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TECHNICAL NOTE

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# Application of PAT Tools for the Safe and Reliable Production of a Dihydro-1*H*-imidazole

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Supporting Information

**ABSTRACT:** The application of two Process Analytical Technology (PAT) tools was studied and implemented for the safe and reliable synthesis of an advanced intermediate (**4*S*,5*R*-7**) of a member of the dihydro-1*H*-imidazole (**1**) class of compounds. Real time data were generated using ReactIR to track the complete breakdown of phosgene precursors (**2**) to phosgene (**3**) and confirm the absence of these hazardous materials prior to batch transfer operations. In addition, the chiral resolution by crystallization of ***rac*** **7** was monitored by a Lasentec FBRM probe-based system. Implementation of the latter helped to track the crystallization process to minimize the risk of cocrystallization of undesired isomer **4*R*,5*S*-7**.

## 1. INTRODUCTION

p53 is a tumor suppressor, which plays a key role in the regulation of the cell cycle. It has been found that the overproduction of the oncoprotein MDM2 in many tumors leads to the disablement of p53 activity. Therefore, the inhibition of MDM2 has been proposed as a novel strategy for cancer therapy.[1] Several classes of MDM2 small molecule inhibitors have been reported, including dihydro-1*H*-imidazoles **1** (Scheme 1).[2]

A representative member of this class of compounds is dihydro-1*H*-imidazole **8**, which can be synthesized from dihydro-1*H*-imidazole **4** as shown in Scheme 2. In the original procedure, bis-trichloromethyl carbonate (triphosgene) (**2a**) was treated with a catalytic amount of 2,6-lutidine in dichloromethane at <0 °C to produce carbonyl dichloride (phosgene) (**3**). To the resulting phosgene (**3**) solution was then added compound **4**, followed by excess *N*,*N*-diisopropylethylamine (DIPEA) to form intermediate **5** *in situ*. To this solution was then added 1-(3-methanesulfonyl-propyl)-piperazine dihydrochloride **6**, and the mixture was stirred at 25 °C overnight to provide the desired product as a mixture of isomers (***rac*** **8**). The mixture was then quenched with water and carried through an extractive workup. Resolution of the product isomers was achieved by crystallization of the desired isomer as the (1*R*)-(−)-10-camphorsulfonic acid salt **4*S*,5*R*-7** from methanol in an overall yield of 38−41% and >98% purity by chiral HPLC. Treatment of this salt with base provides dihyrdo-1*H*-imidazole **8**.

In order to accomplish the safe and reliable multikilogram scale production of **8**, two main areas needed to be addressed in the synthesis of key intermediate **4*S*,5*R*-7**. One of these is the implementation of the appropriate tool to monitor phosgene (**3**) levels during the synthesis of intermediate **5**. Also of importance was the development of a method to monitor the resolution of isomers by crystallization to ensure the isolation of product **4*S*,5*R*-7** in the desired chiral purity and yield.

## 2. DISCUSSION

Various analytical methods have been reported for the detection of phosgene (**3**). However, infrared spectroscopy has been identified to be particularly suitable, due to this compound's strong absorption bands at 849 and 1827 $cm^{-1}$. In addition, advances in the application of FTIR have made it possible to apply this technique as a real time monitoring tool.[3,4] For these reasons, we opted to use a Mettler-Toledo iC10 process mid-infrared analyzer with a 2 m AgX fiber optic probe (diamond window) for our laboratory work. Although 2,6-lutidine is a suitable catalyst to initiate the breakdown of phosgene precursors (**2**), for an optimized synthesis of carbonyl chloride **5** we envisioned using HCl salt **4** as the catalyst for the reaction of **2** to phosgene (**3**). The implementation of this approach would allow the controlled generation of **3** in the presence of a scavenger (**4**), which could be activated by the addition of DIPEA and lead to the controlled formation of intermediate **5**. The proposed mechanism for the breakdown of phosgene precursors **2a** and **2b** by chloride ions is shown in Scheme 3.[3b]

We began our studies by identifying a fingerprint region for triphosgene (**2a**), diphosgene (**2b**), phosgene (**3**), dihydro-1*H*-imidazole **4**, carbonyl chloride **5**, and product **8**, which could be tracked by ReactIR. Once key wavelengths were selected, a profile for the production of ***rac*** **8** from starting material **4** was generated. Figure 1 shows the changes tracked in the fingerprint regions throughout the synthesis of ***rac*** **8** using triphosgene (**2a**) as the phosgene precursor. This data showed that addition of intermediate **4** to a solution of triphosgene (**2a**) in dichloromethane was successful in initiating the formation of phosgene (**3**). Complete reaction conversion was observed in approximately 3 h. Attempts to track diphosgene (**2b**) during the

