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Development of a Safe, Scalable Process for the Preparation of an Oxaisoxazolidinone

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Supporting Information

ABSTRACT: This report describes the development and scale up of the synthesis of oxaisoxazolidinone **1**, a significant synthon in the synthesis of the MRSA development compound AZD5847. Studies were carried out to ensure a short-term, risk based preparation of **9** on a 5 L scale with a solid isolation procedure and a safe, long-term manufacturing process for both **1** and **9** through extensive hazards evaluation.

INTRODUCTION

The oxazolidinone antibiotic AZD5847 (**2**), a reprofiled drug of AZD2563, is part of a new class of Gram-positive antibacterial agents targeting bacteria's resistant to Vancomycin and other established antibiotics and is currently in phase IIb clinical trials.[1] Linezolid **3**, a synthetic antibiotic,[2] is the only member of this class available in the market used for the treatment of serious infections caused by Gram-positive bacteria that are resistant to several other antibiotics (Figure 1). Oxaisoxazolidinone **1** was envisaged as a key building block in the synthesis of key intermediate **4**.

Retrosynthetic analysis of oxaisoxazolidinone **1** indicated the possibility of using two different starting materials as shown in Scheme 1.

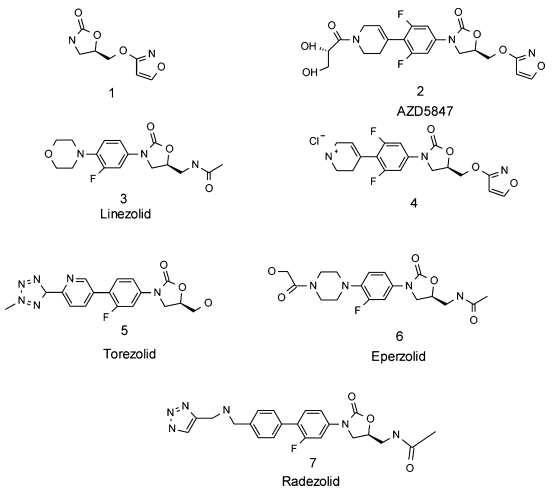
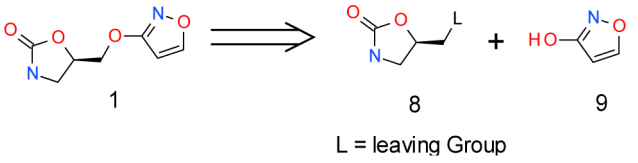


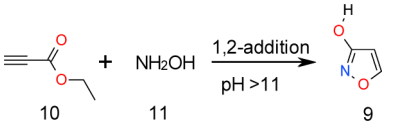
Figure 1. Antibiotics developed for the treatment of serious infections caused by Gram-positive bacteria.

Scheme 1. Retrosynthetic approach for 1



Several reports[3] are available for the preparation of **8** where the leaving group can be hydroxyl (**8a**), mesyl (**8b**), or tosyl (**8c**). All the literature reported methods for the synthesis of 3-hydroxyisoxazole **9** involve the use of hydroxylamine free base (Scheme 2) and the isolation of the solid product **9**.[4] The

Scheme 2. Synthesis of 3-hydroxyisoxazole



known potential operational hazard associated with the handling of hydroxylamine free base prompted us to investigate and develop a suitable synthesis for the manufacture of **9**.

Preparation of 3-Hydroxyisoxazole. Whilst many industries use hydroxylamine free-base, utmost precautions are required to facilitate its handling with stringent measures for safe operation, some of which are detailed below:

(a) It is recommended to use glass lined reactors, as aqueous hydroxylamine is not compatible with most of the metals.

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(b) It should be handled in a way that avoids pressure build up.

(c) Low temperature reaction conditions should be preferred wherever possible.

Several incidents involving hydroxylamine free base are reported in the literature.[5] Incidents at Concept Chemicals in Allentown, Pennsylvania, and at Nissin Chemical in Japan illustrate the severity of the hazard. The hazardous nature of hydroxylamine free base prompted us to evaluate, at the earliest opportunity, the kinetics of the reaction as well as the thermal stability of the various mixtures generated in the process.

