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Development of a Safe Continuous Manufacturing Route to 2-(4-Isopropyl-1*H*-1,2,3-triazol-1-yl)acetic Acid

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ABSTRACT: Starting from sodium azide, methyl-bromoacetate, and 3-methylbut-1-yne, a safe and efficient three-step continuous process was developed to obtain 2-(4-isopropyl-1*H*-1,2,3-triazol-1-yl)acetic acid. Isolation of hazardous intermediates was avoided, and by using FT-IR in-line monitoring of the azides involved, risks associated with these components were minimized. Furthermore, the use of FT-IR as a tool for optimization in real time facilitated the understanding of the kinetics of the reaction steps and resulted in a rapid optimization of parameters. The continuous method was used for multihundred grams manufacturing of the triazole which was used as a key building block in one of our drug development projects.

INTRODUCTION

In one of our drug development projects we were in immediate need of kilogram quantities of the building block **1** (Figure 1).

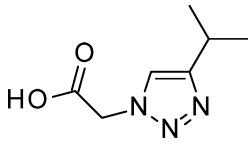

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Figure 1. Target molecule 2-(4-isopropyl-1*H*-1,2,3-triazol-1-yl)acetic acid **1**.

Although this compound is commercially available from a few suppliers, it is only available in small quantities and to a very high cost. Therefore, we felt that an in-house manufacturing of **1** would be necessary to secure a long-term supply of this building block. However, among various existing methods to synthesize analogues to **1**, the one used to obtain the first milligram quantities of **1** in our laboratories involved hazardous azides and a volatile and flammable reagent.[1] Thus, it was clear that in order to develop a robust large scale route to **1**, the synthetic strategy had to be changed and a process safety evaluation undertaken for the synthesis.

RESULT AND DISCUSSION

1,2,3-Triazoles of type **1** are conveniently prepared starting from an alkyne, a haloester, and an azide salt.[2] To supply the project with the first gram quantities of **1** for further synthesis of bioactive candidate drugs, the first generation synthesis depicted in Scheme 1 was used. Thus, the commercially available azidoacetate **2** as a solution in CH_2Cl_2 was reacted with the alkyne **3** at 20 °C overnight via a copper(I) catalyzed cycloaddition to give triazole **4** in good yield. The ester was further hydrolyzed using LiOH to give the lithium carboxylate **5**. This carboxylate was used as such in the subsequent amide coupling due to the high water solubility of the corresponding carboxylic acid **1** upon protonation, resulting in a troublesome extractive workup.

For many reasons the first generation synthesis was deemed unsuitable for large scale applications, and the most important issues that had to be addressed were as follows:

(1) Certain azidocarbonyl compounds are reported as having energetic decomposition properties.[3] Internal AZ testing of azidoacetate **2** confirmed that this compound is a potential explosive and therefore should not be isolated.[4] Although commercially available as a solution, it is only available in a small set of solvents and not readily accessible in large quantities.
(2) Avoidance/mitigation of any hydrazoic acid generation if preparation of the azidoacetate **2** was considered.
(3) The potential for formation of copper azide which is a very shock-sensitive explosive.[5]
(4) Alkyne **3** is a volatile and flammable compound which is difficult to handle in a batch process especially at elevated temperatures.
(5) Isolation of the lithium salt **5** on a large scale would be troublesome, and an impractical process was foreseen. Thus, to be able to deliver large quantities of **1**, an alternative workup must be developed.
(6) To be able to develop a safe large scale process, an analytical method must be identified where levels of hazardous intermediates can be determined and kept to a minimum before workup.
(7) An extensive process safety evaluation of all included components was needed to identify potential incompatibility of reagents.

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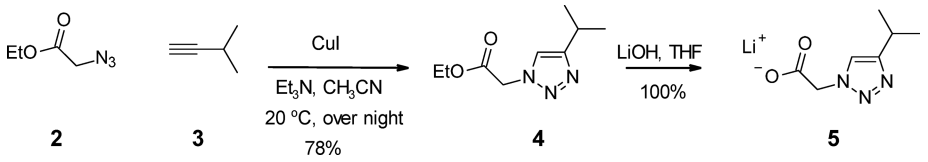
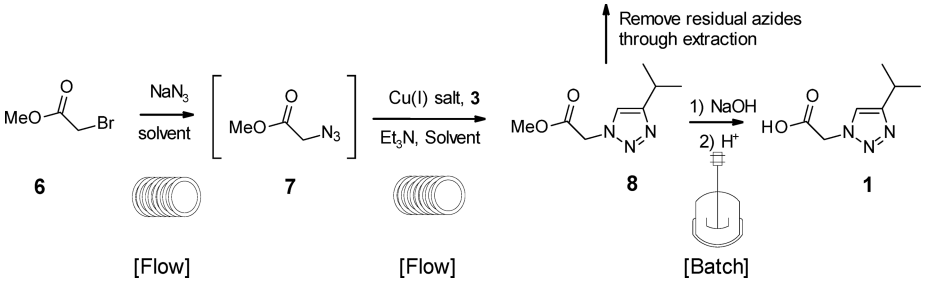
Scheme 1. First Generation Synthesis of 1