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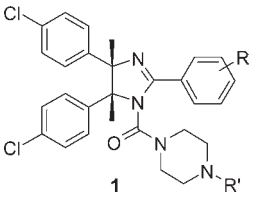
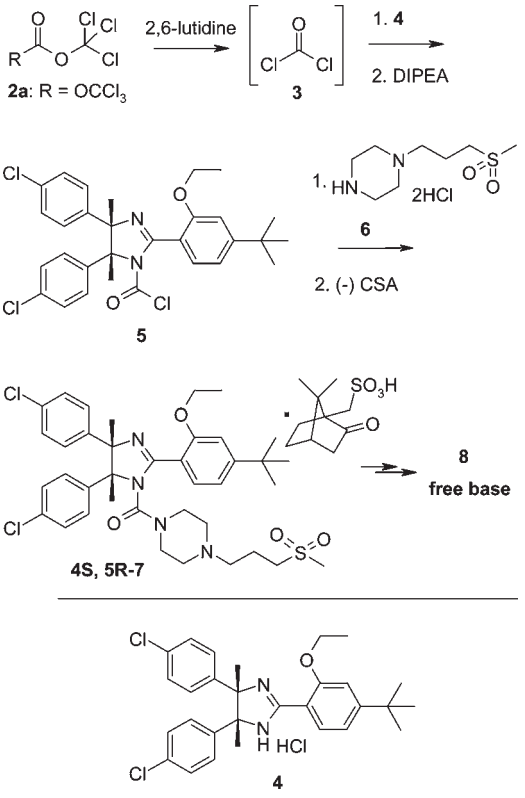
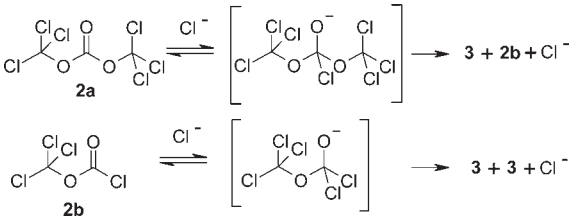
**Scheme 1. Dihydro-1*H*-imidazoles**




**Scheme 2. Synthesis of dihydro-1*H*-imidazole 8**




**Scheme 3. Reaction of precursors 2a,b to phosgene (3)**




breakdown of triphosgene (**2a**) to phosgene (**3**) were unsuccessful, presumably due to the low concentration of this intermediate and possible overlap of the fingerprint regions under these conditions. The mixture containing intermediate **5** was held for 2 h, and piperazine **6** was added to complete the synthesis of *rac* **8**.

Additional information on the phosgene formation process was generated by using diphosgene (**2b**) as the precursor. As shown in Figure 2, the conversion of diphosgene (**2b**) to

