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# Continuous flow synthesis of β-amino α, β-unsaturated esters in aqueous medium

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## Abstract

Continuous flow synthesis of many β-amino α, β-unsaturated esters has been demonstrated, through the reaction of a β-ketoester compound with ammonia and primary amines. Several combinations have been studied in detail in batch mode and a few have been taken for continuous flow synthesis based on their suitability. Upon studying the feasibility of continuous flow synthesis of different β-amino crotonates, the synthesis of methyl amino crotonate in the presence of a recyclable and reusable homogeneous acid catalyst has been studied in detail. Tubular reactors were seen to overcome the heat and mass transfer limitations, thereby providing a simple device for even a pilot scale production. A similar approach can be used for the synthesis of other β-amino crotonates. The continuous flow synthesis approach for producing methyl amino crotonate, in the absence of any external solvent, makes it a green process technology.

**Keywords:** β-amino crotonate; continuous flow synthesis; Hantzsch synthesis; microreactor.

## 1. Introduction

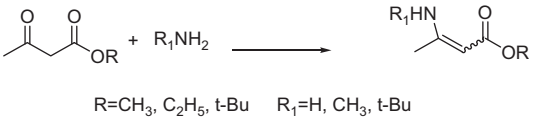
β-Amino α, β-unsaturated esters are useful synthetic intermediates, particularly in the construction of heterocyclic compounds such as 1,4-dihydropyridines, pyrimidines and indoles. 1,4-Dihydropyridines are an important class of compounds due to their pharmacological activity as calcium channel blockers [1] and are prescribed in the treatment of coronary diseases. In general, 1,4-dihydropyridines induce relaxation of vascular smooth muscles in arteries. This class of drugs includes a few high turnover drugs, e.g., amlodipine, which is a multibillion dollar selling drug. The symmetrical 1,4-dihydropyridine derivatives are prepared by condensation of aromatic aldehydes, with two moles of β-ketoester and ammonia. The synthesis of 3,5 unsymmetrical esters involves condensation of molar quantities of β-ketoester and β-amino crotonate with required aldehyde. Among the various β-amino crotonates, methyl β-amino crotonate and ethyl β-amino crotonate are important intermediates for the manufacture of amlodipine and felodipine, respectively. A few more alkyl β-amino crotonates are used for the synthesis of 1,4-dihydropyridines having pharmacological activity (nislodipine etc). With growing demand for calcium channel blocker drugs like amlodipine and felodipine in the treatment of high blood pressure, a green and scalable method for the synthesis of β-amino α, β-unsaturated ester will be useful.

Several methods for the preparation of β-amino α, β-unsaturated esters have been reported. The generally employed method for their preparation involves a reaction between β-keto ester and ammonia in methanol [2], acetic acid [3], introduction of gaseous ammonia in neat acidic catalyst [4], and use of ammonium carbamate [5] and ammonium acetate [2]. The use of solvent with simultaneous removal of water using Dean Stark is also reported. The yield of the product alkyl β-amino crotonate is usually 65–70% and involves prolonged heating, longer reaction time period and also evaporation of reaction mass to dryness [5]. The reaction of ammonia with β-keto esters is exothermic and requires external cooling and a controlled rate of ammonia addition [6]. Recently, a method for the preparation of β-amino α, β-unsaturated ester has been reported using silica gel catalyst under solvent free conditions [7]. While some of these methods can be adapted for lab scale synthesis, the others are not suitable for large scale manufacturing. With these shortcomings of the reported procedures, it is necessary to develop a methodology to take care of the exothermic nature of the reaction and to allow the use of low boiling amines, which are amenable for scale up based on flow chemistry.

In this manuscript, we demonstrate the batch to continuous transformation of synthetic procedure for β-amino crotonates starting from three different β-ketoesters [methyl acetoacetate (Spectrochem), ethyl acetoacetate (Spectrochem), tert-butyl acetoacetate (Sigma)] and three condensation reagents i.e., aqueous ammonia (25%) (Merck, India) and aqueous solutions of two primary amines [methyl amine (Loba Chemie, India) (40% MA in water) and tertiary butylamine (TBA, Loba Chemie, India)]. A typical reaction scheme is shown in Scheme 1. In the end, one case has been studied in detail and taken for close to the kilogram scale production/h using a simple experimental system.