Scheme 2. Proposed Continuous/Batch Approach for Safe Manufacturing of Compound 1

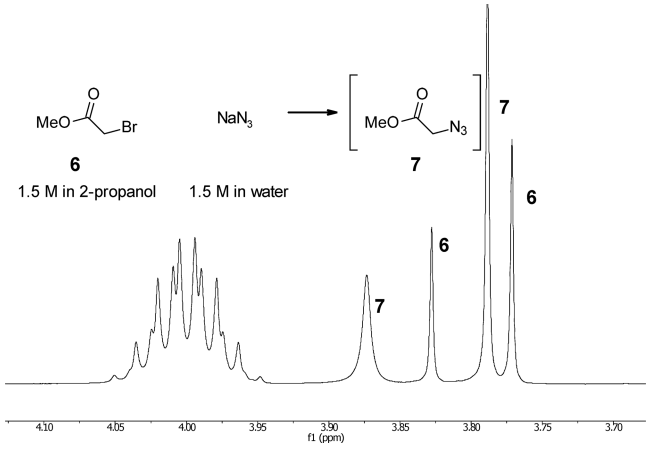


To address most of these issues, a continuous process was planned where handling of large amounts of all hazardous components could be avoided.[6] Using such an approach would also allow us to handle the volatile alkyne **3** at elevated temperatures by operating at higher pressures. At the same time, a better temperature control would be obtained for potentially exothermic steps. To avoid the dependence of suppliers of azidoacetate **2** in a limited set of solvents, we planned instead to generate an azidoacetate in a continuous flow starting from an azide salt and a halo-acetate and then react it directly in the next continuous cycloaddition step (Scheme 2). We envisaged a process where we could start from NaN_3 as an azide source and methyl 2-bromoacetate **6** which both are readily available cheap reagents. However, using such an approach demanded further safety assessment, as it is known that azide salts upon protonation will form hydrazoic acid which is a known highly toxic and explosive compound.[7] Thus, an analytical technique to detect NaN_3 was needed for this purpose. Also control of levels of the intermediate potential explosive azidoacetate **7** was needed to avoid handling of unreacted **7** in the workup. Finally, in order to obtain an efficient continuous process a prerequisite is to find a common solvent composition suitable for all reaction steps and which does not cause blockage due to precipitation. We envisaged a sequential two-step continuous approach followed by a hydrolysis in batch mode as depicted in Scheme 2. We believed that such an approach would fulfill our requirements for a safe process.

Thus, starting from bromoacetate **6**, a reaction with NaN_3 would furnish intermediate **7** which was planned not to be isolated but used directly in the following continuous cycloaddition with alkyne **3** to give triazole **8**. At this stage a basic extractive workup of **8** was planned in order to remove any residual azide salts. Then in a separate hydrolysis in batch mode, **1** could be obtained free from hazardous azides.[8] Before we were ready to evaluate the proposed continuous route we had to identify a common solvent to solubilize all components involved. This was not an easy task since the starting bromoacetate **6** is only soluble in organic solvents whereas NaN_3 is highly soluble only in water. Moreover, the highly lipophilic alkyne **3** does not dissolve in water and is immiscible in many highly polar solvents. In addition to this, copper(I) salts such as CuI are known to exhibit very low solubility in both water and most organic solvents and it is also sensitive to oxidation to form Cu(II) salts which are inactive as catalysts in this case.

Azidoacetate Generation. With the aim of identifying suitable conditions for a continuous process, we first performed the optimization on a small scale in batch mode using small vials. After screening various solvents for the azidoacetate generation **7**, eventually we found that the bromoacetate **6** could be dissolved as 1.5 M solutions in 2-propanol and then mixed with an equimolar solution of NaN_3 in water (1.5 M) to give one clear homogeneous phase (Scheme 3). Fortunately

Scheme 3. Identifying Solvent and Analytical Technique for Azidoacetate Generation



this solvent composition was also well suited for the azidoacetate generation, and at reflux, full and clean conversion was obtained within 1 h. The solvent composition was also appropriate for long time storage of **7**, as we did not see any decomposition or precipitation after aging for a few days at 20 °C.

As an analytical technique for monitoring the azidoacetate generation **7**, ^1H NMR could be used by recording the crude mixture directly after dissolving in $CDCl_3$. Thus, despite the excess of 2-propanol and water in the analytical sample, a window free of interferring signals was found in the region 3.75−3.90 ppm. Although, ^1H NMR could be used for

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controlling levels of the hazardous azidoacetate **7**, it could not be used for quantification of unreacted NaN_3 that might be present in the crude reaction mixture. Therefore, we searched for other analytical techniques that could be used for monitoring of both NaN_3 and the azidoacetate **7**. Azides generally have a strong absorption band in the infrared spectrum above 2000 cm^{-1}, and we hoped that FT-IR could be used as a good analytical technique for monitoring the azidoacetate generation (Figure 2).