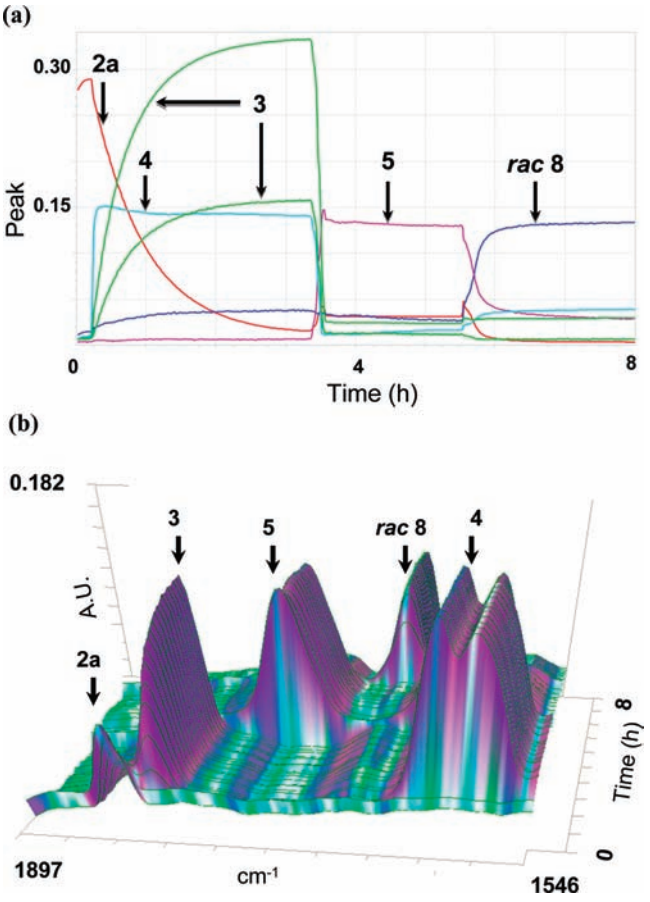



**Figure 1.** (a) Trends recorded for the reaction of triphosgene (**2a**) to phosgene (**3**), the reaction of phosgene (**3**) with intermediate **4**, and the reaction of carbonyl chloride **5** with piperazine **6** over time (h). (b) Surface plot for the reactions.

phosgene provided **3** in quantitative conversion in less than 20 min. As expected, addition of DIPEA to the mixture led to the controlled formation of carbonyl chloride **5**.

From a safety point of view, the option of adding DIPEA as phosgene (**3**) is produced, and the phosgene precursor (**2**) is still present in the mixture, representing an attractive approach to keep the phosgene (**3**) levels low throughout the synthesis of **5**. However, free amines, such as **4**, have been known to react directly with **2** to form carbamic acid *tert*-butyl esters.[3] Figure 3 shows the IR profile of a reaction, where DIPEA was added to a solution of triphosgene (**2a**), phosgene (**3**) and intermediate **4**. As it can be seen in Figure 3, the presence of a new IR stretch in the reaction profile indicated the formation of a new impurity. This impurity was also observed in the synthesis of **5** under similar conditions when diphosgene (**2b**) was used as the precursor. The isolation of this compound proved to be difficult due to its instability.[5d] However, structure **9** was proposed for this impurity based on IR data and literature reports describing the reaction of substituted amines with triphosgene (**2a**) and diphosgene (**2b**).[5] Attempts to convert **9** to product **7** were unsuccessful.[6] Further processing of reaction mixtures containing this byproduct (**9**) led to a reduced overall yield in the synthesis of intermediate **7**; therefore, complete conversion of **2** to phosgene (**3**) was deemed necessary to achieve the expected levels of product **7**.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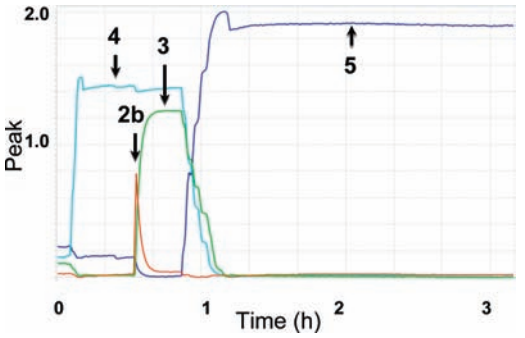


**Figure 2.** Trends recorded over time (h) for the reaction of diphosgene (**2b**) to phosgene (**3**), followed by the reaction of phosgene (**3**) with intermediate **4** upon addition of DIPEA.

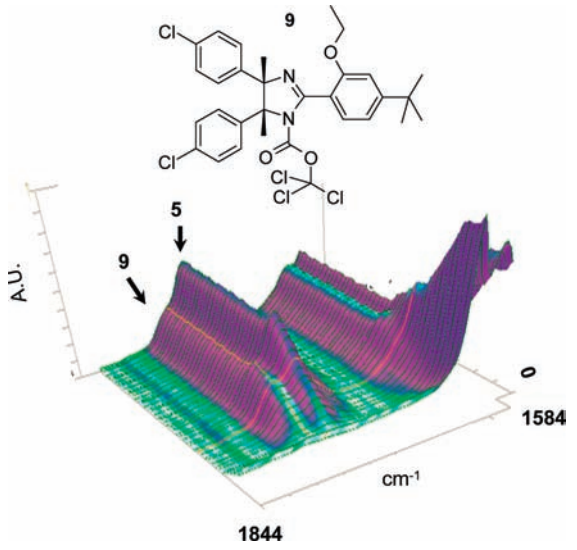


**Figure 3.** Surface plot of the IR profile from a reaction of triphosgene (**2a**) and phosgene (**3**) with intermediate **4** in the presence of DIPEA.

