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# Development of a Scalable and Safe Process for the Production of 4-Chloro-2,3-dimethylpyridine-*N*-oxide as a Key Intermediate in the Syntheses of Proton Pump Inhibitors†

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**Abstract:**

**2-(Pyridin-2-ylmethanesulfinyl)-1*H*-benzimidazole-based drugs belong to the most prominent and successfully applied proton pump inhibitors. To fulfill the demand for a flexible and safe procedure for the synthesis of early-stage intermediates which are known to possess a strong exothermal decomposition potential, we have developed a high-yielding telescoped procedure for the synthesis of a key intermediate in the synthesis of these drugs. This strategy turned out to be highly reproducible in laboratory as well as on pilot-plant scale. As the starting material, as well as some of the intermediates, shows a highly exothermal decomposition potential, extensive safety investigations were undertaken. The whole process was adapted in a safe and reliable manner based on the outcome of this systematic approach. Considering these precautions, no safety issues were observed, neither in the laboratory nor in the pilot plant.**

## Introduction

Among modern antiulcer lead structures the 2-(pyridin-2-ylmethanesulfinyl)-1*H*-benzimidazole group turned out to be of special interest as derivatives like omeprazole (**1**), pantoprazole (**2**), lansoprazole (**3**), and rabeprazole (**4**) (Figure 1) were found to be powerful therapeutic agents for treating gastric and duodenal ulcer disease. The antisecretory activity of these compounds has been ascribed to a specific inhibition of the ($H^+$,$K^+$)-ATPase. This gastric acid pump was one of the major medical targets in the development of gastric acid secretion inhibitors since proton transport by the gastric ($H^+$,$K^+$)-ATPase is the final step in acid secretion.[1]

Omeprazole was the first clinically useful compound of this class of proton pump inhibitors (PPIs) and was introduced in 1989[2] followed by pantoprazole,[3] whereas lansoprazole and rabeprazole are the actual compounds of choice, being well-tolerated PPIs which have proven efficacy in healing, symptom relief, and prevention of relapse of peptic ulcers.[4]

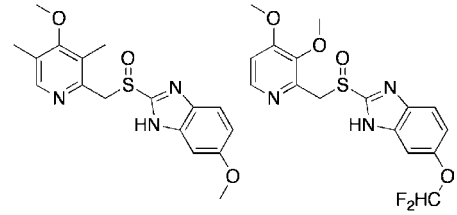


***Figure 1.*** **Structures of the proton pump inhibitors 1−4.**

Several methods for the syntheses of these active pharmaceutical ingredients (APIs) have been reported so far.[5−8] The most common strategy involves the coupling of 2-mercaptobenzimidazole derivatives **A** with the appropriately substituted methylpyridine derivatives **B** followed by oxidation to the corresponding sulfoxides **1**−**4** (Scheme 1).[9] Accordingly, diversity is normally already achieved early on in the sequence. Due to the recent interest in lansoprazole (**3**) and rabeprazole (**4**) and because of the fact that these two compounds differ only in the 4-alkoxy substituent of the pyridine moiety **B**, the main focus of this work was the development of a flexible, safe, and scalable process en route to methylpyridine synthons **B** (lansoprazole synthon **5**: $R^1$ = H, $R^2$ = $CF_3CH_2O$, $R^3$ = Me, X = AcO; rabeprazole synthon **6**: $R^1$ = H, $R^2$ = $MeO(CH_2)_3O$, $R^3$ = Me, X = AcO), giving access to both drugs on an industrial scale.

† Dedicated to Mr. Hiroshi Inoue and Mr. Yutaka Hasegawa.