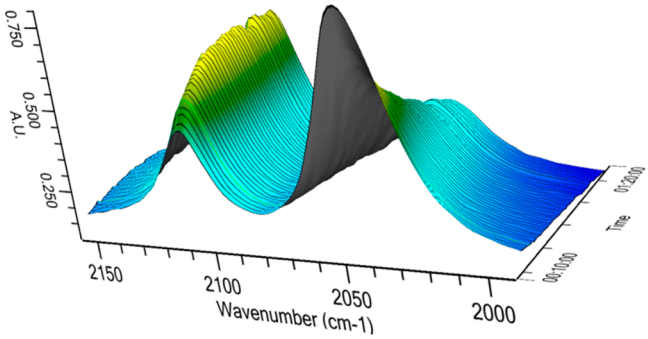

Figure 2. FT-IR monitoring of azidoacetate generation **7** (2112 cm^{-1}) from **6** and NaN_3 (2050 cm^{-1}).

We were pleased to find that by mixing an equimolar concentration of NaN_3 in water and bromide **6** in 2-propanol, the decrease in level of NaN_3 with time was easily recorded using FT-IR by looking at the strong absorption band for NaN_3 at 2050 cm^{-1}. At the same time, an increase in level of the desired azidoacetate **7** was observed by looking at the well resolved absorption band for **7** at 2112 cm^{-1}. Having established a robust and efficient process for generation of the azidoacetate **7** and an analytical technique to monitor levels of the hazardous NaN_3 and intermediate **7**, we were ready to optimize conditions for the subsequent cycloaddition step.

Cycloaddition. A delicate challenge remained to identify solvent composition for all components involved in the cycloaddition reaction and that also should be compatible with the conditions already optimized for the azidoacetate generation. Since the cycloaddition reaction of the type depicted in Scheme 2 is known to be compatible with an array of different solvents, we primarily focused on finding a solvent to dissolve the copper(I) salt.[2,9] One way to avoid the dependence of such salts is to use a copper coil reactor instead for continuous processing. This has successfully been demonstrated by several researchers.[10] However, after some attempts using such an approach we found that the continuous processing was not stable over time, presumably due to change of the copper surface which needs to be reactivated from time to time. Also, we believed that using a copper coil in combination with possible traces of unreacted azide salts would constitute a potential risk for buildup of hazardous copper azide on the copper surface. The use of a more soluble copper(II) salt in combination with a reductant is another approach that has proven to be efficient in some instances.[11] In our case, we were not able to find suitable conditions for such an approach, as precipitation of either the reductant or the copper salt was observed and the reactions also gave inconsistent results. Therefore, this strategy was abandoned and we searched for other methods. It is known that ligands as additives can stabilize Cu(I) salts and improve solubility.[12] However, to reduce the complexity of the reaction we focused on minimizing the number of reagents and additives required and to identify a robust approach that was stable over time. Therefore, copper(I) iodide which is known to be among the least sensitive salts toward oxidation was selected as the catalyst for the cycloaddition and an extended screen of solvents for dissolving this was performed. Eventually we found that pyridine as solvent gave solutions of CuI in high concentrations, and with some margin 0.075 M solutions were prepared which were stable for a few days.[13] We reasoned that, in addition to the excellent ability to dissolve CuI, the pyridine may prevent Cu(I) oxidation. Also, ensuring solubility of copper salts would avoid deposition of any copper azide if formed. Next, to reduce complexity in the planned continuous processing by reducing the number of pumps required, we aimed to find conditions where the alkyne and triethylamine could be dissolved in the same solvent as the CuI. Fortunately it was found that up to 3 M solutions of the alkyne in pyridine could be obtained containing also CuI (0.075M) and triethylamine (0.75M).[14] Fortunately, this solution could be stored for a few days with no notable decomposition or deactivation when stored under nitrogen. However, after exposure to air, some oxidation of the alkyne occurred resulting in dimerization. This was easily monitored by recording ^1H NMR on the crude mixture. Having identified a good solvent for dissolving the CuI, alkyne, and the triethylamine, it was time to investigate whether this mixture was compatible with the best solvents used for the azidoacetate generation. Since copper(I) salts are known to exhibit very low solubility in aqueous solutions, we feared that the 50% content of water used for the azidoacetate generation would cause severe precipitation which would result in blockage in the planned continuous processing. We were a bit surprised and relieved when we found that mixing a 0.75 M solution of the azidoacetate **7** in 50% 2-propanol in water, with a slight excess of a solution of the alkyne (3 M, 1.3 equiv)/CuI (0.075 M, 0.03 equiv)/Et_3N (0.75 M, 0.3 equiv) in pyridine, resulted in a homogeneous clear solution and no precipitation was observed even after several days of storage! Moreover, we were pleased to find that not only the solvent composition was suitable for dissolving all components but also the reaction itself worked satisfactorily and was complete within a few hours at 20 °C. To monitor the cycloaddition reaction, ^1H NMR was recorded on the crude mixture using $CDCl_3$ as solvent. Using ^1H NMR allowed us to detect most components involved and also made it possible to quantify levels of the volatile alkyne which would have been difficult to achieve using other analytical techniques (Figure 3).

