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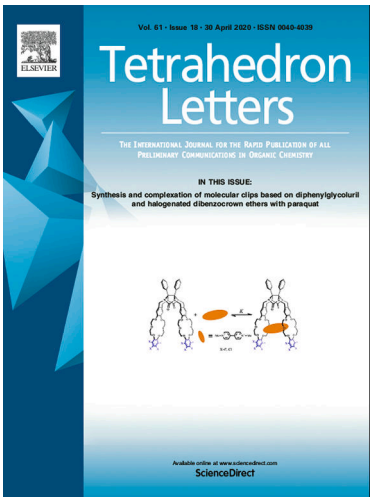

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Synthesis of 4-((1*H*-benzo[*d*]imidazol-2-yl)oxy)-3-methylpicolinic acid，a key related substance of Rabeprazole sodium

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ABSTRACT

4-((1*H*-benzo[*d*]imidazol-2-yl)oxy)-3-methylpicolinic acid (**11**) is a key related substance of Rabeprazole sodium. In this article, this key related substance is synthesized by using 3-methylpicolinonitrile as a starting material via a five-step processes. By converting 3-methylpicolinonitrile to 4-hydroxy-3-methylpicolinonitrile (**13**), the preparation of TM becomes practical. This work provides a guarantee for quality standard establishment of Rabeprazole sodium.

1. Introduction

Rabeprazole sodium, [2-[[4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl-sulfinyl]benzimidazol-1-yl] (Figure **1**), is an effective proton pump inhibitor to treat acid-related diseases. It was discovered by Eisai and commercialized in 1998. Rabeprazole sodium exhibited identical therapeutic effects in duodenal and gastric ulcers as omeprazole according to clinical research, while it performed better in symptom improvements and showed fewer side effects. It is a new and promising proton inhibitor.[1]

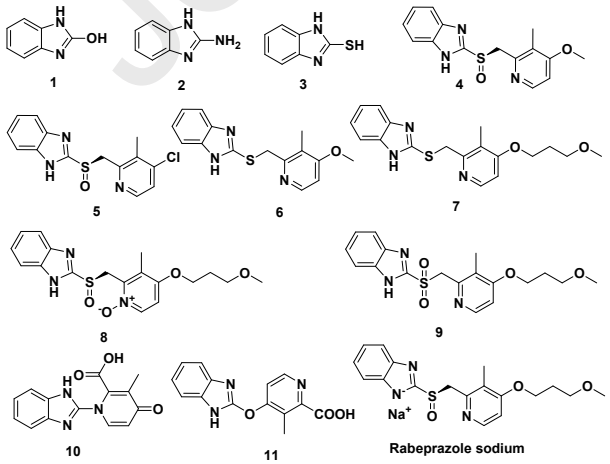


Figure 1 The structure of Rabeprazole sodium and its related substances family.

Several kinds of impurities are produced during the production and preparation processes of Rabeprazole sodium azole active pharmaceutical ingredient (API). Therefore, it is of pivotal importance to study and control the amount of impurities to ensure the efficacy of Rabeprazole sodium. The synthesis of related substances is a very meaningful work in API production.[2] Eleven kinds of impurities (Figure **1**)[3-5] have been reported up to date, including: 1*H*-Benzoimidazol-2-ol (**1**), 1*H*-Benzoimidazol-2-ylamine (**2**), 1*H*- Benzoimidazole-2-thiol (**3**), 2-(4-Methoxy-3-methyl-pyridin-2-ylmethanesulfinyl)-1*H*-benzoimidazole (**4**), 2-(4-Chloro-3-methyl-pyridin-2-ylmethanesulfinyl)-1*H*-benzoimidazole (**5**), 2-(4-Methoxy-3-methyl-pyridin-2-ylmethyl-sulfanyl)-1*H*-benzoimidazole (**6**), 2-[4-(3-Methoxy-propoxy)-3-methyl-pyridin-2-ylmethylsulfanyl]-1*H*-benzoimidazole (**7**), 2-[4-(3-Methoxy-propoxy)-3-methyl-1-oxy-pyridin-2-ylmethanesulfinyl]-1*H*-benzoimidazole (**8**), 2-[4-(3-Methoxy-propoxy)-3-methyl-pyridin-2-ylmethanesulfonyl]-1*H*-benzoimidazole (**9**), 1-(1*H*-Benzoimidazol-2-yl)-3-methyl-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid (**10**) and 4-(1*H*-Benzoimidazol-2-yloxy)-3-methyl-pyridine-2-carboxylic acid (**11**).

