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RESEARCH ARTICLE

Condensation of secondary amines with CH-acids and formaldehyde under the influence of microwave radiation

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Abstract

Objectives. *To synthesize tertiary amines containing gem-dichlorocyclopropane or 1,3-dioxolane fragmentusing the Mannich reaction, as well as obtain ethyl ester of β-aminopropionic acidbydecarboxylation of tert-amine, a derivative of diethylmalonate containing a gem-dichlorocyclopropane fragment.*
Methods. *In order to obtain tertiary amines by the Mannich reaction, the microwave activation method was used. To determine the qualitative and quantitative composition of the reaction masses, gas chromatography, electron ionization mass spectrometry, and ^{1}H-, ^{13}C-nuclear magnetic resonance spectrometry methodswere used.*
Results. *Under microwave radiationconditions, tertiary amines containing gem-dichlorocyclopropane or 1,3-dioxolane fragment were synthesized by condensation of secondary amines, CH-acids, and paraformaldehyde.*
Conclusions. *Tertiary amines containing a gem-dichlorocyclopropane or cycloacetal fragment in their structure were obtainedin high yields under microwave radiation.*

Keywords: *secondary amines, CH-acid, microwave radiation*

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НАУЧНАЯ СТАТЬЯ

Конденсация вторичных аминов с СН-кислотами и формальдегидом под действием микроволнового излучения

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Аннотация

Цели. *Синтезировать по реакции Манниха третичные амины, содержащие гем-дихлорциклопропановый или 1,3-диоксолановый фрагмент, а также получить этиловый эфир β-аминопропионовой кислоты декарбоксилированием трет-амина – производного диэтилмалоната, содержащего гем-дихлорциклопропановый фрагмент.*
Методы. *Для получения третичных аминов по реакции Манниха был использован метод микроволновой активации. Для определения качественного и количественного состава реакционных масс были использованы следующие методы анализа: газовая хроматография, масс-спектроскопия с электронной ионизацией, и ^{1}H-, ^{13}C-спектроскопия ядерного магнитного резонанса.*
Результаты. *Третичные амины, содержащие гем-дихлорциклопропановый или 1,3-диоксолановый фрагмент, синтезированы конденсацией вторичных аминов, СН-кислот и параформальдегида в условиях микроволнового излучения.*
Выводы. *С высокими выходами в условиях микроволнового излучения получены третичные амины, содержащие в своем строении гем-дихлорциклопропановый или циклоацетальный фрагмент.*

Ключевые слова: *вторичные амины, СН-кислота, микроволновое излучение*

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INTRODUCTION

Polyfunctional secondary and tertiary amines are widely used in the synthesis of biologically active drugs and drugs [1–3]. In particular, three-component condensation of the corresponding amines with formaldehyde and compounds containing a mobile hydrogen atom has been successfully used to obtain secondary and tertiary amines with carbonyl or ester substituents [4, 5]. For this, as a rule, alkylphenols, dialkylphosphites and 1,3-carbonyl compounds, as well as various other CH-acids, are used [6, 7].

Previously, we have shown that substances containing a *gem*-dichlorocyclopropane or cycloacetal fragment exhibit a wide spectrum of biological activity and their synthesis is of considerable interest [8, 9].

In this connection, we studied the condensation of secondary amines containing a *gem*-dichlorocyclopropane- or cycloacetal fragment with formaldehyde and CH-acids, diethyl malonate and acetoacetic ester.

MATERIALS AND METHODS

After analyzing the reaction masses, the mass spectra of the compounds were recorded using the Chromatec-Crystal 5000M hardware-software complex (*Chromatec*, Russia) against the installed NIST 2020 database (*National Institute of Standards and Technology*, USA). Conditions for gas chromatographic (GC) analysis were as follows: capillary quartz column – 30 m long; analysis time – 20 min; ion source temperature – 260°C; transition line temperature – 300°C; scanning range – 30–300 Da; pressure – 37–43 mTorr; carrier gas – helium; heating rate – 20°C/min. The mass spectra of the compounds were obtained using the electron ionization (EI) method with an ionization potential of 70 eV. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AM-500 spectrometer (*Bruker*, Germany) at operating frequencies of 500 and 125 MHz, respectively; the used solvent was $CDCl_3$. Chemical shifts are given in δ (ppm) scale relative to tetramethylsilane as an internal standard; spin-spin coupling constants (*J*) are given in Hz.

Microwave activation was performed using a Mars 6 system (*CEM Corporation*, USA) with a temperature control system.

Parameters of the installation of microwave radiation (MWR): radiation power 1000 W; reaction mass volume up to 100 mL; with standing pressure up to 100 atm; programming of the temperature from 35°C to 280°C.

Secondary amines **IIIa** and **IIIb** were obtained by a method described elsewhere [10, 11].