## 2. Experimental

This section is divided into two parts, one related to batch experiments and the other on continuous flow synthesis. As mentioned previously, batch experiments were carried out to realize the typical reaction time, issues related to solubility/homogenization of the phases, the rise in reaction temperature, precipitation of the product during the course of reaction etc. From the findings of the batch experiments, continuous




**Scheme 1** Synthesis of β-amino crotonates.

flow experiments were planned and executed to realize the possibility of making the process continuous.

### 2.1. Experimental set-up

**2.1.1. Batch reaction** In a batch experiment R-acetoacetate (R=ethyl, methyl, t-butyl) was taken in a 100 ml jacketed glass reactor. To the alkyl acetoacetate, 2 or 3 equivalent of ammonia (25% solution)/alkyl amine was added slowly with constant stirring. The experiment was carried out with and without isopropanol as the solvent media. The effect of the mole ratio of ammonia solution/amines to the β-keto ester was studied. The reactor temperature was maintained constant by circulating heating/cooling fluid from a constant temperature bath (Julabo, ME12, Germany). After addition, a sample is withdrawn in different time intervals to track the reaction progress, and samples were analyzed using GC. Experiments were carried out at different reaction temperatures, as well as for different mole ratios of ammonia.

**2.1.2. Continuous experimental setup** For the continuous flow experiments, typically the experimental setup consisted of two HPLC/syringe/peristaltic pumps (Lab Alliance, USA/ Longer Pumps, China) followed by a simple T-micromixer (0.8 mm inner diameter (i.d.) or 1.38 mm i.d.), which was then connected to a 1 m long stainless steel (SS316) tube (1.58 mm outer diameter (o.d.) and 1.38 mm i.d.). The SS tube was immersed in a thermostat (Julabo, ME12, Germany), and the samples were collected at the outlet of the tube. In a few experiments, the mixer and reactor were immersed in an ultrasound bath at constant temperature. A wider range of residence time (0.01 ml/min to 12 ml/min) was maintained in the experiments to achieve the desired residence time for individual cases. Upon optimization of the reaction conditions and the inlet composition, experiments were carried out for synthesizing the product at a higher scale, using 6.35 mm o.d. (4.25 mm i.d.) tubular reactor.

### 2.2. Analysis

**2.2.1. Sample preparation** For the case of aqueous ammonia and methyl amine as condensation reagents, to the reaction mixture withdrawn from vessel, sodium chloride was added and the organic layer was extracted by addition of diethyl ether. The ether layer was separated and used for GC analysis. For the case of tert-butyl amine as condensation reagents, β-keto ester and t-butyl amine are both organic compounds. Hence, initially, the product mixture was collected in water and then the above process of making a sample for GC analysis was followed. The results in terms of yield are based on the GC analysis and in some cases they were confirmed by quantitative measures in terms of mass of the actual product.

**2.2.2. Analytical method** The samples were analyzed by gas chromatography (Thermo Trace Ultra GC) equipped with a HP-5 (30 m×0.25 mm i.d.; film thickness=25 μm) capillary column and an flame ionization detector (FID). Specific program conditions (temperature program, 100°C to 240°C at 20°C/min, held for 5 min; injection volume=1.0 μl) were used for the analysis. The injector and detector temperature was maintained at 240°C. Purity of some of the products was checked by proton NMR and the physical properties (i.e., the melting point) were also measured to assess the product quality.

## 3. Results and discussion

The objective of this work was to understand the feasibility and demonstrate the batch to continuous transformation of the process for the synthesis of β-amino crotonates. We synthesized 9 different β-amino crotonates arising out of the reactions of three different β-keto esters with ammonia and two primary amines. In the end, one case has been studied in detail and taken to situations that can easily be used for the commercial scale production.

### 3.1. Feasibility studies for batch and continuous flow synthesis

As discussed earlier, three different β-ketoesters were subjected to react with three different condensation reagents. Batch experiments were carried out for 9 different β-amino crotonates and conditions were identified that can suggest the feasibility towards their transformation to continuous flow synthesis. Below, we give a detailed account of the observations for every case for batch experiments, as well as for continuous flow experiments.