From the NMR analysis, we could conclude that, apart from the generation of some MeOH, a quite clean conversion was obtained. The methanol was formed via hydrolysis of the esters **7** and **8**, and this side reaction was consistent in all experiments performed. Moreover, the rate of the hydrolysis was directly correlated to the amount of triethylamine added. To minimize the hydrolysis, attempts were made to reduce and even exclude the loading of the triethylamine. It was found that, in the absence of triethylamine, a very slow cycloaddition reaction was observed and the rate of the desired cycloaddition was also correlated to the loading of the triethylamine. In order to obtain an efficient continuous process with high throughput of **8**, it was concluded that ~30 mol % of Et_3N was needed for the reaction but this also resulted in ~30% of hydrolysis. That left us with three options: (1) Sacrifice formed carboxylic acid in the extraction and isolate the ester **8**. (2) Evaluate more stable

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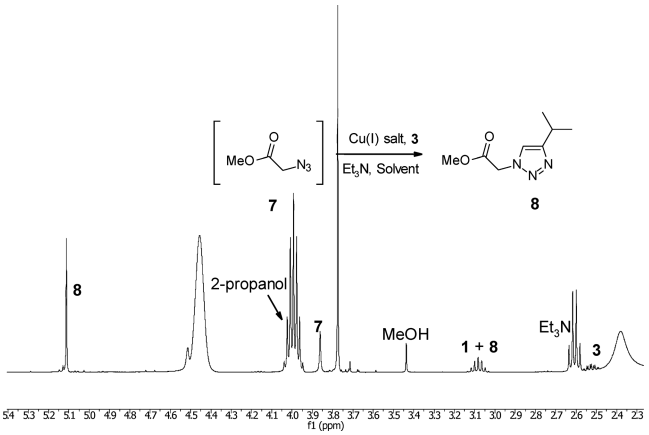

Figure 3. ^{1}H NMR spectrum of the crude mixture of the cycloaddition reaction in $CDCl_3$.

esters that are resistant to hydrolysis. (3) Add an extra hydrolysis step to the sequence to obtain a three-step continuous process where the acid **1** can be isolated after extractions.[15] The first option was deemed inefficient and would result in a too high loss of product whereas the second option was evaluated starting from both the ethyl and iPr ester of **6**. As expected, these esters were far more stable than the methyl one and only a small amount of hydrolysis was observed starting from isopropyl 2-bromoacetate. However, the more lipophilic character of these two esters resulted in the different solubility in the best solvents identified for the methylester **6**. Thus, inhomogeneous mixtures were obtained, and it was clear that more time would be needed to identify a new suitable solvent composition for these esters. Due to limited time for further optimization, we decided to go for the third option and introduce a third hydrolysis step to the already optimized two-step sequence. Thus, we planned to introduce a fourth pump delivering a solution of hydroxide in the continuous processing followed by an extractive workup of the carboxylic acid **1** obtained. This demanded a more thorough investigation of the process safety parameters since a trace amount of unreacted NaN_3 might be present which upon protonation of the alkaline hydrolytic mixture will form the highly toxic and explosive hydrazoic acid. Thus, a process safety evaluation was undertaken, and necessary precautions were performed.[16] On a small scale in batch mode, aqueous solutions of NaOH was added to the mixture of **8** after the cycloaddition. It was found that independent of the concentration of the NaOH solution, precipitation occurred, and we could foresee blockage in the continuous processing setup.[17] Therefore, various additives such as citric acid and EDTA were studied which potentially could prevent precipitation through complexation of the copper salts.[18] It was found that EDTA prevented precipitation but the complexation was deemed too slow in the continuous process and inconsistent results were often obtained resulting in cloudiness and turbidity. Therefore, to minimize all risks of blockage, it was decided that the hydrolysis step should be performed in a fed batch mode instead. Thus, by collecting the reaction mixture after the cycloaddition in a reactor containing NaOH in excess, a continuous hydrolysis was expected where the carboxylic acid finally could be isolated after an acidic workup. This approach was investigated on a small scale in 2 mL vials using authentic concentration of all components. Thus, the reaction mixture after the cycloaddition was treated with a mixture of 3.8 M NaOH (1.2 equiv) containing also EDTA (0.38 M, ∼10 mol %) which resulted in a rapid hydrolysis of the ester, and a clear homogeneous solution was obtained.[19] To our delight, no precipitation was observed after long storage, and the product carboxylate was also stable over a long time. What remained to be investigated was the protonation of the carboxylate formed and selection of extraction solvent. Initial attempts using $KHSO_4$ in excess resulted in immediate precipitation, and a troublesome workup was foreseen on a large scale. Therefore, a selection of other acids such as HCl, citric acid, sulfuric acid, and phosphoric acid were screened. It was found that only citric acid resulted in a clear homogeneous phase. However, the recovery of acid **1** was low even after multiple extractions with EtOAc which was found to be the best organic extraction solvent. The inefficient extraction was probably due to the low acidity of citric acid which resulted in incomplete protonation of the carboxylate of