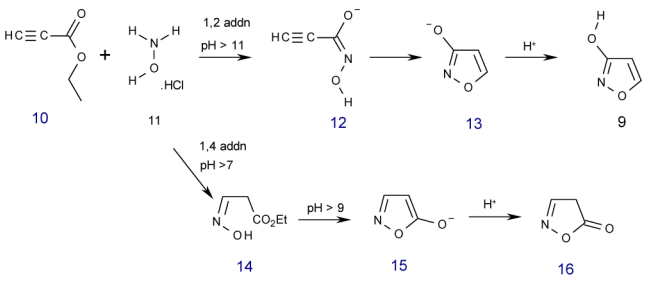
Initial Campaigns—5 L Scale. Further to successful previous scale up of 3-hydroxyisoxazole (**9**) on a 20 L scale, it was deemed that the isolation of **9** as a solid on a plant scale would be unsafe. There were also issues on the scale-up potential of the existing process, as attempts to scale up to 100 L had failed to deliver the desired quality of intermediate **9**.

The medicinal chemistry approach to **9** involved the reaction of ethyl propiolate with hydroxylamine free base (the latter being liberated from hydroxylamine·HCl) in the presence of NaOH in H_2O. In some preliminary work carried out on this reaction, the following observations and changes to the process were made:

(a) pH seems to be critical for the reactions involving hydroxylamine in terms of O, N selectivity.[6] At pH > 11, ethyl propiolate is consumed rapidly to form the intermediate propiolohydroxamic acid **12**. Subsequent cyclization to **9** was slow, and the reaction was heated to 40 °C in order to effect completion.

(b) At pH 7–9, hydroxylamine underwent Michael addition to ethyl propiolate, providing access to intermediate **14** that cyclised to give isoxazolin-5-one **16** (Scheme 3).

Scheme 3. Effect of pH toward Product Formation



(c) Carius Tube test results showed two exotherms when ethyl propiolate was added to hydroxylamine and aqueous sodium hydroxide solution. The first peaked at 148 °C with rapid gas evolution at 99 bar and the second at 192 °C with gas evolution at 138 bar.

(d) It was apparent that the accumulation of ethyl propiolate was problematic in the aqueous system, and therefore, a cosolvent should be employed. Addition of the ethanolic solution of ethyl propiolate to hydroxylamine free base was carried out at 20–25 °C (hydroxylamine degradation occurs slowly at the higher temperature).

(e) A delay time of at least 1 h is introduced prior to heat-up to 50–55 °C.

(f) It was expected that **9** would have to melt (melting point: 98–99 °C when pure) before decomposition, and therefore, low temperature isolation with appropriate dilution was required.

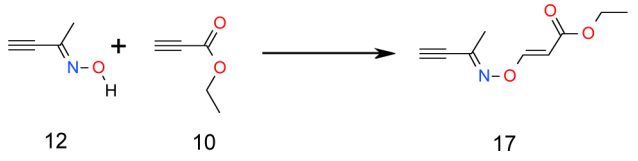
(g) Ethanol and toluene distillations would have to be carried out at a bath temperature not higher than 30 °C under vacuum.

Thus, modification of the original procedure allowed us to operate on a 5 L scale with the restrictions detailed above. A representative procedure can be found in the Experimental Section.

During the course of our early investigations into a suitable isolation method for 3-hydroxyisoxazole (**9**), we noticed that some of the latter coprecipitated with NaCl (formed in the neutralization step) from solution. Over the longer term, it would be advantageous to pursue this observation.

However, ambiguities over the purity of **9** led to further development work in the form of a telescoped synthesis and solution isolation methodology. A thermal stability test carried out on a sample of **9** showed the presence of an endotherm associated with melting from 59 °C, followed by a very large exotherm from 110 °C. It is very difficult to determine the onset temperature when an endotherm runs directly into an exotherm. Further larger scale stability work would have been necessary in order to determine safe operating and drying temperatures. Another potential problem was that the rate of pressure rise was too fast for the standard equipment to record. Additional testing using a modified Carius Tube high rate apparatus did confirm that **9** would not be classifiable as an explosive but the exotherm associated with its decomposition was certainly large and fast enough to cause structural damage if accessed. Later lab experiments aimed toward modification of the process to allow for a solution isolation of 3-hydroxyisoxazole (**9**) with a view to telescoping into the subsequent reaction giving rise to the key intermediate **1**. The addition of caustic gave a high pH solution that is essential for conversion to **9**. However, careful monitoring of the addition of ethyl propiolate in ethanol showed a significant rise in the number of impurities in the reaction concomitant with a fall in pH. The impurities had previously been removed by hot extraction with toluene after acidification and crystallization from cyclohexane. As this was not a viable option for scale up, both the selectivity in the reaction and the choice of extraction solvent needed to be investigated to give a clean solution and good reaction profile/product quality in downstream chemistry. One of the impurities was mainly dimeric in nature (**17**, Scheme 4, resulting from hydroxamic acid intermediately