**3.1.1. Ethyl amino crotonate** The reaction in batch mode between ethyl acetoacetate (EAA) and aqueous ammonia (25% solution) at 20°C was performed at different mole ratios of EAA to aqueous ammonia (i.e., 1:1, 1:2 and 1:3, which needed 600 min, 210 min and 75 min, respectively, to achieve 100% conversion of EAA). Subsequently, the experiments in continuous flow tubular reactor at mole ratio of 1:3 were studied at different temperatures. At 50°C, 94% conversion of EAA was observed for residence time of 22 min. An increase in reaction temperature was seen to enhance the reaction rate.

**3.1.2. Ethyl 3-methyl amino crotonate** In the batch synthesis of ethyl-3-methyl amino crotonate, MA was added drop wise to EAA with constant stirring. At 20°C, the complete conversion was monitored for different mole ratios of reactants. For the mole ratio of 1:1.2, 1:2 and 1:3, the completion of reaction required 90 min, 13 min and 1 min, respectively. Hence, further studies were carried out

to check the effect of temperature at a mole ratio of 1:2. At 0°C, precipitation took place during addition, while at 10°C, completion of the reaction was seen in 15 min. The reaction was largely dominated by the amount of MA used in the reaction. Since the reaction is mildly exothermic, thermal decomposition of amine was possible depending upon the local temperature. Further intensification was carried out in continuous mode using the system shown in Figure 1, with a micromixer and a 2 m long 1.58 mm tubular reactor. In the continuous flow system, experiments were carried out at a higher temperature (>20°C) and at and a ratio of 1:3. At 40°C, at a mole ratio of EAA:MA~1:2 and 1:3, complete conversion of the ester was achieved in residence times of 90 s and 10 s, respectively. With a very high heat transfer area of the tubular reactor (~5040 $m^2/m^3$), it was possible to maintain the isothermal condition throughout the tube and thereby enhance the reaction rates further, without decomposing the primary amine. An experiment with a 1:2 mole ratio at 40°C was carried out for a long time, to collect as much as 100 g of the product from a single 1.58 mm tubular reactor. Since the reaction is largely homogenous (if product precipitation is not allowed) scale-up by numbering-up is effective to directly use this simple system for large scale production without using any solvent.

**3.1.3. Methyl 3-methyl amino crotonate** The batch reaction between methyl acetoacetate (MAA) and methyl amine in isopropanol at 20°C in a 100 ml reactor, resulted in a significant rise in temperature (>35°C), with the product getting isolated as a solid. Reaction completion was achieved in about 120 s. The reaction temperature could not be increased further due to a very rapid rise in temperature. Upon performing the experiments in the continuous flow reactor, it was possible to carry out the reaction at a higher temperature without much problem and completion of the reaction was seen to occur in <30 s at 40°C, which could further be brought down to 5 s, by increasing the reactor temperature. Since the melting point of the product is close to 38.6°C, it was necessary to carry out this reaction at a higher temperature to avoid solidification.

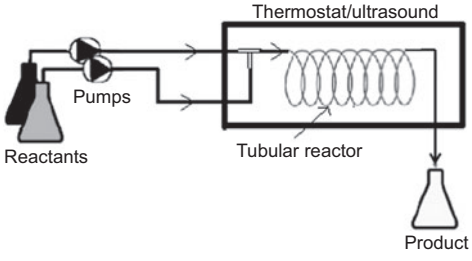



**Figure 1** Experimental set-up for continuous flow experiments. The reactants included β-keto ester either neat (with/without catalyst) or along with the solvent and the condensation reagent, i.e., aqueous ammonia or primary amine. Syringe pumps were used for lab scale screening experiments while peristaltic pumps were used for kilo scale production.

**3.1.4. Methyl 3-butyl amino crotonate** The batch experiments of the reaction between MA and tert-butyl acetoacetate (TBAA) were carried out at a constant mole ratio of TBAA:MA~1:2 and at 20°C. Since the reaction is mass transfer limited, the nature of liquid-liquid dispersion controls the reaction progress. In the batch experiment with vigorous stirring, 97% conversion was achieved in about 15 min, while it needed only 60 s in a continuous flow reactor at identical conditions. Reactions in a 6.35 mm diameter tubular reactor with a 10 m long reactor, helped to keep sufficient inlet velocities, which helped overcome the mass transfer limitation due to an increase in slug diameter. Further increase in the reactor diameter for increasing the production scale was not recommended (as the overall mass transfer coefficient decreases with increase in the slug diameter) and hence, the numbering-up approach (with an average residence time of 60 s), was adapted for further enhancement in production capacity.