In order to ensure full conversion of **4** to **5** and maximize the yield for product **7**, we opted to use a slight excess of phosgene (**3**) in the process. Due to the hazardous nature of this reagent, it became important to determine the fate of the excess phosgene remaining in the system. An experiment was devised to determine the levels of phosgene (**3**) in the headspace. The data collected showed that no significant amounts of this reagent were lost from the solution.[7] This information combined with the data collected by IR during the synthesis of **5** indicated that any excess phosgene (**3**) remaining in the system was being scavenged under the reaction conditions. Additional experiments were then run to study the reaction of phosgene (**3**) with DIPEA. For this purpose, a solution of phosgene (**3**) in dichloromethane was treated with DIPEA using similar reaction conditions to the ones used in the synthesis of **5**. The resulting product mixture was analyzed by nuclear magnetic resonance (NMR) spectroscopy. Previous studies have reported that in the reaction of tertiary amines with phosgene (**3**) one of the alkyl groups in the amine is transferred and released in the form of an alkyl chloride.[3a] Suspecting that an isopropyl group would be more likely to migrate away from the amine under the reaction conditions, the reaction of *N*-ethylisopropylamine with phosgene (**3**) was

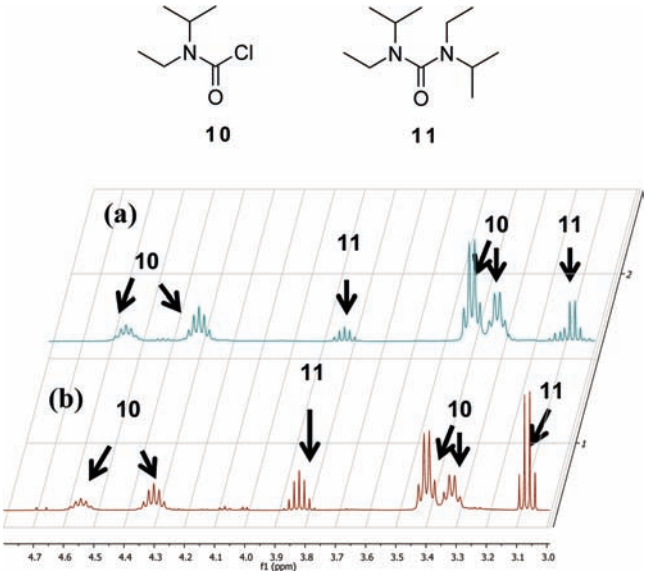


**Figure 4.** (a) Product mixture obtained from the reaction of DIPEA with phosgene (**3**). (b) Product mixture obtained from the reaction of *N*-ethylisopropylamine with phosgene (**3**).

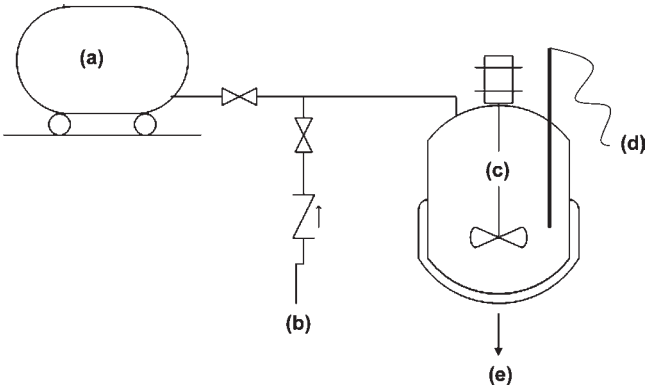


**Figure 5.** Setup for the addition of diphosgene (**2b**) to the reactor. Diphosgene (**2b**) is transferred from a mobile unit (a) to a reactor (c). The line is cleared using low pressure nitrogen (b). Diphosgene (**2b**) and phosgene (**3**) are monitored in real time using IR (d). After complete consumption of phosgene (**3**), the reaction mixture is transferred to a second reactor (e).

investigated in parallel to confirm the identity of the products formed. Analysis of the data collected showed that both reactions generated a similar product mixture, which was composed of amidoyl chloride **10** and urea **11** (Figure 4). These results confirmed that excess DIPEA acts a suitable scavenger for excess phosgene (**3**).[3a,8]

From the data collected up to this point it was concluded that both triphosgene (**2a**) and diphosgene (**2b**) could be used as phosgene precursors for the synthesis of **5**. However, for the first multikilogram production runs, we opted to use diphosgene (**2b**). Diphosgene (**2b**) could be effectively contained and transferred in our plant setting by configuring the equipment as shown in Figure 5.[9]