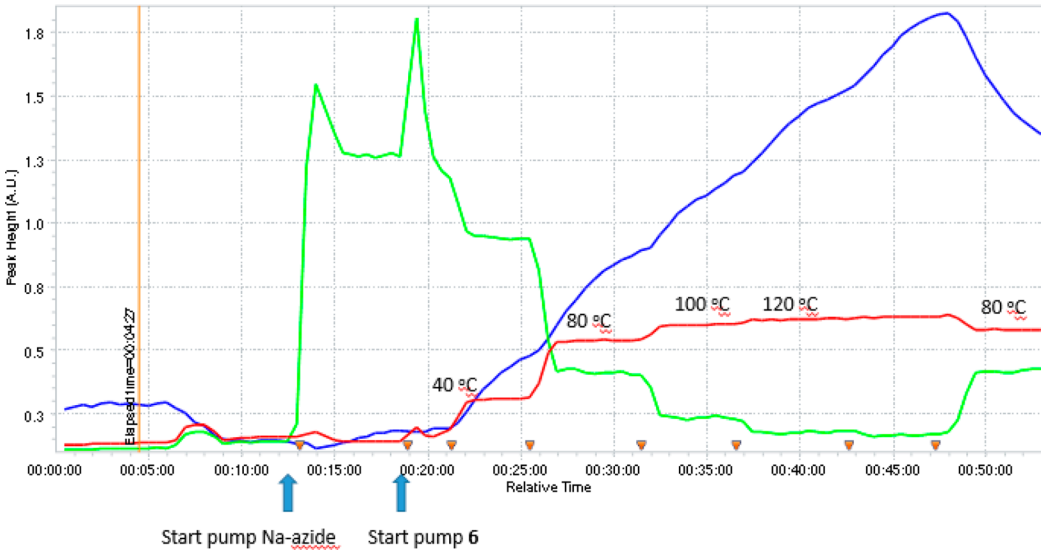

Figure 4. Real time FT-IR optimization of the azidoacetate generation. Green line = Na-azide (2050 cm^{-1}), Red line = azidoacetate **7** (2112 cm^{-1}), blue line = temperature.

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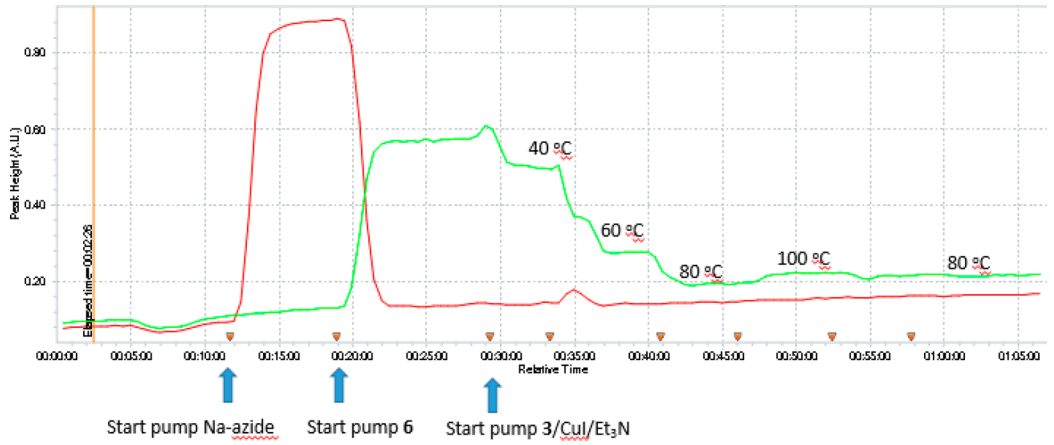

Figure 5. Real time FT-IR optimization of the cycloaddition. Red line = Na-azide (2050 cm^{-1}), Green line = azidoacetate **7** (2112 cm^{-1}).

