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SHORT COMMUNICATION

Optimization of the reaction conditions for the synthesis of 2,3,5-trimethylpyridine from 3-amino-2-methylpropenal and methylethylketone

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Abstract: The influence of temperature, reaction time, and type of the catalyst on the yield of the 2,3,5-trimethylpyridine (collidine) from 3-amino-2-methylpropenal and methylethylketone was investigated. 3-Amino-2-methylpropenal was synthesized from 3-ethoxy-2-methylacrolein previously synthesized from methylmalondialdehyde tetraethyl acetal, obtained from triethyl orthoformate and propenyl ether. The optimal conditions for the investigated synthesis were temperature of 150 °C, reaction time 24 h, and the CH_3COOH/pTsOH catalyst. This synthesis is the first successful attempt to synthesize 2,3,5-trimethylpyridine in an acid medium.

Keywords: cyclic condensation; GC–MS; side reactions.

INTRODUCTION

The importance of 2,3,5-trimethylpyridine (collidine) is reflected in the fact that it is the starting compound for the synthesis of esomeprazole which is used to treat symptoms of gastroesophageal reflux disease (GERD, Fig. 1).[1]

The production of 2,3,5-trimethylpyridine can be achieved either from natural products or synthesis. 2,3,5-Trimethylpyridine was isolated at the beginning of the 20th century from the tar of the stone coal,[2,3] and then from shales[4] by the fraction distillation at 186–190 °C with the yield of 7 %.

According to the literature, there are few published works on the synthesis of 2,3,5-trimethylpyridine. They can be divided into two groups: 1) the synthesis in the gaseous phase and 2) the synthesis in the liquid phase (solution).

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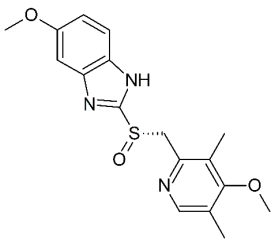


Fig. 1. Structure of esomeprazole.

The synthesis of 2,3,5-trimethylpyridine in the gaseous phase

The synthesis belongs to the condensation reactions of aldehydes and ammonia and can be delivered in homogenous or heterogeneous media.

Homogenous synthesis[5] occurs under high pressure and high temperature with the propionaldehyde, paraformaldehyde, and concentrated ammonia in an autoclave, followed by fraction distillation in a vacuum with the yield up to 14 %.

The heterogeneous synthesis produces 2,3,5-trimethylpyridine from methylethyl acrolein, ethanol, ammonia, and the catalyst (SiO_2, Al_2O_3) at elevated temperature and pressure for a longer time with the yield of up to 28.5 %.[6]

The synthesis of 2,3,5-trimethylpyridine in the liquid phase (solution)

The characteristic of reactions in the solution is that all of them happened in numerous stages, so the overall yield is modest.

Some of the most representative examples are synthesis *via* 3-carbetoxy-2,5--dimethyl-6-hydroxypyridine (the overall yield 8 %),[7] cyclic condensation *via* 3-carbetoxy-2,5-dimethylpyridine (the overall yield 22 %).[8]