**3.1.5. Tertiary butyl amino crotonate** The reaction of TBAA with aqueous ammonia was inherently slow. A typical batch reaction needed almost 240 min to get 40% conversion (at 20°C and a mole ratio of 1:3). In continuous mode, a longer residence time was not feasible as interfacial mass transfer rates are much smaller due to poor internal circulation rates. At T>30°C, a significant portion of ammonia was in the gas phase, and dead-end systems would be necessary to achieve better conversion. In the batch mode at 50°C, it takes more than 120 min at lab scale (50 ml) completely closed system (with complete consumption of ester). In the continuous mode, at 50°C the conversion of TBAA was 20% (for a residence time of 22 min and a mole ratio of 1:3) and 44% (for a residence time of 50 min and a mole ratio of 1:5). Since this reaction is inherently slow, a catalytic route would be useful to enhance the reaction rate.

**3.1.6. Butyl 3-ethyl amino crotonate** The reaction of EAA with tertiary butyl amine (TBA) in batch condition was observed to be relatively slow yet exothermic (Table 1). Even a higher reaction temperature (30°C) and higher concentration of TBA (1:3) yielded only 37% conversion. Thus, while it is possible to intensify the reactions involving TBA, it need not be made continuous unless the reaction rate increased significantly.

**Table 1** Summary of batch experiments for the synthesis of β-amino crotonates at 20°C.

| Alkyl acetoacetate (a) | Condensation reagent (b) | Mole Ratio (a:b) | Reaction time (min) | % Yield |
|---|---|---|---|---|
| EAA | $NH_3$ | 1:3 | 75 | 100 |
| EAA | MA | 1:3 | 0.5 | 100 |
| EAA | TBA | 1:2 | 90 | 26 |
| TBAA | $NH_3$ | 1:3 | 240 | 40 |
| TBAA | MA | 1:2 | 15 | 97 |
| TBAA | TBA | 1:2 | 90 | 13 |
| MAA | $NH_3$ | 1:3 | 75 | 73 |
| MAA | MA | 1:1 | 2 | 100 |
| MAA | TBA | 1:2 | 90 | 23 |

**3.1.7. Methyl amino crotonate** Further to these different systems we chose the synthesis of methyl amino crotonate as a model system to demonstrate synthesis at relatively large scale. Conventionally, the synthesis is carried out in a solvent viz. isopropanol. Since the product can easily crystallize and may clog the continuous flow reactor initial experiments were carried out with and without isopropanol as the solvent media.

Initially, the effect of the concentration of ammonia was studied at room temperature for different mole ratios (MAA:$NH_3$~1:1, 1:2 and 1:3) in identical quantity of solvent (isopropanol) in batch mode. With increasing concentrations of ammonia, the reaction time decreased from 180 min to 75 min, while the product yield increased from 59% to 73%. On the other hand, at a constant MAA:$NH_3$ mole ratio (1:2), an increase in the solvent to ester mole ratio (1:0, 1:1 and 1:3) required a longer reaction time (from 75 min to 120 min) to achieve complete conversion, which is natural due to the dilution effect. At a low concentration of solvent, the product crystallizes out and forms needle shaped crystals as shown in Figure 2A and B. However, higher amounts of solvent helped to keep the product in the solution phase. An increased reaction temperature (from 25°C to 50°C) resulted in a reduction in the $NH_3$ concentration [8] and hence a reduction in the conversion of MAA 78% to 52% in 1 h. No further intensification was possible in the batch mode, because of either the loss of ammonia or the prolonged reaction time. Further experiments were carried out in a continuous mode, and details are discussed after summarizing the batch observations from all the systems.