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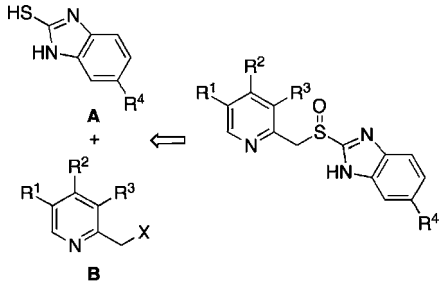
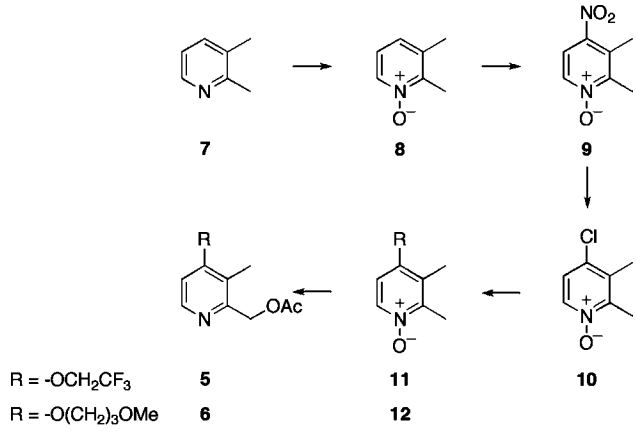
***Scheme 1.*** **Common coupling strategy for the synthesis of 2-(pyridin-2-ylmethanesulfinyl)-1*H*-benzimidazole-based PPIs**



***Scheme 2.*** **Syntheses of the pyridine intermediates 5 and 6 starting from 2,3-lutidine (7)**



## Results and Discussion

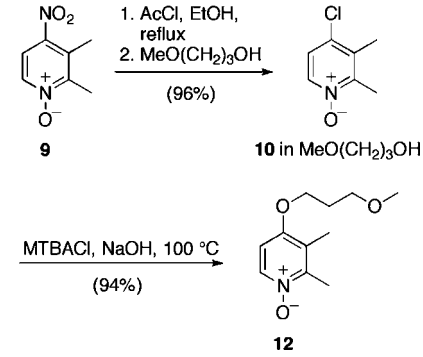
The acetoxymethylpyridine compounds **5** and **6** are typically prepared starting from 2,3-lutidine (**7**) via the following key transformations.[5−8] The first step is oxidation to the corresponding *N*-oxide **8**, followed by nitration giving the 4-nitrolutidine-*N*-oxide **9**. This compound can then be converted to the 4-chlorolutidine-*N*-oxide **10** which is the key intermediate in the synthesis of **1** and **2**. This chloro-compound can then be substituted with either trifluoroethanol or 3-methoxypropanol, giving the lansoprazole synthon **11** or the rabeprazole analogue **12**, respectively. Both *N*-oxides then undergo a *Polonovski*-type rearrangement, forming the targeted acetoxymethylpyridines **5** and **6**, respectively (Scheme 2).

Over the years several reports about optimized reaction conditions, use of different reagents and also modifications of this route have been reported[5−8,10] but in general the sequence itself has mostly been as depicted in Scheme 2 in all these reports.

In contrast to a recent report on the optimization of the final coupling and oxidation towards **1**[9] our investigations focused primarily on the development of a scalable and safe process for the earlier steps in the sequence to obtain the rabeprazole synthon **12** on an industrial scale starting from 4-nitrolutidine-*N*-oxide **9**.

**Development of a Scalable Process for the Conversion of 9 to 12.** Literature procedures for the direct conversion of the nitro-compound **9** to the corresponding alkoxy-pyridines **11** and **12** have been reported[11,12] using phase transfer catalysis

***Scheme 3.*** **Synthesis of the rabeprazole synthon 12 starting from 9 on an industrial scale**



(PTC) to achieve the *ipso*-substitution of the nitro-group by either an alcohol together with a base or the corresponding alkoxide. Although this route would save one step in comparison to the sequence shown in Scheme 3, we decided to go via the chloropyridine **10** instead, as the direct conversion of **9** to **12** requires a rather large excess (4−5 equiv) of the precious alcohol, making this procedure less attractive due to the high raw material consumption. Furthermore, laboratory experiments to reduce the amount of alcohol to an economically interesting level were not fruitful.