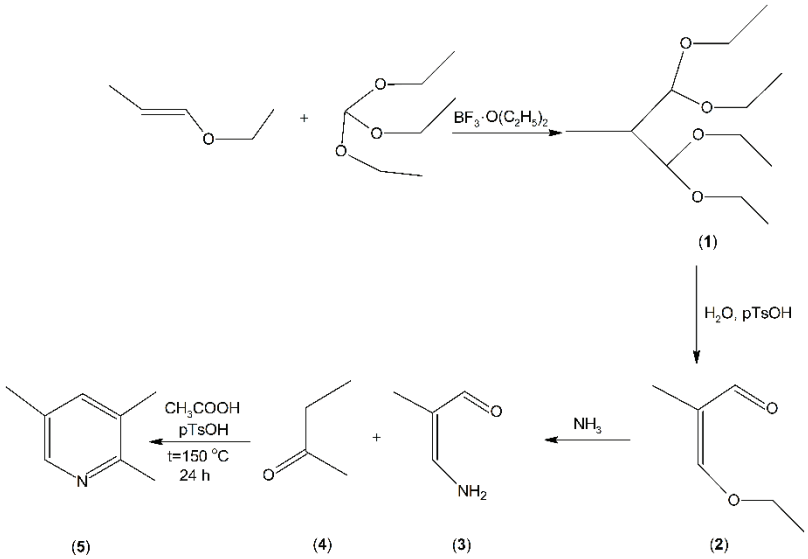
Direct synthesis of collidine from mono-substituted acetylenes and nitriles in the presence of cobaltocene was achieved (yield in this step 45%), and the composition of the reaction mixture was estimated using gas–liquid chromatography (GLC).[9] Srinivas *et al.* reported a synthesis of 2,3,5-trimethylpyridine from 2-butanone, formaldehyde, ammonia and zeolite 5% PbZSM-5 (Si/Al = 15) as a shape selective catalyst with a yield of 43 %.[10] Substituted pyridines syntheses were reported from allylamines and alkynes *via* Cu(II) promoted oxidation and C–H bond activation by Rh (III).[11] Good yield of substituted pyridines was achieved in the reaction of Rh (III)-catalysed decarboxylative coupling of α,β--unsaturated carboxylic acid and α,β-unsaturated *O*-pivaloyl oximes.[12]

Given the low yields or complex conditions for the synthesis and the importance of 2,3,5-trimethyl pyridine, optimization of the reaction conditions for its synthesis from 3-amino-2-methylpropenal and methylethylketone was set for the purpose of this study.

EXPERIMENTAL

*Synthesis of methylmalondialdehyde tetraethyl acetate (**1**)*

In Kolbe's flask with three necks, 13 mL boron trifluoride at 30 °C was added in drops for 1 h to the mixture of triethyl orthoformate and propenyl ether (4 kg, 16.73 mol) in the inert atmosphere in a stream of nitrogen. Then the reaction mixture was stirred for an additional 6 h at 30–40 °C and left overnight. Sodium carbonate (100 g, 0.94 mol) was added to the reaction mixture and stirred for 1 h at room temperature. After that, the mixture was filtered through a sintered glass filter, and the filtrate was distilled in a vacuum.[13] The first fraction (56–110 °C)/30 mmHg was triethyl orthoformate (around 5 kg), which can be used again, and the second was methylmalondialdehyde tetraethyl acetyl as the main product (Scheme 1, **1**) at 118––122 °C/30 mmHg (3.93 kg (83 %), n_D^{20} = 1.4130, where n_D^{20} is a refractive index at 20 °C and a dimensionless number.



Scheme 1. The synthesis of compounds **1**–**5**.

*Synthesis of 3-ethoxy-2-methylacrolein (**2**)*

Methyl malondialdehyde tetraethyl acetal (2.34 kg, 9.99 mol), *p*-toluenesulfonic acid (5.4 g, 0.03 mol), and 180 mL water were mixed at 80 °C until the disappearance of the aqueous phase. Afterward, the reaction mixture was left for 2 h at 80 °C, then to cool down, and finally, with stirring, sodium bicarbonate was added (50 g, 0.6 mol) for 2 h at room temperature. The reaction mixture was filtered, the solid residue was washed with ethanol, and the filtrate and the ethanolic extract were distilled in a vacuum.[13] The first fraction (~115 g) at 34–78 °C/14 mm Hg was ethanol (n_D^t = 1.3788), the second (1.050 kg, 92 %) at 78–81 °C/14 mm Hg was 3-ethoxy-2-methylacrolein (Scheme 1, **2**), n_d^{22} = 1.4738, the maximum absorption in UV (ultraviolet) spectrum is at 242 nm.

*Synthesis of 3-amino-2-methylacrolein (**3**)*

3-Ethoxy-2-methylacrolein (114 g, 1 mol) and 750 mL conc. solution of ammonia (25 %) was emulsified at –10 °C with mixing and cooling using a mixture of ice and sodium chlo-

ride for 6 h. After that, the temperature was allowed to reach 25 °C with constant stirring. The yellow solution was evaporated, using a rotary vacuum evaporator, to dryness and the remaining raw yellow solid was recrystallized from ethanol (100 mL) with the addition of 200–300 mL carbon tetrachloride. The obtained product was filtered and washed with petroleum ether at 30–50 °C and dried in a vacuum desiccator (p = 1.33 kPa) under the influence of phosphorus pentoxide at room temperature.[14] The yield of 3-amino-2-methylacrolein (Scheme 1, **3**) is 0.9 mol (103 g), 90 %, m.p., 113–114 °C, IR.[15]

The total yield of the synthesis of 3-amino-2-methylacrolein was 68 %.