Synthesis of *tert*-amines IVa, IVb, Va, Vb

A mixture of 0.15 mol CH-acid, 0.15 mol paraformaldehyde, 1 mol benzene, 0.1 mol secondary amine was stirred under MWR conditions at a temperature of no more than 60°C until complete conversion of the starting amine (2–6 h, control by GC). Following the completion of the reaction, the reaction mixture was cooled to room temperature, washed with water, extracted with methylene chloride, dried over calcium chloride, and evaporated. Target compounds were isolated by vacuum distillation.

Diethyl ({butyl[(2,2-dichloro-1-methyl-cyclopropyl)-methyl]amino}methyl)malonate **IVa**. Colorless viscous liquid. $T_{b.p.}$ = 138–140°C (1 mm Hg). Yield 90%. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.90 (t, 3H, CH_3 *J* = 12.7 Hz), 1.01 (t, 2H, CH_2 *J* = 8 Hz), 1.22 (t, 6H, 2 CH_3 *J* = 6.9 Hz), 1.25 (s, 3H, CH_3), 1.71–1.83 (m, 4H, 2 CH_2), 1.91–1.96 (m, 2H, CH_2), 2.41 (t, 2H, CH_2 *J* = 6.1 Hz), 2.61 (t, 2H, CH_2 *J* = 10.7 Hz), 3.66 (t, 1H, CH *J* = 9.5 Hz), 4.25 (q, 4H, 2 CH_2 *J* = 11.8; 7.4 Hz).^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 14.1 (2 CH_3),14.38 (CH_3), 21.45 (CH_3), 27.66 (CH_2), 29.34 (CH_2), 41.55 (CH), 57.15 (CH_2), 62.25 (2 CH_2), 64.76 (CH_2), 64.99 (CH_2), 66.82 (CH_2), 66.99 (C), 171.01 (C=O).

Mass spectrum *m*/*z*, (I_{rel}, %): (282)/(30), (254/256)/(10/5), (238/240)/(40/20), (186)/(15), (170)/(30), (128)/(60), (109/111/113/)/(50/30/12).

Diethyl ({butyl[(2-(1,3-dioxolan-2-yl)ethyl]amino}-methyl)malonate **IVb**. Colorless viscous liquid. $T_{b.p.}$ = 125–127°C (1 mm Hg). Yield 88%. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.92 (t, 3H, CH_3 *J* = 12.7 Hz), 1.26 (t, 6H, 2 CH_3 *J* = 6.9 Hz), 1.67–1.74 (m, 4H, 2 CH_2), 1.88–1.91 (m, 2H, CH_2), 2.48–2.63 (m, 6H, 3 CH_2), 3.66 (t, 1H, CH *J* = 9.5 Hz), 3.84 (t, 2H, CH_2 *J* = 6.2 Hz), 3.98 (t, 2H, CH_2 *J* = 6.3 Hz), 4.20 (q, 4H, 2 CH_2 *J* = 11.8; 7.4 Hz), 5.01 (d, 1H, CH *J* = 6 Hz). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 13.84 (2CH_3), 14.42 (CH_3), 21.38 (CH_2), 28.22 (CH_2), 32.11 (CH_2), 41.89 (CH), 54.77 (CH_2), 55.29 (CH_2), 56.43 (CH_2), 63.18 (2 CH_2), 66.77 (2 CH_2), 103.27 (CH), 170.66 (C=O).

Mass spectrum *m*/*z*, (I_{rel}, %): (345)/(14), (282)/(40), (238)/(70), (173)/(40), (86)/(30), (129)/(60), (73)/(100).

Ethyl 2-({butyl[(2,2-dichloro-1-methyl-cyclopropyl)-methyl]amino}methyl)-3-oxobutanoate **Va**. Colorless viscous liquid. $T_{b.p.}$ = 131–133°C (1 mm Hg). Yield 85%. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.89 (t, 3H, CH_3 *J* = 12.7 Hz), 0.95 (t, 2H, CH_2 *J* = 10 Hz), 1.22 (t, 3H, CH_3 *J* = 6.0 Hz), 1.44 (t, 3H, CH_3 *J* = 6.3 Hz), 1.69–1.77 (m, 4H, 2 CH_2), 2.41 (s, 3H, CH_3), 2.63 (t, 2H, CH_2 *J* = 9.5 Hz, 2.78 (t, 2H, CH_2 *J* = 7 Hz), 2.98 (t, 2H, CH_2 *J* = 7.8 Hz), 3.78 (t, 1H, CH *J* = 9.1 Hz), 4.33 (q, 2H, CH_2 *J* = 11.0; 7.0 Hz). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 14.1 (CH_3),14.38 (CH_3), 21.45 (CH_3), 21.66 (CH_2), 28.31 (CH_3), 27.48 (CH_2), 51.84 (CH), 57.17 (CH_2), 63.33 (CH_2), 65.94 (CH_2), 65.98 (C), 66.39 (CH_2), 66.85 (CH_2), 171.01 (C=O), 201.66 (C=O).