Conversion of **9** to **10** can be achieved by several ways. We first opted for a PTC-mediated chlorination with aqueous HCl as the chlorine source and benzyltributylammonium chloride as phase transfer catalyst using acetonitrile as the organic solvent.[10] Unfortunately, this solvent is hydrolyzed to acetamide during the reaction. Therefore methyl *iso*-butyl ketone was tested instead. However, this solvent was halogenated during the reaction, and prolonged reaction times of 24 h were necessary to achieve a reasonable conversion, making this method not feasible for large-scale productions. Accordingly, our main focus was on the development of a one-phase procedure using aqueous HCl to avoid side reactions of the used solvent and to ensure a reasonable conversion rate. During an extensive solvent and additive screening it was found that the presence of $H_2O$ was slowing down the reaction significantly. Therefore, a water-free procedure was necessary to speed up the reaction and enhance the throughput. In principle, the use of gaseous HCl would be a possibility but was not considered for pilot-scale production. The alternative idea was to look for systems that would generate water-free HCl *in situ*. Such a system could be an alcohol together with an electrophilic agent such as acetyl chloride (AcCl) or thionyl chloride. After some optimization we found that adding 2.5 equiv of AcCl as the chlorine source to a mixture of **9** in 7 equiv of ethanol (methanol was less satisfactory) allowed us to achieve a reproducible good conversion (>98%) to the hydrochloride of **10** within 5 h at reflux. Reducing the amount of reagents still gave sufficient conversion but required a significantly longer reaction time. In early laboratory experiments, the workup of the reaction was done via addition of water and distillation of the organic material (EtOH, EtOAc, chlorinated alcohols, etc.), pH neutralization,

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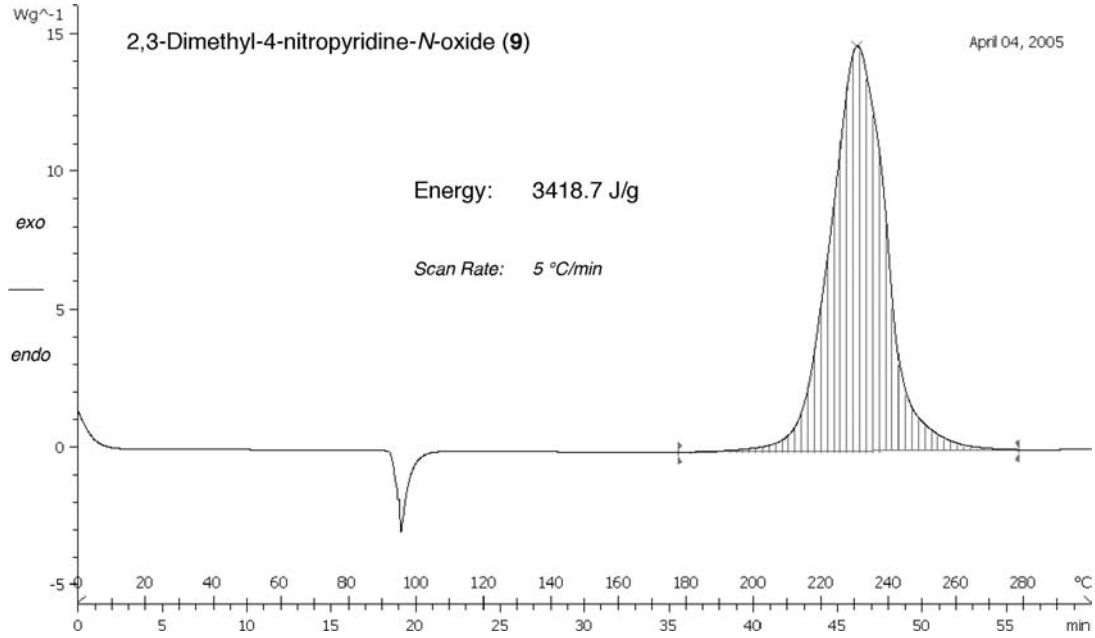


***Figure 2.*** **DSC thermogram of 9 measured in a gold-coated sealed pan.**

extraction with toluene, and crystallization from a toluene/heptane mixture giving **10** in 85%. In order to increase the efficiency and to avoid isolation via crystallization, the process was then changed in such a way that **10** was not isolated as a solid, but directly used as a solution in the alcohol required for the next step. Therefore, 3-methoxy-1-propanol (the required coupling partner for the synthesis of **12**) was added during the solvent exchange, allowing the direct use of this solution in the next step. This procedure was successfully transferred to our pilot plant. Carrying out the synthesis on 30 kg scale **10** was obtained in 96%. Furthermore, the isolated product mixture was successfully telescoped into the next step.