*Synthesis of 2,3,5-trimethylpyridine (**5**)*

The reaction mixture consisted of 3-amino-2-methylacrolein (2.3 g, 0.025 mol), methylethylketone (2.5 g, 0.03 mol), glacial acetic acid (4.4 g, 0.075 mol), *p*-toluenesulfonic acid (0.02 g, 0.09 mmol), was refluxed for 24 h at 150 °C under the inert atmosphere of nitrogen, and then distilled in vacuum (p = 40 kPa). The fraction after 105 °C, yellow oily liquid, in quantity 1.60 g (49 %) represented the raw product, *i.e.*, the mixture of pyridine derivatives. There is 48 % 2,3,5-trimethylpyridine in the mixture separated and identified from the rest of the components by GC–MS, so the total yield of 2,3,5-trimethylpyridine (Scheme 1, **5**) is nearly 24 %, b.p., 187 °C, d_4^{25} = 0.9310, n_d^{25} = 1.5057.

Analysis of the products of the reaction

After distillation in a vacuum, the analysis of the reaction mixture was performed using GC–MS.

Gas chromatography

Instrument: gas chromatograph HP 5890 series II Hewlett Packard; integrator: HP 3396A Hewlett Packard; detector: FID (flame ionization); column: length 2.0 m, Chromosorb: W-HP 80/100; liquid phase: FFAP 10 %, gaseous phase: nitrogen (80 kPa); temperature: 120–220 °C (5 °C min^{-1}); sample: 0.2 μL.

Mass spectrometer was operated in electron-impact (EI) mode. The scan range was 33––651 amu (atomic mass unit), and the ionization energy was 70 eV.

MS spectra of the compounds, with a content higher than 1% in the mixture, are available as the Supplementary material to this paper (Figs. S-1–S-10).

RESULTS AND DISCUSSION

Numerous experiments of the synthesis of 2,3,5-trimethylpyridine from 3--amino-2-methylpropenal and methylethylketone were carried out to optimize the reaction conditions: temperature, reaction time and type of the catalyst. The results are presented in Table I.

TABLE I. Reaction conditions used

Serial No.	Temperature, °C	Reaction time, h	Yield of the 2,3,5-trimethylpyridine in the mixture, %
1	200	12	10
2	230	12	14
3	150	20	39
4	150	24	42.6
5	150	24	48

The synthesis was investigated under the influence of different catalysts: glacial CH_3COOH, resin Lewiatit-80, $CH_3COOH/C_6H_5NO_2$, CH_3COOH/CH_3COONH_4 and in the inert atmosphere in a stream of nitrogen. The best yields were achieved with acetic acid and pTsOH, so other parameters were varied only with this catalyst.

According to the obtained results, the following conditions were optimal: temperature 150 °C, reaction time 24 h, and the catalyst CH_3COOH/pTsOH.

Analysis of the products of the reactions was performed using GC–MS (Table II) because the separation of the products was not possible either with fraction distillation or thin-layer chromatography. The identification of the components of the reaction mixture was performed based on their mass spectra, available as Supplementary material (Figs. S-1–S-10).