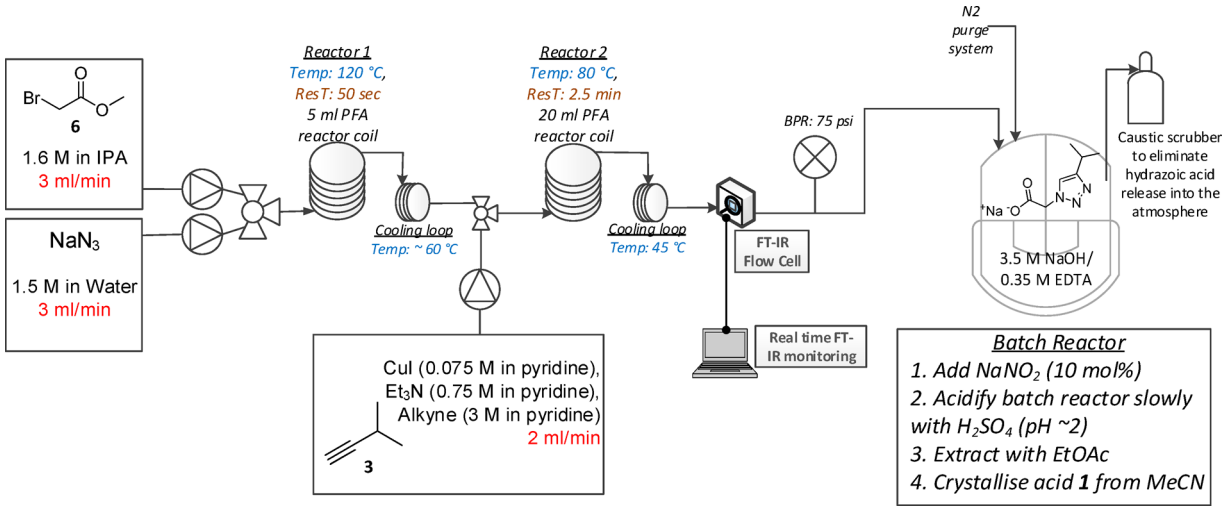

Figure 6. Continuous manufacturing process to obtain carboxylic acid **1**.

1. We were running out of time and had to select an acid for the extraction even though it caused precipitation, and for this purpose, sulfuric acid was chosen for reasons of volume efficiency. It was found that, on a small scale and using this acid and EtOAc as organic solvent, phase separation was possible and, through repeated extractions of the aqueous layer with EtOAc, a good yield of the acid **1** was obtained. A solvent screen for washing of the crystalline **1** revealed that CH_3CN efficiently removed all discoloration and furnished the final pure acid **1** in good recovery.

Continuous Manufacturing Process. It was time to set up a continuous manufacturing process built on the experiences gained in the small scale batch optimization. Also, process parameters such as reaction temperature needed to be investigated under authentic conditions in order to obtain an efficient process with minimized residence times for each step. For this purpose, a Vaportec instrument was used equipped with three peristaltic pumps which can deliver a flow up to 10 mL/min. The reaction is conducted in tubular PFA reactors in variable sizes up to 10 mL. Since we already had shown that FT-IR could be used for monitoring of the azidoacetate generation, we planned to connect an FT-IR flow cell for real time monitoring of the reaction. This would enable us to quickly optimize the reaction steps in real time and to supervise the manufacturing process to have control of the hazardous azides. To be able to supply the project with multihundred grams of compound **1** within a reasonable time frame, we aimed for a continuous process with a throughput of approximately 50 g of **1**/hour which meant that the residence time for each of the steps should be within the minute range. Using a small flow setup for the azidoacetate generation and by connecting an FT-IR flow cell in-line, we were able to quickly optimize the conditions for the azidoacetate generation in real time (Figure 4).

Thus, we found that, at 40 s residence time, the optimal reaction temperature was 120 °C. Using the same optimization approach for the subsequent cycloaddition step by monitoring the consumption of the intermediate azidoacetate **7** by FT-IR, we found that at 150 s residence time the optimal temperature for the cycloaddition reaction is ~80 °C (Figure 5). Higher reaction temperatures resulted in lower conversions probably due to the low boiling point of the alkyne **3** and should therefore be avoided.

With the optimized conditions established for the synthesis of **1**, we were ready to set up the manufacturing process equipment and evaluate the performance (Figure 6).

Thus, a 5 mL PFA coil at 120 °C was selected for the azidoacetate generation with a total flow of 6 mL/min resulting in a residence time of 50 s. The Na-azide solution was pumped at 3 mL/min as a 1.5 M solution in water whereas the