Recently an efficient PTC-mediated process for the conversion of **10** into **12** was reported, affording the alkoxypyridine-*N*-oxide **12** in 85%.[10] On the basis of this result, optimization of the reaction conditions was undertaken especially with respect to the new combined two-step procedure. The phase transfer catalyst of choice for this reaction was methyltributylammonium chloride (MTBACl). The best results were obtained using 2.2 equiv of the 3-methoxy-1-propanol, 50% aqueous NaOH, and 0.1 equiv of MTBACl and stirring the mixture at 100 °C for 8 h. Attempts to reduce the amount of MTBACl or even substituting it for a tertiary amine such as triethylamine resulted in a significantly slower conversion. Due to the high costs of 3-methoxy-1-propanol, attempts to recover the unconverted excess during the workup were undertaken. It turned out that after phase separation and distillation of the organic phase more than 70% of the excess 3-methoxy-1-propanol could be recovered in high quality (>95%w/w). The pure product **12** remained in the sump of this distillation. This procedure was successfully transferred to 30-kg pilot-plant scale, yielding **12** in 94% for this second step (90% combined over both). Fortunately, the combined reaction sequence not only reduced cycle time and operational effort but also resulted in a significantly increased yield compared to the initial procedure. The transformations to access the rabeprazole synthon **6** could easily be achieved by following the methods reported in the literature.[5−8]

Altogether, we have developed a straightforward and telescoped procedure for the conversion of the nitro-compound **9** to the rabeprazole synthon **12** (Scheme 3) which turned out to be highly reproducible in laboratory as well as on 30-kg scale. As it was possible to avoid crystallizations and carry out isolation and purification by extractions mainly, the cycle times were significantly reduced, and the combined yield of 90% was more than satisfactory.

**Safety Investigations.** Most safety investigations were undertaken in our in-house safety laboratory. Stability measurements of **10** and its hydrochloride were made by the Swiss Institute for the Promotion of Safety and Security. On the basis of the fact that **9**, **10**, and **12** contain unstable functional groups[13] it was judged necessary to perform a systematic risk assessment of the isolated compounds (especially with respect to storage) and the single operational units (synthesis reactions, decomposition reactions, distillation processes, etc.).[14] Recently, Moehs Iberica S.S. published a report about a runaway reaction in the synthesis of the lansoprazole intermediate **11** resulting in an explosive rupture of the reactor.[11] The safety investigations of compound **9** showed a strong exothermal decomposition of 1797 J/g[15] visible from 240 °C with a narrow and sharp peak. Furthermore, this decomposition is accelerated by potassium carbonate.[11] On the basis of these results and the unstable functional groups, the presence of an autocatalytic decomposition behavior of this nitro-compound was considered probable. Our own differential scanning calorimetry (DSC) data showed