For large scale runs, real time monitoring of diphosgene (**2b**) and phosgene (**3**) in the reactor (c) was done with a Mettler-Toledo MonARC process mid-infrared analyzer. A 3 m AgX fiber

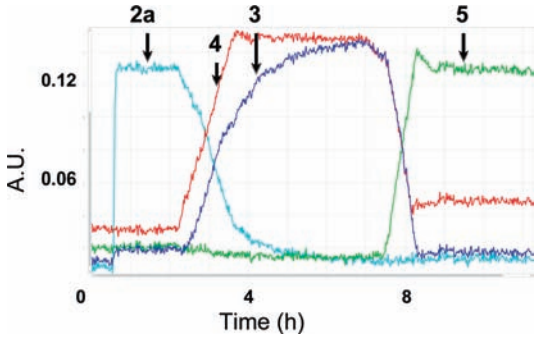


**Figure 6.** Trends recorded over time (h) during a production run for the reaction of triphosgene (**2a**) to phosgene (**3**), followed by the reaction of phosgene (**3**) with intermediate **4**.

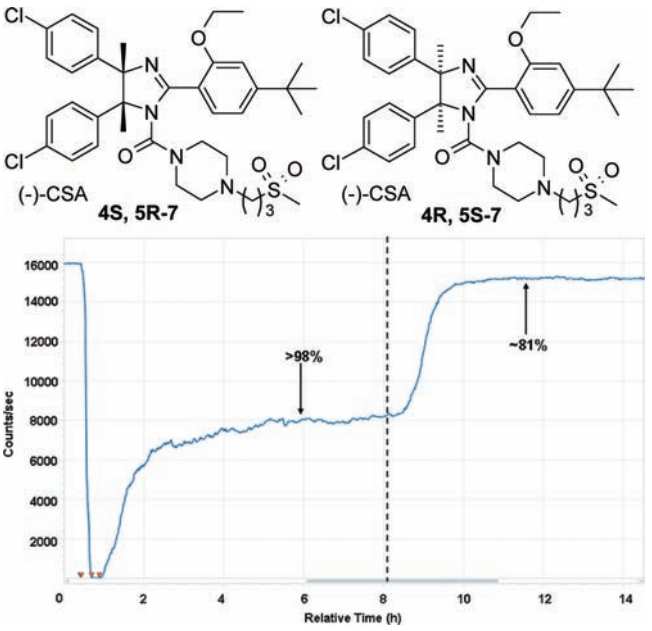


**Figure 7.** Profile of the particle changes tracked (counts/sec, No Wt, 10−50) in the crystallization of product **4*S*,5*R*-7** from a methanol solution over time (0.055 °C/min). Analysis of the solids by chiral HPLC after 10 h showed a decrease in the product purity. Values in % indicate the purity by chiral HPLC.

optic probe with a diamond window was inserted into the reactor via a dip tube fitted to the solids charging port. As it had been observed in the laboratory runs, addition of DIPEA after conversion of diphosgene (**2b**) to phosgene (**3**) initiated the reaction of dihydro-1*H*-imidazole **4** with phosgene (**3**) to generate intermediate **5**. Once a solution of **5** was generated and phosgene (**3**) was no longer detected by IR in the reactor (c), the reaction mixture was transferred to a second reactor (e) containing piperazine **6**, where the reaction of **5** with **6** was completed. Compartmentalization of the reaction from compound **4** to intermediate **5** in a single reactor prevented the accumulation of residual amounts of reagents or solvents used in other operations in the synthesis of **7**. This approach minimized the risk of an uncontrolled generation of phosgene (**3**) gas in subsequent batches, which could be triggered by the incompatible exposure of diphosgene (**2b**) with these solvents and reagents.[10] Despite the successful completion of the first multikilogram campaign of