Compounds **1**, **2** and **3** are commercially available. Synthesis of **4**, **5** and **6** was reported by Pingili in 2005[4]. Compound **7** is a synthetic intermediate of Rabeprazole. Reddy published the synthetic methods of **8** and **9** recently. [6] The compound **10** can be

obtained according to the synthesis of Omeprazole related substances under the phosphoric acid buffer salt condition.[7] The synthesis of compound **11** has been only reported by He *et al.*,[8] but they employed a tedious synthetic procedure and started from a rare and expensive raw material (Figure **2**).

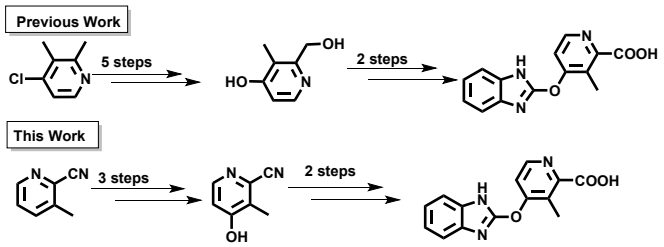


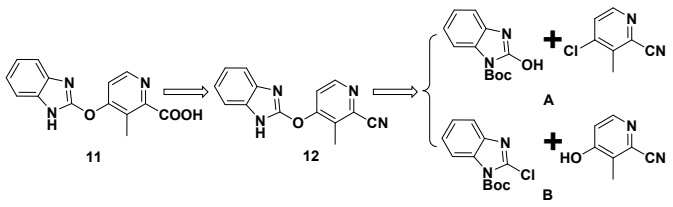
Figure 2 Comparison of current work and previous work.

The production of **11** through a convenient and reliable method is of great value for the establishment of the quality control method of Rabeprazole sodium. In this paper, we will introduce a method of building compound **11** through a 5 steps procedure by using an easily available starting material (Figure **2**).

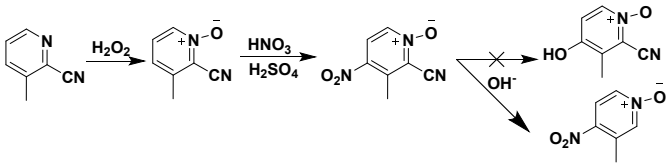
Results and Discussion

There are two strategies to synthesis **11** by breaking the ether bond in the middle of the structure according to retrosynthesis as shown in Scheme **1**. Pathway **A**: 2-hydroxy-benzoimidazole-1-carboxylic acid *tert*-butyl ester reacts with 4-chloro-3-methyl-pyridine-2-carbonitrile through a coupling reaction. Pathway **B**: a coupling reaction between 2-chloro-benzoimidazole-1-carboxylic acid *tert*-butyl ester and 4-hydroxy-3-methyl- pyridine-2-carbonitrile is another possible way. The strategy **A** was abandoned, due to the tautomerism of the double bond of the starting material 2-hydroxy-benzo-imidazole-1-carboxylic acid *tert*-butyl ester, which led to the difficulty in isolation and identification of two possible products.

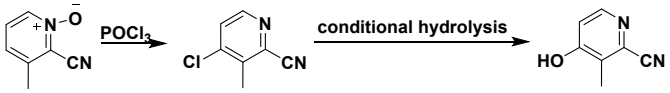
The synthesis of 2-chloro-benzo- imidazole-1-carboxylic acid *tert*-butyl ester, an intermediate in pathway **B**, has been reported in the literatures.[9] While, the synthesis of the other key intermediate, 4-hydroxy-3-methylpicolinonitrile has not been reported so far to the best of our knowledge. Veerareddy *et al.* published a synthesis method of 4-chloro-3-methyl-picolinonitrile (**14**),[10] which involved the usage of the highly toxic reagent trimethylsilyl cyanide and ethyl chloroformate, but the idea of nitration was used as our reference. We adapted the synthetic route and 3-methylpicolinonitrile was tried as a starting material to prepare 4-hydroxy-3-methylpicolinonitrile (Scheme **2**). 3-methyl-picolinonitrile was oxidized by hydrogen peroxide to generate 3-methyl-1-oxy-pyridine-2-carbonitrile, followed by a nitrification reaction to produce 3-methyl-4-nitro-1-oxy-pyridine-2-carbonitrile. Unfortunately, the following hydrolysis reaction under the alkaline condition failed to afford the target compound. A decyanation product, 3-methyl-4-nitro-pyridine 1-oxide, was isolated (Scheme **2**). Reduction of the nitro group to an amino group followed by hydroxylation through a Sandmeyer reaction was also confirmed to be infeasible.



Scheme 1 Retrosynthesis of compound **11**.



Scheme 2 Nitrification route.