(13) For an overview about unstable functional groups see: Bretherick, L. *Bretherick's Handbook of Reactive Chemical Hazards*, 6th ed.;Urben, P. G., Ed.; Butterworth Heinemann: Oxford, Boston, 1999.
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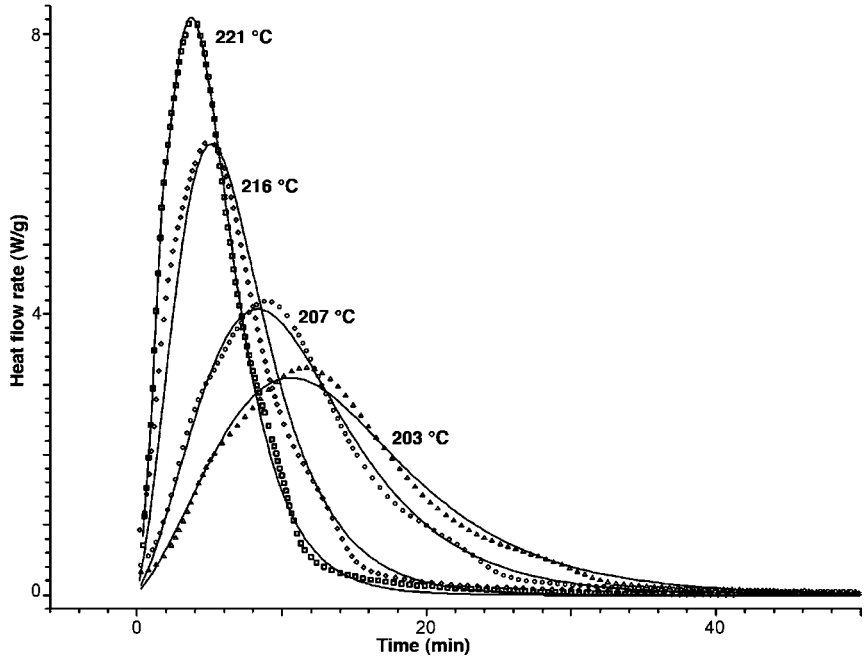


***Figure 3.*** **Isothermal decomposition behavior of 9 between 203 and 221 °C (straight = simulated, dotted = measured).**

an even higher decomposition energy of **9** (3419 J/g, the exothermal decomposition being visible above 180 °C, sharp peak) as depicted in Figure 2.

On the basis of this decomposition energy and an estimated specific heat capacity ($c_p$) of 2 kJ/(kg·K) the adiabatic temperature rise in the case of decomposition is found to be 1710 K. According to the method described by Stoessel,[14] the severity for a runaway reaction has to be classified as high. As **9** would be our starting material for large-scale production which we would intend to store for a longer period, investigations concerning the time to maximum rate at adiabatic conditions ($TMR_{ad}$) were required. We therefore determined the kinetic parameters of the decomposition from measured DSC data in the range of 203−221 °C using the Netzsch software. Once these were known, isothermal measurements at different temperatures (203 to 221 °C) were simulated. Figure 3 shows the resulting plot of the heat flow rate vs time. These simulated curves perfectly match those of the measured values. Accordingly, a $TMR_{ad}$ of approximately 6 years at 40 °C was determined. This means that, although the severity for a runaway reaction has to be classified as high, the probability is very low even for long-term storage resulting in a low overall risk with respect to a thermally initiated decomposition, which would allow us to store the starting material in-house under controlled conditions. The autocatalytic nature of the decomposition could be confirmed by these measurements and simulations, as the peak maxima of the single isothermal curves are shifted towards $t = 0$ with increased temperature.

Autocatalytically decomposing substances with long induction times can be stored safely provided some precautions are taken, for example:

(i)The quality of the product with regard to autocatalytic decomposition is checked regularly. This can be done by, for example, observing the peak position in a temperature-programmed DSC.

(ii)Open drums of the product should be used straight away and their contents not mixed with the same product of other drums.

To ensure a safe handling of the solid starting material **9**, data concerning the dust explosion behavior are mandatory. The minimum ignition energy (MIE) of **9** in a Hartmann tube (MIKE 3 apparatus) for particle size <63 $\mu$m was found to be between 3 and 10 mJ, illustrating a very high ignition probability. Furthermore, during ignition in the MIKE 3 apparatus serious controlled dust explosions were observed. Powders and dust should therefore be handled under inert atmospheres. As the decomposition energy was very high, the impact and friction sensitivity of **9** were determined. However, no explosions were detected with a maximum impact energy of 39 J and a limiting friction load of 360 N. This means that, under standard handling conditions and avoiding extraordinary high mechanical forces, the probability for explosions to occur is very low.