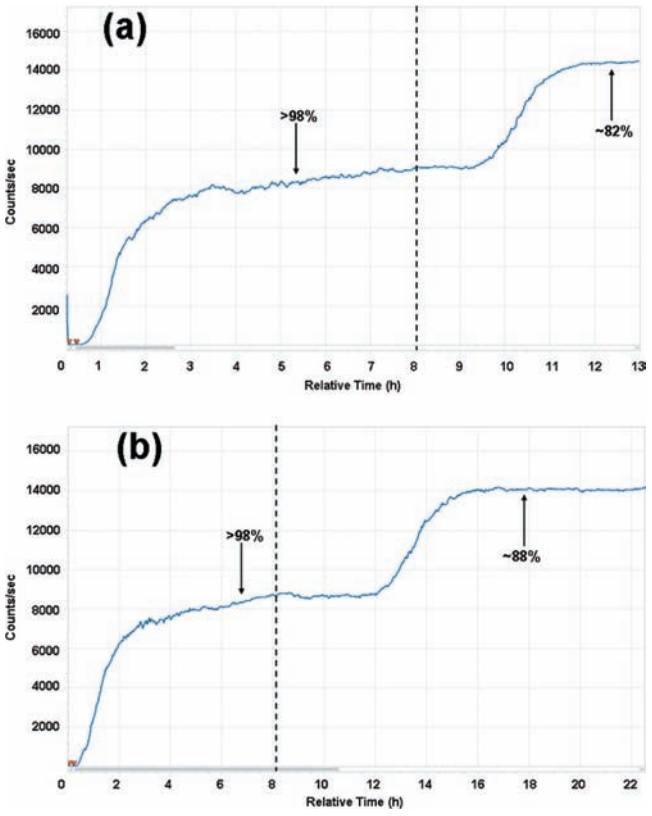


**Figure 8.** Profile of the particle changes tracked (counts/sec, No Wt, 10−50) in the crystallization of product **4*S*,5*R*-7** from a methanol solution over time (0.055 °C/min). (a) Mixture diluted by a factor of 1.13 before crystallization. (b) Mixture diluted by a factor of 1.23 before crystallization. Values in % indicate the purity by chiral HPLC.

**7** using diphosgene (**2b**), the continued use of this reagent was hindered by its low commercial availability and the restrictions associated with the transportation of a liquid phosgene precursor. For this reason, the use of a DoverPac containment unit for solid charges was investigated and ultimately implemented to transfer solid triphosgene (**2a**) to the reactor (c) (Figure 5).[11] Figure 6 shows the ReactIR profile acquired during a production run for the reaction of **4** to **5** using triphosgene (**2a**).

As an optimized process for the synthesis of **5** was being developed, the resolution of the mixture of isomers by crystallization of salt **4*S*,5*R*-7** was also investigated. For this purpose we opted for the use of a Lasentec FBRM model D600VL,[12] which is a probe-based system that allows for the real time tracking of the change of particles in the process. In a standard crystallization procedure, the reaction mixture containing the product isomers in methanol is treated with (1*R*)-(−)-10-camphorsulfonic acid and seeded at 50 °C.[13] A linear ramp of 0.055 °C/min is applied, and the slurry is filtered at 23 °C.[14] Figure 7 shows the trend for particle changes tracked during the crystallization process.

As shown in Figure 7, the rate of crystal growth was fastest in the first 2 h of the cooling process. Once the temperature reached 23 °C and the crystallization appeared to have reached a state of equilibrium, a second nucleation stage was observed. A sample of the slurry was collected after the second nucleation point, and the solids were filtered and analyzed by chiral HPLC. The results showed that this sudden crystal growth was indicative of the crystallization of the undesired isomer **4*R*,5*S*-7** from the


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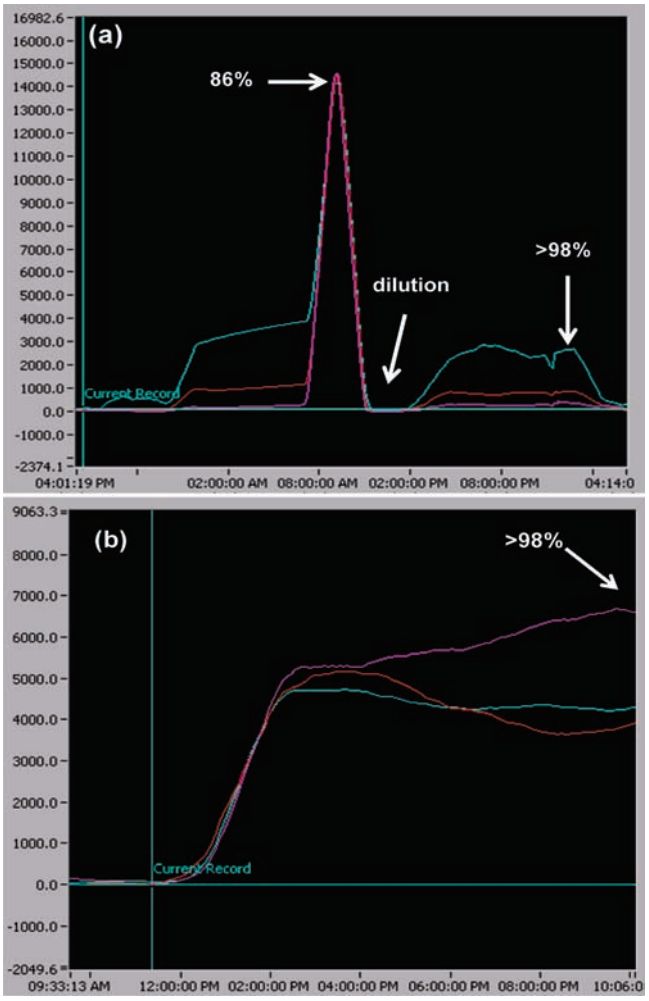