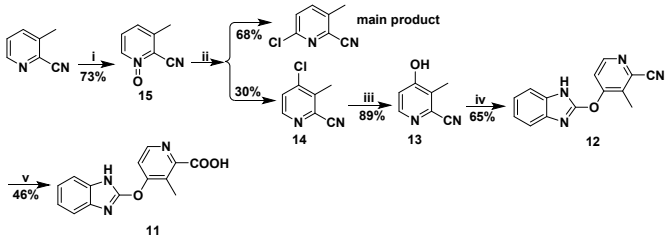
Scheme 3 Synthesis of 4-hydroxy-3-methyl-pyridine-2-carbonitrile.

The chlorination reaction of 3-methylpicolinonitrile by $POCl_3$ affording 6-chloro-3-methyl-picolinonitrile attracted our attention,[11-13] but the production of 4-chloro-3-methyl-picolinonitrile has not been reported. We anticipated that if the conditions were controlled carefully, 4-chloro-3-methyl-picolinonitrile would be obtained under this condition. Therefore, the chlorination of 3-methylpicolinonitrile followed by conditional hydrolyzation synthetic route was adopted to prepared 4-hydroxy-3-methyl-picolinonitrile. In line with our expectations, 3-methyl-1-oxy-pyridine-2-carbonitrile was chlorinated by phosphorus oxychloride at 80 °C resulting in 4-chloro-3-methyl-picolinonitrile in the yield of 30% (Scheme **3**). 68% of the product was 6-chloro-3-methyl-pyridine-2-carbonitrile owning to the steric hinderance of methyl group on position 3.

The identification of these two products was confirmed by ^{1}H-NMR. The chemical shifts of three protons in 3-methyl-pyridine-2-carbonitrile are 7.43 ppm, 7.69 ppm and 8.55 ppm with respects to position 5, 4 and 6 in the pyridine ring (Figure S1). Therefore, the spectrum with chemical shifts 8.45 ppm and 7.53 ppm in the aromatic region was assigned to target product 4-chloro-3-methyl-pyridine-2-carbonitrile (Figure S5). The peaks of hydrogens in the pyridine ring of the side product, 6-chloro-3-methyl-pyridine-2-carbonitrile, appeared on 7.65 ppm and 7.46 ppm (Figure S7).

Hydrolysis of 4-chloro-3-methyl-pyridine-2-carbonitrile was carefully carried out under strict condition to ensure the selectively hydrolyze the chlorine but not cyan group. We optimized the conditions to 3 mol/L sulfuric acid aqueous solution and ethanol to react 48 hours at 85 °C.

Cupric iodide was confirmed to be an effective catalyst for the Ullman coupling reaction of 2-chloro- benzoimidazole-1-carboxylic acid *tert*-butyl ester and 4-hydroxy-3-methylpicolinonitrile. The application of Suzuki reaction conditions (palladium catalyst) failed to afford the desired product. The final step was the selective hydrolysis of the 4-((1*H*-benzo[*d*]imidazol-2-yl)oxy)-3-methylpicolinonitrile, to avoid production of the amide by-product.



Scheme 4 i: H_2O_2, HAc, H_2O, 90 °C, 20 h; **ii**: $POCl_3$, 80 °C, 4 h; **iii**: 3 mol/L H_2SO_4, EtOH, 85 °C, 48 h; **iv**: CuI, K_2CO_3, *tert*-butyl-2-chloro-

1*H*-l
NaOH, EtOH, 80 °C, 4 h.

Conclusions

In summary, a novel method of producing 4-(1*H*-benzoimidazol-2-yloxy)-3-methyl-pyridine-2-carboxylic acid was established in this work (Scheme **4**), applying 3-methyl- pyridine-2-carbonitrile as a starting material and followed by oxidation, chlorination, hydrolyzation, Ullman reaction and hydrolyzation. It provides an economic, environment friendly, and easy-to-operate way to produce the reference compound for the industrial manufacture of Rabeprazole sodium. Through this method, the synthesis of 4-hydroxy-3-methyl-picolinonitrile was reported for the first time.

Acknowledgments

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Supplementary Material

Experimental details and structure identification data can be found in supplementary material in the online version, at http://

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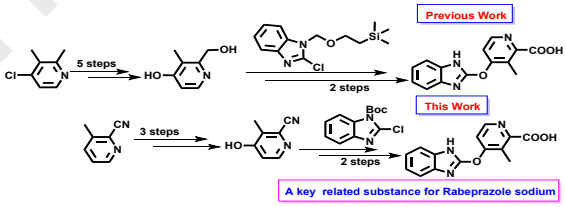

Title compound is important in the process control of Rabeprazole sodium API

The synthetic route of title compound is rarely reported

This method provides an economic, environment friendly, and easy-to-operate way

Synthesis of 4-hydroxy-3-methyl-picolinonitrile was reported for the first time