After measuring all data for the isolated starting material **9**, a risk assessment for the conversion to **10** was necessary. Herein, our focus was mainly on a cooling failure scenario.[14] Reaction calorimetry (RC1) experiments confirmed the highly exothermal potential of the conversion of **9** to **10** with a heat of reaction ($Q'_r$) = 250 kJ/$kg_{reaction\ mass}$. This heat of reaction corresponds to an adiabatic temperature rise ($\Delta T_{ad}$) of 96 K (measured $c_p$ = 2.6 kJ/(kg·K)) resulting in a maximum temperature of the synthesis reaction (MTSR) of 161 °C. To classify the criticality of this process, the method by Stoessel was used.[14] Therefore, the $TMR_{ad}$ for the reaction mixture after the end of the synthesis reaction was required. Because of the identical peak shapes, peak maxima, and the temperature of the beginning of the exothermal decomposition, it was decided to determine the $TMR_{ad}$ of the isolated hydrochloride of **10** instead of the $TMR_{ad}$ of the reaction mixture. The hydrochloride of **10** showed a strong exothermal decomposition of 906 J/g becoming visible at 124 °C. The $TMR_{ad}$ was determined using

series of scans with different heating rates and modeling the adiabatic case using the AKTS software. The relevant value with respect to production is always the temperature at which the $TMR_{ad}$ is 24 h ($T_{D24}$) which was calculated to be 88 °C for the hydrochloride of **10**. To judge the criticality the relative positions of four different temperature levels have to be considered: process temperature (65 °C), boiling point of the mixture (73 °C), $T_{D24}$ (88 °C), and MTSR (161 °C). Accordingly, the reaction can be classified as criticality class 4. This means that a runaway is prevented only by the boiling of the solvent, which (and its eventual reflux) must be possible also in the case of a cooling failure.

Due to the high exothermal decomposition potential of **9** the question arose whether the leaving group might form an explosive gas mixture during the reaction. By monitoring a laboratory reaction we found that the maximum gas evolution occurred after 2 h with a gas production of 0.84 L/(min·kg). The resulting gas contained mainly $N_2O$ (19%), NO (31%), and HCl (14%), thus resembling a mixture of HCl and $HNO_x$, known for its high corrosive potential. In addition, the formation of an explosive mixture of organic compounds such as EtOH and EtOAc with NO and $N_2O$ had to be avoided which could be achieved by heavily purging the reaction vessel with $N_2$ all the time. No formation of less volatile nitrogen-containing byproduct was observed.

During the synthesis of the chloro-*N*-oxide **10** several distillations and solvent exchanges are necessary; therefore, the thermal decomposition behaviors as well as the stabilities of the intermediate hydrochloride and the final free base **10** had to be investigated. As described above, the hydrochloride of **10** showed a strong exothermal decomposition of 906 J/g starting at 124 °C, and the $T_{D24}$ was calculated to be 88 °C. To ensure safe distillation conditions, the following maximum temperatures were defined for production: the internal temperature was limited to 75 °C, and the jacket temperature was limited to 100 °C. In addition, the distillation must not take longer than 24 h under these conditions.

The free base **10** showed a strong autocatalytic decomposition of 1378 J/g starting at 202 °C, resulting in a $T_{D24} = 98$ °C. Accordingly, the severity for a runaway reaction has to be classified as high, but the probability of occurrence at process temperature is low, resulting again in a low overall risk for a thermally initiated decomposition. Furthermore, our strategy to isolate **10** as a solution even lowers the risk for a runaway reaction as the heat of decomposition is lowered significantly and the shape of the exothermal peak (DSC) indicates a change in the kinetic parameters towards a less pronounced autocatalytic decomposition.

Further on in the sequence, no serious safety issues requiring extraordinary high precautions were observed. The conversion of **10** to **12** was found to be slightly exothermal with a heat of reaction ($Q'_r$) = 43.3 $kJ/kg_{reaction\ mass}$ (determined by RC1 measurements). Carrying out the same systematic approach as described above, the criticality class for this reaction is 3. The isolated product **12** showed an exothermal decomposition of 585 J/g with a $T_{D24} = 116$ °C.