**Figure 9.** Lasentec profiles for the crystallization of product **4*S*,5*R*-7** from methanol over time in a plant setting. (a) Plant profile showing the cocrystallization **4*R*,5*S*-7** and subsequent recrystallization profile to isolate **4*S*,5*R*-7** with the desired chiral purity. (b) Representative crystallization profile of subsequent batches, for which a 10% dilution was implemented.

mixture. The concentration of the reaction mixture containing the product isomers was then varied to study the effect of changes in supersaturation on the rate of crystal growth. The profiles shown in Figure 8 show the particle changes recorded at two different dilution levels over time. As expected, dilution of the process by a factor of 1.13 (Figure 8a) and 1.23 (Figure 8b) led to a time expansion in the overall crystallization profile.

The data in Figure 8 suggested that unexpected delays could result in the crystallization of the undesired isomer **4*R*,5*S*-7**. These data also confirmed that a 10 to 25% dilution of the system would allow for extended holding times, while keeping the reaction yields within the expected range. To monitor the particle changes in the crystallization process in a plant setting we chose a Lasentec FBRM model D600R with an Alloy C22 400 mm probe. For the scale-up of the crystallization process, measures were taken to ensure careful review of the Lasentec profile before proceeding with subsequent operations. Review of the real time data could help to prevent the isolation of **4*S*,5*R*-7** containing high levels of **4*R*,5*S*-7** in the event a second nucleation point was observed. As shown in Figure 9a, implementation of the original crystallization process at multikilogram scale generated a profile showing the cocrystallization of compound **4*R*,5*S*-7**. Once analysis of a sample of the material confirmed the presence of isomer **4*R*,5*S*-7** in the solids of the slurry, the batch was heated to dissolve the material and the solution was diluted by 10% with methanol. The cooling ramp was repeated, and the desired product **4*S*,5*R*-7** was isolated with the expected chiral purity. These results confirmed that dilution of the system allows for extended processing times to achieve the desired product quality. Figure 9b shows a representative Lasentec profile for subsequent batches, for which a 10% dilution was implemented in the crystallization process.

## 3. CONCLUSIONS

The synthesis of dihydro-1*H*-imidazole **5** is a key step in the production of dihydro-1*H*-imidazole **8**. Formation of **5** requires the use of a phosgene precursor (**2**) to generate phosgene (**3**) *in situ*. Key to the safe and reliable formation of **5** was the implementation of IR as a real time monitoring tool to ensure the complete breakdown of the phosgene precursor (**2**) to phosgene (**3**) and confirm the absence of these hazardous materials prior to transfer operations. In addition, particle changes in the crystallization of intermediate **4*S*,5*R*-7** were tracked using a Lasentec FBRM probe-based system. Implementation of the latter helped to understand the overall crystallization process and to identify conditions which could minimize the risk of crystallization of undesired isomer **4*R*,5*S*-7**.

## 4. EXPERIMENTAL SECTION

**4.1. General Methods.** All solvents and reagents were acquired from commercial sources and used without further purification unless otherwise stated.

*4.1.1. Chiral HPLC Analysis.* Chiral HPLC analysis was performed on an Agilent 1200 or equivalent equipped with a UV detector at 254 nm and a Chiralcel OD column (250 mm × 4.6 mm, 10 $\mu$m). Injection volume: 10 $\mu$L. Flow rate: 1.0 mL/min. Isocratic Gradient: 80:20 hexanes/ethanol. Run time: approximately 25 min.

