until used.

Thermal Stability Studies of Acryloyl Azide. Acryloyl azide solution was prepared (0.25 mol) according to procedure described above. The solution was charged to a reactor equipped with a heating mantle, thermometer, temperature controller, and reflux condenser. It was gently heated to 40 °C and maintained at 40 °C. Slight gas evolution was noticed, but the temperature remained at 40 °C. After 45 min, the formation of an insoluble material was noticed. After 4 h, the temperature was raised to 50 °C and maintained for 2 h. Brisk gas evolution occurred, but no exothermic reaction was noticed. Gradual heating was resumed to raise the temperature to 70 °C when the decomposition became exothermic. At 75 °C the heating mantle was removed. Within minutes gas evolution slowed, and the temperature began to fall. The heating mantle was then replaced without turning it on. The temperature gradually rose to 85 °C. Good reflux was noticed, and the temperature remained steady until the reaction subsided.

In a second experiment, a solution of acryloyl azide was maintained at 50 °C for 5 h. Exothermic decomposition of acryloyl azide did not occur, although gentle gas evolution was noticed throughout. The mixture was very slowly heated to 60 °C and maintained for 2 h. Gas evolution was brisk, but again, uncontrolled reaction did not occur. On the basis of HPLC analysis at the end of this period, it was estimated that 70−75% of the starting acryloyl azide remained undecomposed. The temperature was raised to 70 °C, and the mixture was stirred for 0.5 h. Since no exotherm was noticed, the temperature was raised to 75 °C. The mixture began to reflux violently, and the temperature went up to 81 °C. The reaction was over in few minutes, and the temperature began to subside.

In a third experiment the azide solution was heated to 75 °C. The heating was turned off, but the mantle was kept in place as an insulator. Vigorous gas evolution occurred, and the temperature rose to 93 °C. After 2 min the mantle was removed, and the flask was cooled in an ice−water bath. The temperature immediately dropped, and the reaction subsided. At 80 °C the heating mantle was replaced, but without turning it on. The temperature again rose to 90 °C, where it stayed for 5 min and then began to drop. The mixture was then maintained at 80 °C until gas evolution stopped. The mixture was cooled to room temperature and filtered. The polymeric residue was washed with acetone and dried. It did not appear to be friction-sensitive when rubbed against a rough surface. It was soluble in 10% sodium hydroxide solution.

Isolation of Impurity 3. A 1 mol-scale preparation of acryloyl azide was carried out as before. A reactor equipped with a temperature controller, and reflux condenser was charged with 108 g of benzyl alcohol (1 mol), 200 mL of toluene, 0.5 g of phenothiazine, and 3 g of triethylamine. The mixture was heated with stirring to 110 °C. The azide solution was pumped into the hot mixture over a period of 1.25 h, maintaining temperature at 108−110 °C. HPLC analysis after the addition of half of the azide solution indicated rapid consumption of benzyl alcohol. Additional 15 g of benzyl alcohol was added. After the addition of the azide, the mixture was stirred for half an hour at 105 °C. The mixture was cooled and stripped in vacuo on a rotary evaporator to obtain a yellow viscous syrup, which began to solidify on standing. The gummy solid was triturated with *tert*-butyl methyl ether (MTBE, 150 mL). The solid that separated out was filtered, washed, and dried. The product was recrystallized from heptane-MTBE (2:1) mixture. HPLC showed one major component (>98%); mp 79−80 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 735−7.23 (m, 10H), 5.26−5.12 (br m, 2H), 5.17 (s, 2H), 4.66−4.52 (dd, J = 30.45 and 11.76 Hz, 2H), 1.37 (d, J = 5.52 Hz, 2); ^{13}C NMR ($CDCl_3$) δ155.78, 138.17, 136.21, 128.58, 128.36, 128.26, 128.17, 127.59, 78.68, 69.91, 66.89, 22.06.

Synthesis of 1, General Procedure. A 1-L flask was equipped with a variable speed pump, mechanical stirrer, temperature controller, a 4-in. column packed with ceramic saddles, distillation head, spiral condenser (cooled with 10−15 °C water), and receiver. The flask was charged with 150−200 mL of toluene and 0.5 g of phenothiazine. The toluene solution was heated to 105−110 °C. The receiver was charged with 86 g (0.8 mol) of benzyl alcohol, 0.05 g of phenothiazine, and 0.1−0.3 g of triethylamine. This mixture was cooled in ice and stirred. A solution of acryloyl azide (1 mol) prepared as described before was pumped in to the distillation flask over a period of 4−5 h, maintaining a pot temperature at 105−110 °C with a heating mantle. The vapor temperature varied, depending on the rate of addition of the azide, but was in the range of 80−100 °C. The distillate was collected directly in the benzyl alcohol mixture. After the addition of acryloyl azide, the distillation continued to distill out 10−20 mL of toluene. The receiver was then isolated from the distillation set up, and its contents were stirred at 0−5 °C for 1−2 h. The product mixture was then allowed to warm gradually to room temperature and stirred until HPLC analysis indicated complete reaction. The mixture was then stripped in vacuo to a weight of 200−250 g. To the residue was added 300−350 mL of heptane and cooled with stirring to 15 °C. A few seed crystals of **1** were added, and the mixture was stirred for 2−3 h. The product was filtered, washed with heptane, and dried in vacuo. Yield 115−128 g (65−72%): mp 41−44 °C. ^{1}H NMR (300 MHz, CD_3CN) δ 7.73 (br s, 1H), 7.42−7.31 (m, 5H), 6.74−6.62 (m, 1H), 5.13 (s, 2H), 4.59 (d, J = 15.8 Hz, 1H), 4.26 (d, J = 8.84 Hz, 1H).

Acknowledgment

I express my appreciation to PPG Industries Inc. for allowing the publication of this paper. I also acknowledge the help of Dr. Tim Flood in recording and interpreting NMR spectra and of Dr. Felicia Tang with HPLC analyses.

Received for review September 20, 2001.

OP0102316