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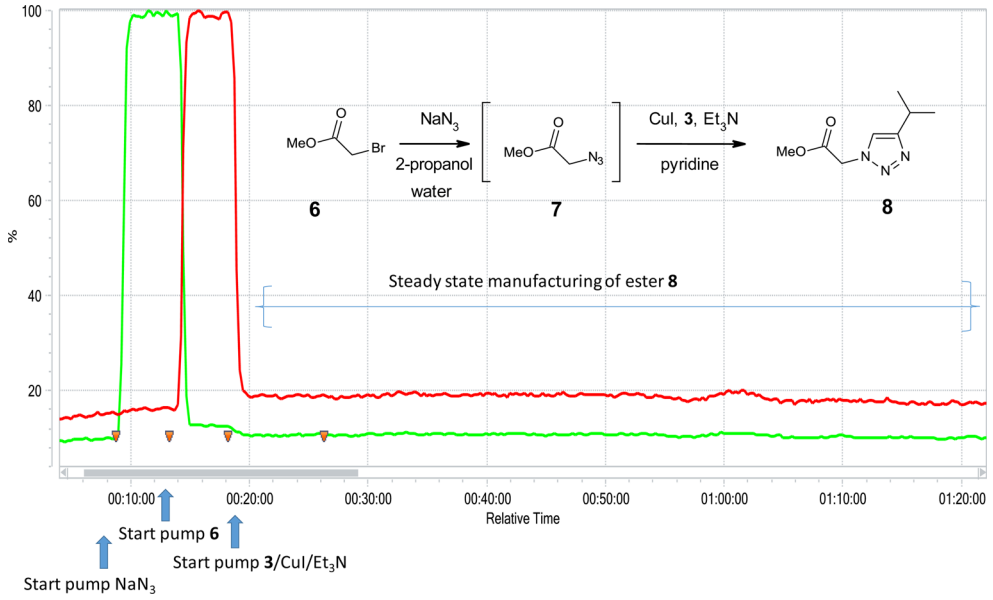

Figure 7. FT-IR monitoring of the consumption of Na-azide and azidoacetate **7** in the manufacturing of acid **1**. Green line = Na-azide (2050 cm^{-1}), red line = azidoacetate **7** (2112 cm^{-1}).

bromoacetate **6** was pumped at 3 mL/min as a 1.6 M solution in 2-propanol. We found that using a slight excess of the bromide did not have a negative effect on the outcome and we minimized the risk of having unreacted Na-azide in the workup mixture. The output stream of the intermediate azidoacetate was precooled in a 0.5 mL PFA coil set at 20 °C (reaction temperature ~60 °C) before it was mixed in a T-piece with a 3 M freshly prepared solution of the alkyne (1.3 equiv), CuI (0.075 M, 3 mol %), and Et_3N (0.75 M, 30 mol %) in pyridine pumped at a rate of 2 mL/min.[20] With a residence time of 150 s, the cycloaddition reaction was performed at 80 °C in 2 PFA coils coupled in series (V_{tot} = 20 mL). The resulting reaction mixture containing ester **8** was cooled in a 2 mL PFA coil set at 20 °C (reaction temperature 45 °C) before it entered the FT-IR flow cell. This made it possible to monitor the manufacturing process in real time (Figure 7).

Finally, the mixture was passed through a back pressure regulator (BPR) operating at 75 PSI followed by collecting the reaction stream in a batch reactor containing 3.8 M NaOH (1.8 L) and EDTA (tetrasodium salt, 0.38 M). The crude mixture of the resulting carboxylate of the acid **1** was protonated/extracted in a separate batch step, and any possible trace of residual Na-azide was destroyed by adding $NaNO_2$ prior to acidification with H_2SO_4. After extractions with EtOAc, concentration, and washing of the crude acid **1** with CH_3CN, the desired carboxylic acid **1** was obtained as a colorless solid (770 g, 20 h continuous manufacturing) in 86% overall yield based on Na-azide.[21] No blockage occurred during the 20 h manufacturing process, and apart from the necessity to replace an adjustable noncompatible BPR to a chemically resistant static one, no interruptions were necessary. During the manufacturing, real time FT-IR measurements showed that the consumption of the Na-azide and the intermediate azidoacetate **7** was complete and stable over time (Figure 7).

CONCLUSION

A three-step continuous manufacturing process was developed to obtain multihundred grams of 2-(4-isopropyl-1*H*-1,2,3-triazol-1-yl)acetic acid **1** in 86% overall yield. Risks associated with hazardous azides involved were minimized through careful analysis of safety parameters and the inclusion of FT-IR in-line monitoring to ensure consumption of all hazardous azides involved. Furthermore, using in-line FT-IR monitoring allowed us to optimize the reaction steps in real time ensuring rapid and accurate determination of optimal conditions for both the azidoacetate generation and the subsequent cycloaddition reaction.

EXPERIMENTAL SECTION

All materials were purchased from commercial suppliers and used as such without further purification. Continuous flow reactions were performed using a Vaportec instrument (E-series) equipped with three peristaltic pumps. An integrated Mettler Toledo React IR 15 instrument equipped with a SiComp (Silicon) in-line flow cell was used for real time monitoring. PFA coated tubular reactors were used for the continuous reactions. Reaction conversions were determined using ^{1}H NMR analysis of the crude reaction mixtures. Assays were determined by ^{1}H NMR integration using benzyl benzoate as internal standards. NMR measurements were performed using a Bruker Avance III spectrometer.