TABLE II. Components from the reaction mixture with a percentage of more than 1 %; component area contribution, % = 100×Area of the component/Total area of all components

Component area contribution, %	t_R / min	Compound
1.9	1.354	Lutidine (2,3-dimethylpyridine)
6.3	4.756	3,7-Dimethyl-1,5-diazocine
43.5	6.876	Collidine
2.3	2.321	2-Ethyl-5-methylpyridine
6.8	7.10	Lutidine (3,5-dimethylpyridine)
15.5	7.51	3,5-Dimethylpyridine-2-carbonitrile
1.3	7.948	(5-Methylpyridin-2-yl)acetonitrile
14.88	8.45	(2*E*)-3-{(*Z*)-[(2*Z*)-3-{(*Z*)-[(2*E*)-3-Amino-2--methylprop-2-en-1-ylidene]amino}-2-methyl-prop-2-en-1-ylidene]amino}-2-methylprop-2-enal
2	8.925	Polycondensate
1	9.228	3-Methylfuro[3,4-*b*]pyridine-5,7-dione

Peak with the retention time $t_R = 6.88$ min represents the main product (43.47 %), and it is 2,3,5-trimethylpyridine.

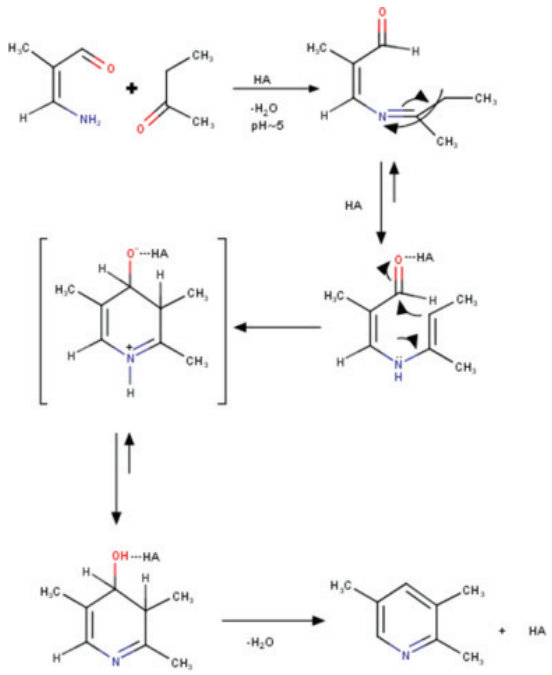
Other peaks of the components in the reaction mixture with more than 1 % represent the side products.

Mechanism of the reaction

The reaction of the cyclic condensation is analogous to the addition in weakly acidic media of carbonyl compounds with H_2N–R derivatives. In case of this condensation, R–NH_2 as a nucleophile can attack the carbonyl compound's conjugated acid, which is in acid media in the form of the enol more stable due to the conjugation effect (Scheme 2).

CONCLUSION

2,3,5-Trimethyl pyridine was synthesized using cyclic condensation under the influence of the acid catalyst in one phase from 3-amino-2-methylpropenal and



Scheme 2. Proposed mechanism of the reaction.

2-butanone. In this synthesis, 2,3,5-trimethyl pyridine was the main component in the mixture with some other pyridine derivatives. The advantage of this method is that it occurs in one phase with approximately the same yield to those of most published syntheses.

SUPPLEMENTARY MATERIAL

Additional data and information are available electronically at the pages of journal website: https://www.shd-pub.org.rs/index.php/JSCS/article/view/11174, or from the corresponding author on request.

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ИЗВОД

ОПТИМИЗАЦИЈА РЕАКЦИОНИХ УСЛОВА СИНТЕЗЕ 2,3,5-ТРИМЕТИЛПИРИДИНА ИЗ 3-АМИНО-2-МЕТИЛПРОПЕНАЛА И МЕТИЛЕТИЛКЕТОНА

ЈОВИЦА УРОШЕВИЋ[1], МИРОСЛАВ МИТИЋ[1], БИЉАНА АРСИЋ[2] и ГОРДАНА СТОЈАНОВИЋ[2]

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Проучаван је утицај температуре, времена реакције и типа катализатора на принос 2,3,5-триметилпиридина (колидина) из 3-амино-2-метилпропенала и метилетилкетона.

3-Амино-2-метилпропенал је синтетисан из 3-етокси-2-метилакролеина претходно синтетисаног из метилмалондиалдехид-тетраетил-ацетала, који је добијен из триетил-ортоформата и пропенил-етра. Нађени оптимални услови за синтезу су били температура од 150 °C, време реакције 24 h, и катализатор CH_3COOH/pTsOH. Ова синтеза је први успешни покушај синтезе 2,3,5-триметилпиридина у киселој средини.

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