A summary of all the batch experiments (without using any solvent) is given in Table 1. The tabulated information clearly indicates that for some of the inherently slow reactions, while it is necessary to identify the ways for their intensification, more promising candidates are those, which even in batch mode operation, show reasonably good yields of the desired product. Also, in some of the cases, the product was liquid phase at room temperatures and separation was not economical even by prolonged cooling at very low temperatures. Some of the combinations of ester and the condensation reagent discussed above for the case of continuous flow synthesis, also support the observations from batch mode, clearly indicating that continuous flow operation will not necessarily enhance the performance significantly. Reactions involving ammonia and MA as condensation reagents, have a significant potential for intensification and also for the transformation of the lab scale process to large scale systems in the continuous flow. In the rest of this manuscript, we demonstrate the case of synthesis of methyl amino crotonate as a model system that can be taken for kilogram scale production/h, using the lab scale system. A similar approach can be followed for other combinations discussed earlier.

### 3.2. Continuous flow synthesis of methyl amino crotonate (MAC)

A continuous flow experiment was carried out in a SS316 tubular reactor of 6.35 mm o.d. and 2 m length at 50°C, with a residence time of 15 min. With the MAA to aqueous $NH_3$ to solvent ratio of 1:3:1, the yield of MAC was 56%. For a residence time >15 min, clogging of the reactor was observed due to accumulation of the solid product in the tubular reactor. Since the use of solvent was still unable to keep the product in the dissolved condition, it was thought desirable to study the reaction in the presence of ultrasound. The reactor was subjected to sonication by submerging it in an ultrasonic bath (60 kHz). The previous experiment was repeated in the presence of ultrasound and a yield of 78% was obtained. Additional experiments were carried out at different conditions, and the observations are tabulated in Table 2. Incomplete conversion of the β-keto ester did not show any choking of the reactor and hence the system was further studied for the effect of reaction temperature. The observations are shown in Figure 3. In the continuous flow system, an increase in temperature helped to achieve complete conversion in a much shorter time than the batch experiment with identical conditions. However, still within the residence time range, the reaction was incomplete and clogging of the reactor after prolonged operation was always possible due to backward precipitation of the product from outlet towards the inlet of the reactor. This phenomenon of solid adhesion on the reactor wall, leading to eventual clogging, is observed quite frequently and demands a smaller residence time in the reactor. Subsequent to this, the reaction rate enhancement by the catalytic route was checked to reduce the reaction time.

**3.2.1. Catalytic route to MAC** Batch experiments were carried out by mixing MAA with aqueous ammonia (25%

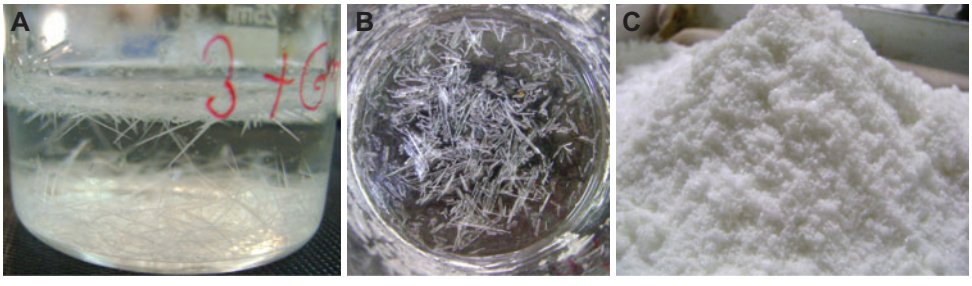



**Figure 2** (A–B) Photographs of the MAC crystals formed in the batch reactor at low solvent quantity (MAA:Aq.NH3:IPA~1:2:0.5 mole ratio) and for incomplete conversion; (C) MAC collected at the outlet of tubular reactor from the catalytic route based procedure discussed in Section 3.2.