Scheme 4. Reaction Pathway Leading to Impurity



adding in a conjugate fashion to ethyl propiolate due to a deficiency of hydroxylamine), and its formation was controlled by increasing the equivalents of hydroxylamine hydrochloride to 1.10 from 1.0.

This, coupled with an increase in caustic charge to ensure high pH throughout the reaction, resulted in a significantly cleaner reaction profile. Addition of ethyl propiolate in THF to a preneutralised solution of hydroxylamine hydrochloride also improved the reaction profile significantly, and THF was preferred over ethanol to avoid competition in reactivity in downstream coupling chemistry. A range of extractive solvents such as dichloromethane, chlorobenzene, ethyl acetate, MTBE,

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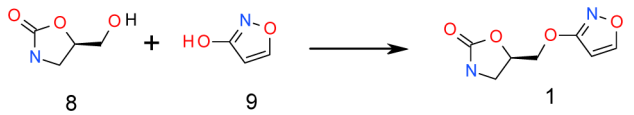
butyl acetate, hot toluene (50 °C), and THF were investigated, and all looked promising. However, only dichloromethane and hot toluene gave product with a good impurity profile coupled with good recovery of 3-hydroxyisoxazole (**9**). As the solubility of **9** was much lower in toluene, the chlorinated solvent was favored. However, attempts to remove the ethanol generated in the process (1.0 equiv) and water from the solution by distillation using dichloromethane proved unsuccessful. Even small quantities of ethanol and water (0.1% w/w) showed a detrimental effect on Mitsunobu or mesylate displacement chemistry required for the production of **1**.

A theoretical exercise was performed with the aim of identifying solvents which may azeotrope ethanol and water from a THF mixture and could therefore be used as potential extractive solvents for the process. *n*-Butyronitrile and chlorobenzene were shown to be suitable for this task. Chlorobenzene had previously been shown to give poorer quality of **9** but was reinvestigated for this purpose. Both solvents were effective in removal of the water and ethanol in model systems. On application to the process, butyronitrile gave excellent quality of **9** in solution. A concentration of **9** in butyronitrile below 18% w/w is acceptable in terms of thermal stability at the temperature required to do a vacuum distillation (60−65 °C). As a result, **9** was isolated as a 8−12% w/w solution in butyronitrile and was always kept at this dilution to avoid potential hazard implications associated with crystallization of this thermally unstable compound. The process gave 3-hydroxyisoaxzole (**9**) of consistently high quality and yield (>80%). The process had been successfully operated on a 4 m^3 scale at a pilot plant of a CRO for the production of over 700 kg of **9** based on the 200G process provided in the Experimental Section.

Preparation of Oxaisoxazolidinone. Our initial attempts to prepare the oxaisoxazolidinone **1** from **9** and hydroxy oxazolidinone **8a** under Mitsunobu conditions (Scheme 5) were promising. However, removal of waste generated from these reactions posed a challenge. Column chromatography was unavoidable and was not a viable option for scale up.

Scheme 5. Mitsunobu Approach toward the Preparation of 1



8 9 1

Initial samples of **1** isolated from column chromatography were submitted for safety studies. DSC indicated exothermicity of −1388 J/g detected from 204 °C (Figure 2) with an endotherm (presumably melting) at 75 °C. This value of energy of decomposition is well above the UN criteria of −800 J/g, indicating potential explosive properties of **1**.

In general, a process should be operated at 100 °C below the onset of a DSC exotherm in order to maintain safe operating conditions on a typical plant scale. Otherwise, further stability testing is required. Therefore, in this case, it is advisible to operate the process below 104 °C. We have performed additional safety tests, such as the Fall Hammer test and Carius Tube test to ensure a safe process to **1** is developed and transferred to the plant for further scale up.