2-(4-Isopropyl-1*H*-1,2,3-triazol-1-yl)acetic Acid (1). *Continuous Manufacturing over 19.5 h.* Methyl 2-bromoacetate (1.6 M in 2-propanol) was pumped at a rate of 3 mL/min and mixed in a T-piece with sodium azide (1.5 M in soft water) pumped at a rate of 3 mL/min. The mixture was then reacted in a 5 mL reactor at 120 °C followed by cooling in a 0.5 mL coil at 20 °C (reaction temperature ~60 °C). The resulting mixture of intermediate azidoacetate **7** was mixed in a second T-piece with a 3 M solution of alkyne **3**, CuI (0.075 M), and triethylamine (0.75 M) in pyridine, pumped at a rate of 2 mL/min. This was followed by reaction in a 20 mL reactor at 80 °C followed by cooling in a 2 mL reactor set at 20 °C (reaction temperature 45 °C). The resulting mixture of ester **8** was sequentially passed through an in-line FT-IR flow cell followed by a static back pressure regulator (75 PSI). Finally, the output stream was collected under an atmosphere of nitrogen in a batch reactor containing aqueous 20 °C 3.8 M NaOH (1.8 L)

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and EDTA (tetrasodium salt, 0.38 M). After 19.5 h of continuous manufacturing corresponding to 3507 mL of Na-azide solution consumed (5.26 mol), sodium nitrite (36.3 g, 526.05 mmol) and water (1 L) were added and the homogeneous blue solution was heated to 40 °C under a strong flow of nitrogen and with no external cooling of a condenser. A scrubber containing 1 M NaOH was connected, and a pH-probe was installed. The mixture was then slowly acidified through slow addition (2.5 h) of concentrated H_2SO_4 (~2.1 L). When pH reached ~7, some minor gas evolution was observed. At pH = 5.6, ethyl acetate (7.5 L) was added. When pH 2 had been attained, agitation was stopped and the layers were separated. Some precipitation occurred of presumed copper salts, but it was still possible to separate the layers. The aqueous layer was extracted with EtOAc (2 × 5 L + 1 × 2.5 L) after which at most only traces of product remained in the aqueous layer (checked by ^{1}H NMR). The combined brownish organic layer was washed with brine (3 L + 1 L) to give a clear organic brown phase. The organic layer was concentrated under reduced pressure to give the crude acid **1** as a brown solid (955 g, 88% w/w, 94% from Na-azide). The crude compound was suspended in acetonitrile (2.5 L) followed by concentration to remove traces of residual water. Acetonitrile (2.5 L) was again added followed by heating to 60 °C. The brown suspension was stirred at 60 °C for 1 h followed by slow cooling to 16 °C overnight. The mixture was then filtered, and the solid collected was washed with ice-cold acetonitrile (1.5 L). This was followed by drying under reduced pressure at 44 °C for 20 h to give **1** as a colorless solid (770 g, 100% w/w, 86% yield based on Na-azide). Mp 176−178 °C, ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 1.23 (d, J = 6.9 Hz, 6H); 2.97 (hept., J = 6.9 Hz, 1H); 5.20 (s, 2H); 7.80−7.82 (m, 1H); 13.35 (s, br, 1H). ^{13}C NMR (100.6 MHz, C_2D_6SO) δ 22.5 (2 Cs), 25.3, 50.5, 121.9, 153.1, 168.8. HRMS: $[M + H]^+$ m/z calcd for $C_7H_{12}N_3O_2$ 170.0929, found 170.0925.

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Notes

The authors declare no competing financial interest.

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(13) Sonication was applied to facilitate the dissolution of the CuI.

(14) Higher concentrations of the alkyne **3** resulted in precipitation of CuI, and a two-phase inhomogenous mixture was obtained.

(15) Starting from 2-bromoacetic acid instead of **6** was also considered as an alternative, but due to the high risk of generating hydrazoic acid or the need for an external base which might give rise to solubility problems, this approach was abandonned.

(16) By adding $NaNO_2$ to the hydrolysis mixture followed by slow acidification, any residual trace of Na-azide is destroyed. A scrubber containing NaOH and the application of a strong nitrogen flow in the workup further reduces the risks associated with hydrazoic acid.

(17) Presumably, the preciptate was due to insoluble copper hydroxides.

(18) By adding Et_3N in excess to affect hydrolysis we were able to obtain a homogeneous solution. However, the reaction was deemed too slow to be practical in a continuous process.

(19) EDTA was added both to obtain a homogeneous solution which resulted in a more easily operational process and to make a complex with the copper salts and thereby minimize risks of formation of hazardous copper azides.

(20) Although an excess of alkyne **3** is undesirable in the workup reaction mixture, most of the excess of this was removed during the nitrogen purging in the receiver batch reactor. It is advised for further scale-up to optimize the conditions so that as little excess as possible of alkyne **3** is used.

(21) For future manufacturing of **1**, further optimization is recommended for the workup procedure. Screening of scavengers for copper salt is advised to facilitate the extraction procedure.

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