*4.1.2. General Laboratory Reaction Setup for the Synthesis of* ***4S,5R-7***. In a typical procedure, a 1 L half jacketed cylindrical vessel was equipped with a 4-neck PTFE lid, overhead stirrer, thermocouple, and ReactIR probe. The reaction was carried out under an inert atmosphere. Upon completion of the extractive workup, the ReactIR probe was replaced with a Lasentec probe and the vessel was equipped with a jacketed distillation head. Cooling and heating were achieved using a Huber Unistat 340w chiller.

**4.2. Representative Procedure for the Synthesis of [(4*S*,5*R*)-2-(4-*tert*-Butyl-2-ethoxyphenyl)-4,5-bis-(4-chlorophenyl)-4,5-dimethyl-4,5-dihydroimidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone (1*R*)-(−)-10-Camphorsulfonic Acid Salt (4*S*,5*R*-7).** Triphosgene (**2a**) (17 g, 0.057 mol) is dissolved in 204 g of methylene chloride. The temperature is adjusted to −10 °C. A solution of dihydro-1*H*-imidazole **4** (71.0 g, 0.133 mol) in 439 g of methylene chloride is charged to the mixture while keeping the temperature below 0 °C. The reaction is monitored by ReactIR. *N*,*N*-Diisopropylethylamine (DIPEA) (127 g, 0.983 mol) is then added at 13 g/min while maintaining the temperature below 0 °C. The mixture is held for approximately 2 h. The reaction is monitored by ReactIR. To the solution is added 1-(3-methanesulfonylpropyl)-piperazine

dihydrochloride (**6**) (45.0 g, 0.161 mol), the temperature is adjusted to 25 °C, and the mixture is agitated overnight. The reaction mixture is washed twice with 284 g of water and concentrated to an oil. The solution is diluted with 236 g of methanol and concentrated two times to remove residual DIPEA and residual methylene chloride. To the resulting oil is then added 400 g of methanol. The temperature is adjusted to 50 °C, and a solution of (1*R*)-(−)-10-camphorsulfonic acid (34.2 g, 0.147 mol) in 95 g of methanol is added. The mixture is seeded with product **4*S*,5*R*-7** (0.24 g, 0.2 mmol), and a cooling ramp of 0.055 °C/min is initiated with a target temperature of 23 °C. The slurry is filtered and washed with 44 g of methanol. The solids are dried under vacuum at 50 °C for 12 h to give product **4*S*,5*R*-7** as a white solid (48.7 g, 38%) in >98% purity by chiral HPLC.

## ■ ASSOCIATED CONTENT

**Supporting Information.** Key wavelengths for compounds **2**, **3**, **4**, and **5**. Solubility data for compounds **4*S*,5*R*-7** and **4*R*,5*S*-7** as well as LCMS data for decomposition products arising from mixtures containing **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Product **9** was formed in approximately 7% by HPLC. This product decomposes during the workup of the reaction. Data obtained from the analysis of the mixture after workup by LCMS suggest that product **9** decomposes to give primarily the corresponding carbamic acid.

(7) Phosgene (**3**) can be trapped by sweeping the headspace with nitrogen into a midget impinger containing a solution of aniline.[3] Quantification of the urea product can help to determine the amounts of phosgene (**3**) present in the headspace. Analysis of the aniline solution produced in our study showed that no significant amounts of phosgene were present in the headspace of the vessel during the synthesis of intermediate **5**.

(8) For information regarding analysis of carbamoyl chloride conformers by $^1$H NMR, refer to: Koyano, K.; Suzuki, H.; McArthur, C. R. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1872.

(9) Diphosgene is a liquid with a bp of 128 °C and a density of 1.65 g/mL.

(10) Phosgene is a gas with a bp of 8.3 °C and a density of 1.43 g/mL at 0 °C.

(11) DoverPac units are commercially available containment systems provided by ILC Dover.

(12) (a) Wheatcroft, H. Use of PAT in Monitoring and Understanding Crystallization and Polymorphic Transformations. Presented at The 5th International Conference and Exhibition on Process Analytical Technologies (PAT) In Organic Process R&D, Clearwater, FL, 2010. (b) Black, S. N.; Quigley, K.; Parker, A. *Org. Process Res. Dev.* **2006**, *10*, 241.(c) The unit was equipped with a D600L Probe (diameter: 19 mm, length: 400 mm) constructed from Alloy C-276 with Kalrez seals.

(13) The mixtures used for crystallization studies were mixtures produced starting from compound **4**.

(14) Different cooling ramps and filtration temperatures were studied for the crystallization of **7**. A linear cooling ramp of approximately 0.055 to 0.065 °C/min provided the highest product yield and purity.