The Fall Hammer test is used to measure the sensitivity of solids and liquids to drop-weight impact. The Lutolf method is used, in which ten samples of 60−70 mg each (±15%) were

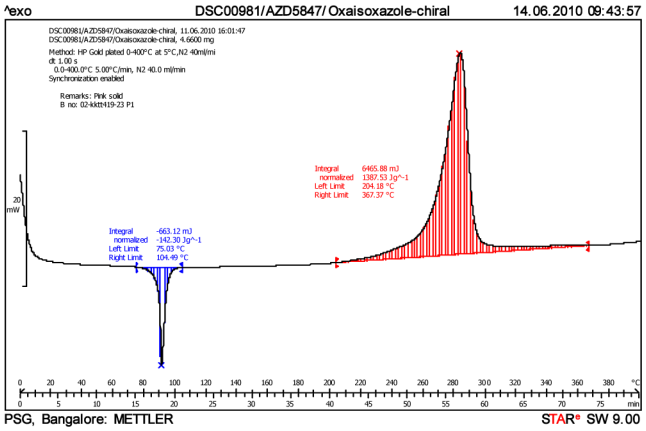


Figure 2. DSC of 1.

placed on circular (diameter = 40 mm) aluminum foil pieces. The samples were then dried for approximately 2 h on the ventilated bench. The aluminum foil pieces were then enclosed and put in the guide ring under the falling hammer. The hammer was dropped from a height of 100 cm. A positive result is recorded if a bang is heard or spark, flame, or smoke is observed immediately following the impact. The result obtained from the Fall Hammer test conducted on **1** was negative (Table 1). So for practical purposes it can be concluded that explosive decomposition of **1** will not be directly initiated by impact or friction.

Table 1. Summary of Fall Hammer

limiting impact energy (J)	results	comments
>49 J	10 negative out of 10 shots	"No reaction" observed. The material is not sensitive to impact, friction.

A thermal stability test (Carius Tube) was carried out on a sample of pure **1**. In the standard test, 3 g of material is charged to a standard Carius Tube (internal volume ∼35 mL), which is fitted with a re-entrant thermocouple. The oven temperature is ramped at 2 °C/min, and potential explosive properties are indicated by very high rates of pressure rise. In general, for a larger scale, UN-approved testing should be carried out if the time taken for the pressure to rise from 200 psig to 400 psig is less than 100 ms. However, the presence of solvent or slow release of gas prior to the onset of the main exothermic event can sometimes slowly raise the pressure to >200 psig; occasionally, this can give misleading results if a conclusion is based solely on a 200−400 psig time criterion. Data that can also be usefully considered are the time taken for the pressure to rise from 300 psig to 500 psig and the maximum pressure rise rate recorded in the test.

High rate Carius testing of compound **1** gave a negative result, indicating that the compound does not possess explosive properties. The time recorded for the pressure rise between the two trigger points of 200−400 psig and 300−500 psig was greater than 100 ms in both the tests.

Having gained confidence on its safe preparation and isolation of **1**, we focused our efforts toward improving the yield and isolation process. We modified our synthetic approach as shown in Scheme 6, as there were scale-up challenges associated with Mitsunobu conditions.

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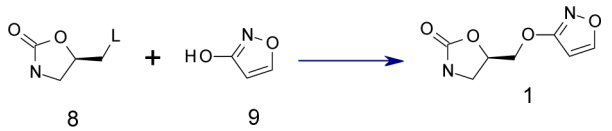
Table 2. Summary of Results from the Carius Tube Test

time from 200 to 400 psig	comments
260 ms	• Not a potential explosive • Time from 300 to 500 psig: 147 ms • Endotherm detected from 60 °C. Exotherm detected from 206 °C • Maximum recorded pressure: 59 barg • Residual pressure data could not be obtained due to test cell rupture
332 ms	• Not a potential explosive • Time from 300 to 500 psig: 204 ms • Endotherm detected from 60 °C. Exotherm detected from 215 °C • Maximum recorded pressure: 63 barg • Residual pressure data could not be obtained due to test cell rupture.