**Table 2** Summary of continuous experiments for the synthesis of β-amino crotonates following the non-catalytic route in the presence of solvent isopropanol (IPA).

| MAA:aq. $NH_3$:IPA | Ultrasound | Residence time (min) | Temperature (°C) | % Yield |
|---|---|---|---|---|
| 1:3:1 | No | 15 | 25 | 56 |
| 1:3:1 | No | 15 | 50 | 71 |
| 1:3:1 | No | 20 | 25 | (Clogging) |
| 1:3:1 | Yes | 15 | 50 | 78 |
| 1:3:0 | Yes | 15 | 20 | 64 |
| 1:3:0 | No | 15 | 20 | 59 |

solution) and acetic acid (AA) as a catalyst [9] and without any solvent. At room temperature, the reaction for 12 h yielded 82% product and at 50°C, within 60 min, yield was between 93 and 96%. On extending the same approach for the continuous flow synthesis (at 50°C with a residence time of 160 s without any solvent and with the MAA:$NH_3$:AA mole ratio of 1:2:1), the yield of the product was 93–96% from the first crop. No choking of the reactor was observed. Using a sufficiently long single tubular reactor, the hourly yield of the product MAC could be taken to 700–710 g (Figure 2C). The collected product upon cooling for 10 min at 10°C was as much as 96% of the expected mass. The balance MAA was found to be unreacted MAA and it remained dissolved in the aqueous phase. This balance MAA could be recovered as MAC after ammonia purging. The filtrate (acetic acid+water) was subjected to ammonia purging and was reused for reaction with MAA. The experiments were repeated three times by reusing of the catalyst and by saturating the solution with ammonia before its further reaction with the next lot of MAA. In each step, the yield of MAC was seen to get

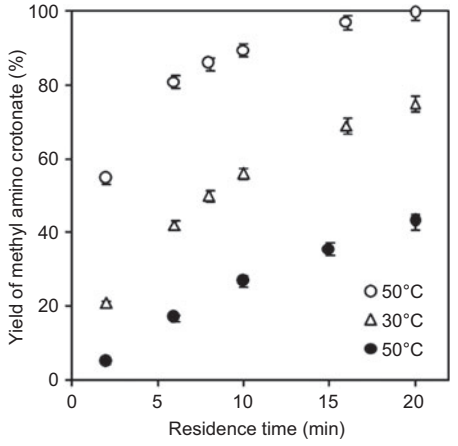



**Figure 3** Effect of temperature on the variation in the % yield of methyl amino crotonate with residence time in a continuous flow reactor with MAA:$NH_3$=1:2. Open symbols indicate the continuous flow experiments (samples collected at the outlet for specific residence time in the tubular reactor) and closed symbols correspond to the data from batch experiments (sample data at different time intervals).

reduced by <2%. Further work on optimizing the time cycle of continuous filtration, ammonia enrichment, recycling and reuse of the catalyst and water mixture, is in progress. This approach would give a zero water discharge solvent free process for the synthesis of methyl amino crotonate.

Thus, a homogeneous catalytic process with negligible loss of catalyst per recycle clearly brings out this process as a green process for the synthesis of β-amino crotonates. A similar approach can be extended for other amino crotonates (mainly using aqueous ammonia and MA as condensation reagents), however, for every product, the separation or product isolation strategy needs to be evolved separately (as, for example, while methyl amino crotonate is a solid, ethyl amino crotonate is a liquid). Typically, the industrial process follows a non-catalytic route in the batch reactor, with a longer reaction time and a lower yield. The use of the continuous flow synthesis approach demonstrated here is far more superior in terms greenness of the process and overall yield, and can easily be scaled-up to produce several hundred kg/day from a simple closed-loop set-up.

## 4. Conclusions

An efficient and practical process for the continuous flow synthesis of β-amino-α,β-unsaturated esters, through the reaction of three different β-ketoesters with different condensation reagents, is studied. The system of methyl amino crotonate has been discussed in detail and demonstrated on continuous flow operation at a scale of 700 g/h, using a recyclable and reusable homogeneous catalyst. The optimized reaction is carried out at 50°C with acetic acid as the catalyst and without using any additional solvent. Yields per pass are of the order of 93–96% and the reaction time is <3 min. All of these observations point to this process as being a green process for the synthesis of β-amino crotonates. More work on understanding the mass transfer with reaction for different systems and numbering-up approach for producing several hundred kg of the product/day are in progress.

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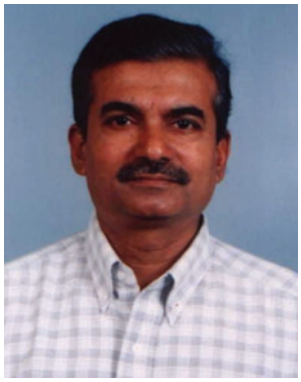

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