## Conclusion

Due to the high interest in the PPI razeprazole (**4**), a high-yielding telescoped procedure for the conversion of the nitro-compound **9** to the rabeprazole synthon **12** (Scheme 3) was developed which turned out to be highly reproducible in the laboratory as well as on 30-kg scale. Due to reduction of crystallizations and optimized reaction conditions, cycle time could be significantly reduced and the throughput increased in comparison to those from the standard laboratory procedures.[5−8] As the starting material **9** is known to possess a strong exothermal decomposition potential, extensive safety investigations were made, and the whole process was adapted in a safe and reliable manner. With these precautions, no safety issues were observed either in the laboratory or in the pilot plant. Furthermore, the chloro-compound **10** would also serve as a starting material for the synthesis of the lansoprazole synthon **11** which presents a cost-saving and safe alternative to the single-step procedure described recently.[11]

## Experimental Section

Differential scanning calorimetry was performed using a Mettler DSC-821e differential scanning calorimeter. RC1 experiments were performed in a Mettler RC1 Classic reaction calorimeter. Calculations of $TMR_{ad}$ were done by using either the Netzsch Thermokinetics or the AKTS software. Monitoring of the reaction progress and assay of the final compounds were done by HPLC and comparison to reference substances.[5,10] As potentially unstable compounds are involved, the noted temperatures and distillation times must not be exceeded.

**4-Chloro-2,3-dimethylpyridine-*N*-oxide (10).** Acetyl chloride (30 kg, 382 mol) was slowly (2 h) added to a cooled (4 °C) solution of **9** (25.8 kg, 153.6 mol) in ethanol (65 L) keeping the reaction temperature below 30 °C. After full addition, the mixture was heated to 65 °C and stirred for 5 h. After distillation of the volatiles, water (22 L) and toluene (33 L) were added followed by pH adjustment by adding aqueous NaOH (50%) (12 L) targeting a pH of 7.5−8.5. After phase separation at 70 °C, the aqueous layer was re-extracted with toluene (16 L), and the combined organic layers were evaporated to a residual volume of 50 L. (Caution: Distillation must not take longer than 24 h due to safety reasons!) Water (1.6 L) and toluene (7 L) were added to the distillation sump, and again the volatiles were distilled off followed by the addition of 3-methoxy-1-propanol (32.4 L) which gave a solution of 23.2 kg of **10** (147.5 mol, 96% yield) in a mixture of 3-methoxy-1-propanol and toluene (61 L, 60 kg).

To obtain an analytically pure sample, this solution was evaporated to dryness and crystallized from cyclohexane, giving **10** in 75% as slightly yellowish crystals, mp 103−106 °C. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 8.10 (d, $J = 6.9$ Hz, 1H), 7.18 (d, $J = 6.9$ Hz, 1H), 2.57 (s, 3H), 2.40 (s, 3H).

**4-(3-Methoxypropoxy)-2,3-dimethylpyridine-*N*-oxide (12).** MTBACl (4.86 kg, 75% in water) and aqueous NaOH (50%) (16 L) were added to a solution obtained in step 1 (61 L containing 23.2 kg of **10** (147.5 mol) and 32.4 L of 3-methoxy-1-propanol (338 mol)). The mixture was heated to reflux (100 °C) and stirred for 8 h. $H_2O$ (34 L) was added, and the phases were separated at 80 °C. After distilling off the volatiles, a residue (37.4 kg) containing **12** (29.3 kg, 138.7 mol, 94% yield)

was obtained, being sufficiently pure for further conversion. The distillate obtained was once again distilled to recover unconverted 3-methoxy-1-propanol (13.7 L) which could be resubmitted into step 1.

Complete evaporation to dryness of the distillation residue afforded **12** as a brown oil (>97% potency). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.15 (d, $J$ = 7.4 Hz, 1H), 6.66 (d, $J$ = 7.4 Hz, 1H), 4.12 (t, $J$ = 6.2 Hz, 2H), 3.55 (t, $J$ = 6.2 Hz, 2H), 3.35 (s, 3H), 2.54 (s, 3H), 2.20 (s, 3H), 2.07 (m, 2H).


## Acknowledgment

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