Scheme 6. Approach toward Preparing 1



Butyronitrile was the choice of solvent as **9** was made available in butyronitrile. We started our optimization work using racemic **8b/c** at the beginning. Our initial attempts with Cs_2CO_3 as base were successful, but the product formed gave back hydroxyl oxazolidinone **8a** during aqueous work up. The ether **1** was found to be unstable at pH > 7.5 in the presence of water. Our efforts toward the screening of organic bases such as DBU, TEA, and DIPEA gave some positive indications where **1** was found to be stable during work up. DBU gave complete conversion with both mesyl (**8b**) and tosyl (**8c**) as leaving groups. However, our efforts toward purging out the *p*-toluenesulfonic acid byproduct were not successful, as it needs a base wash and under such basic conditions the product **1** was not stable. Interestingly, using mesyl oxazolidinone (**8b**), the isolation was easy as the methanesulfonic acid formed as a byproduct from the reaction is purged out during aqueous work up and the required product can be easily crystallized out.[7] This was demonstrated on 150 g scale multiple times.

■ CONCLUSIONS

A significant amount of chemical hazard assessment work has been carried out toward making a safe and scalable process for **1**. The modified processes evaluated have been shown to be acceptable from both a product quality and yield standpoint. This paper highlights the need for process development chemists to be aware of the potential hazards that could be associated with their processes and the advantages that can be gained from the early involvement of process safety groups.

■ EXPERIMENTAL DETAILS

Synthesis of 3-Hydroxyisoxazole (9) by Solid Isolation. 10 M aqueous NaOH (288 mL, 2.88 mol, 2.0 equiv) was added to a solution of hydroxylamine hydrochloride (100 g, 1.44 mol, 1.0 equiv) in water (200 mL). Ethyl propiolate (141.2 g, 1.44 mol, 1.0 equiv) in ethanol (300 mL) was then added dropwise over 1.5 h, maintaining the reaction temperature at 20−25 °C. The resulting reaction mixture was stirred for an additional 1 h 45 min at the same temperature and then gradually warmed to 50−55 °C over 1 h. The temperature was maintained at 50 °C for an additional 2.5 h. The mixture was then cooled to ambient temperature and acidified to pH ∼3 with conc HCl (192 mL, 2.3 mol, 1.6 equiv). Solvent ethanol (about 270 mL) was then removed by distillation under reduced pressure and the residue was extracted with warm toluene (600 mL × 3, ca. 55 °C). The organic layer was concentrated to low volume (approx 200 mL) by distilling toluene under reduced pressure, during which time some 3-hydroxyisoxazole (**9**) precipitated from the solution. Cyclohexane (600 mL) was added to the residue, and the resulting suspension was then cooled to room temperature. The precipitated product was then filtered and dried *in vacuo* at ambient temperature to constant weight to provide 64 g of **9** (52% yield).

Preparation of 3-Hydroxyisoxazole (9)—Solution Isolation Method. Aqueous NaOH (10 M, 604 mL, 6.04 mol, 2.1 mol equiv) was added to a solution of hydroxylamine hydrochloride (200 g, 2.88 mol, 1.0 mol equiv) in water (1.0 L) below −3 °C under an inert atmosphere. The resulting mixture was diluted with water (100 mL), and the clear solution was then warmed to 12 °C over 15 min. A solution of ethyl propiolate (254.82 g, 2.6 mol, 0.95 mol equiv) in tetrahydrofuran (THF) (400 mL) was then added at a uniform rate, maintaining the reaction temperature below 15 °C. THF (100 mL) was added, and the resulting solution was warmed to 55 °C. The reaction temperature was further maintained at 55 °C for an additional 3 h. The reaction mixture was then cooled to −5 °C, and concentrated hydrochloric acid (300 mL) was added through a pressure equalized dropping funnel, maintaining the temperature below 3 °C. Water (30 mL) was added through the funnel, and the mixture was warmed to 20 °C. THF (300 mL) and butyronitrile (1.0 L) were then added, and the mixture was agitated for 10 min. The aqueous layer was then separated and washed with butyronitrile (1.0 L). The combined organic layer was washed with 2 M hydrochloric acid (1.3 L). The organic layer was diluted with butyronitrile (2.0 L), and the solution was concentrated by distillation under reduced pressure at 60 °C until the volume is equal to that of the reaction mixture prior to addition of THF/butyronitrile (approx 1.6 L). The moisture content of the solution was 0.05−0.07% w/w, and the strength of the resulting **9** in butyronitrile was about 11.8% (190.1 g of **9** in 1611 g of butyronitirile solution, yield 81%)

Preparation of Oxaisoxazolidinone (1). *Example 1: Preparation of 1 Using Mitsunobu Reaction.* Hydroxy oxazolidinone **8a** (9.5 g, 1.00 equiv) was added to a 500 mL three necked flask. THF (95.0 mL), solution of **9** in butyronitrile (1 equiv, 30.0 mL, 2.7 M solution), and triphenylphosphine (1.37 equiv, 29.4 g) were then added to the flask. The contents were stirred to give a clear solution, and the solution was then cooled to 0 °C. Diisopropyl azodicarboxylate (1.17 eq., 20.2 g) was added to the reaction mixture dropwise at temperature 0−5 °C. On completion of the addition, the mixture was stirred for an additional 2 h at 0 °C and stirred overnight at 22−25 °C. The reaction mixture was concentrated under reduced pressure, and the resulting residue was column chromatographed over 100−200 mesh silica gel using 2% methanol in chloroform to provide **1** (3 g, yield: 20%).

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Example 2: Preparation of ***1*** *Using Racemic Tosyl Oxazolidinone* ***8c***. Racemic (2-oxo-1,3-oxazolidin-5-yl)-methyl-4-methylbenzenesulfonate (**8c**, 1.71 g, 6.3 mmol, racemic), **9** (solid, 643 mg, 1.2 equiv, 7.56 mmol), Cs_2CO_3 (2.46 g, 1.2 equiv, 7.56 mmol), and acetone (20 mL) were charged into a 50 mL round-bottom flask. The reaction mixture was heated to 50 °C for 8 h. On completion of the reaction, the solids were filtered and the filtrate was concentrated under reduced pressure. The resulting residue was column chromatographed over silica gel eluting with $CHCl_3$, MeOH (8:3). The pure fractions obtained were combined and concentrated under reduced pressure to get 350 mg of **1** (yield 30%).

Example 3: Preparation of ***1*** *Using Chiral Mesyl Oxazolidinone* ***8b***. 1,8-Diazabicyclo[5.4.0]undec-7-ene (163.8 g, 1.08 mol, 1.4 equiv) was added to 3-hydroxyisoxazole (**9**, 694.16 g, 11.3% solution in butyronitrile, 922.15 mmol, 1.2 equiv) at 25 °C. Addition was found to be exothermic, and the temperature rose to 38 °C. The resulting mixture was stirred for an additional 10 min, and mesyl oxazolidinone (**8b**, 150 g, 768.46 mmol, 1.0 equiv) was added to the mixture. The reaction mass was then warmed to 70 °C for 18 h. The reaction mass was cooled to room temperature, and butyronitrile (1.95 L) was charged to the above solution followed by water (450 mL). The resulting mass was stirred for 5 min, and then the layers were separated. The organic layer was evaporated to 1 rel vol (approx 150 mL) under reduced pressure. Isopropyl alcohol (600 mL) and heptane (600 mL) were then added, and the mixture was cooled to 0−4 °C for 12−15 h (seeded if necessary). The solids thus obtained were filtered and dried under vacuum to provide 65.6 g of **1** in 46.36% yield.

^{1}H NMR (400 MHz, $CDCl_3$): 8.08 (s, 1H); 5.95 (s, 1H); 5.5 (bs, 1H); 4.96−4.91 (m, 1H); 4.43−4.34 (m, 2H); 3.7−3.70 (m, 1H); 3.49−3.46 (m, 1H).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR and MS of oxaisoxazolidinone (**1**) and 3-hydroxyoxazole (**9**). This material is available free of charge via the Internet at http://pubs.acs.org/.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

MRSA methicillin-resistant *Staphylococcus aureus*
NaOH sodium hydroxide
NaCl sodium chloride
THF tetrahydrofuran
MTBE methyl *tert*-butyl ether
MeCN acetonitrile
DSC differential scanning calorimetry
Cs_2CO_3 caesium carbonate
DBU 1,8-diazabicycloundec-7-ene
TEA triethylamine
DIPEA *N*,*N*-diisopropylethylamine
psig pounds per square inch (gauge)

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