Mass spectrum *m*/*z*, (I_{rel}, %): (295/297/299)/(21/16/8), (165/167/169)/(70/45/15), (123/125/127)/(45/23/10), (89/91)/(80/35), (51/66).

Diethyl ({butyl[(2-(1,3-dioxolan-2-yl)ethyl]amino}-methyl)-3-oxobutanoate **Vb**. Colorless viscous liquid. $T_{b.p.}$ = 122–123°C (1 mm Hg). Yield 83%. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.85 (t, 3H, CH_3 *J* = 12 Hz), 1.22 (t, H, CH_3 *J* = 6.7 Hz), 1.43–1.58 (m, 4H, 2 CH_2), 1.77–1.83 (m, 2H, CH_2), 2.14–2.20 (m, 4H, 2 CH_2), 2.38 (t, 3H, CH_3 *J* = 8 Hz), 2.46 (t, 2H, CH_2 *J* = 9 Hz), 3.78 (t, 1H, CH *J* = 9 Hz), 3.86 (t, 2H, CH_2 *J* = 6.0 Hz), 3.90 (t, 2H, CH_2 *J* = 6.0 Hz), 4.24 (q, 2H,

CH_2 J = 11.6; 7.0 Hz), 5.00 (d, 1H, CH J = 6.2 Hz), ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 13.55 (CH_3), 14.58 (CH_3), 21.40 (CH_2), 27.78 (CH_2), 28.67 (CH_3), 32.11 (CH_2), 54.43 (CH_2), 54.77 (CH_2), 55.29 (CH_2), 59.34 (CH), 63.18 (CH_2), 66.77 (2 CH_2), 103.27 (CH), 170.61 (C=O), 201.60 (C=O).

Mass spectrum m/z, (I_{rel}, %): (314)/(3), (244)/(50), (169)/(60), (128)/(60), (87)/(40), (73)/(100).

Synthesis of β-aminopropionic acid ethyl ester VI

A mixture of 0.1 mol of compound **IVa**, 0.3 mol of lithium chloride, 0.3 mol of DMSO, and 0.2 mol of water was heated by stirring to 150°C for 1 h until complete conversion of the starting compound (GC control). Upon completion of the reaction, the reaction mixture was cooled to room temperature (20–22°C), washed with water, extracted with methylene chloride, dried over calcium chloride, and evaporated.

Ethyl *N*-butyl-*N*-[(2,2-dichloro-cyclopropyl)--methyl]-β-alaninate **VI**. Colorless liquid. $T_{b.p.}$ = 115–117°C (1 mm Hg). Yield 88%. ^1H NMR spectrum ($CDCl_3$, δ, ppm): 0.98 (t, 3H, CH_3 J = 7.9 Hz), 1.21 (t, 3H, CH_3 J = 8.1 Hz), 1.26 (s, 3H, CH_3), 1.38 (q, 2H, CH_2 J = 13; 8 Hz), 1.51–1.66 (m, 4H, 2 CH_2), 2.71 (d, 2H, CH_2 J = 6.9 Hz), 2.76 (m, 4H, 2 CH_2), 3.66 (d, 1H, CH_a J = 8.2 Hz), 3.71 (d, 1H, $CH_б$ J = 8 Hz), 4.10 (q, CH_2 J = 11; 8 Hz).^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 14.8 (CH_3), 15.1 (CH_3), 21.8 (CH_3), 26.3 (CH_2), 38.1 (CH_2), 51.0 (CH_2), 53.2 (CH_2), 58.7 (CH_2), 62.5 (CH_2), 69.3 (CH_2), 70.1 (CH_2), 171.1 (C=O).

Mass spectrum m/z, (I_{rel}, %): (275/277/279)/(21/16/8), (165/167/169)/(70/45/15), (139/141/143)/(100/50/10), (123/125/127)/(65/42/18), (89/91)/(80/40).

RESULTS AND DISCUSSION

As a result of three-component condensation of CH-acids **I**, **II** with paraformaldehyde and secondary amines **IIIa** and **IIIb**, tertiary amines **IVa**, **IVb**, **Va**, and **Vb** were obtained in 2–5% yields. Increasing the temperature in the range of 80–120°C and the reaction time up to 25 h did not lead to an increase in the yield of target amines **IVa**, **IVb**, **Va**, and **Vb** (Scheme 1).

To stimulate condensation (Table), MWR was used, as described for the reaction of amino alcohols with formaldehyde and diethyl phosphite [12, 13].

At the same time, it was possible to reduce the reaction time to 2–6 h and the process temperature to 60°C at the same as increasing the conversion of amines **IIIa** and **IIIb** to 90% with selectivity for the formation of target products **IVa**, **IVb**, **Va**, and **Vb** equal to 75–95%.

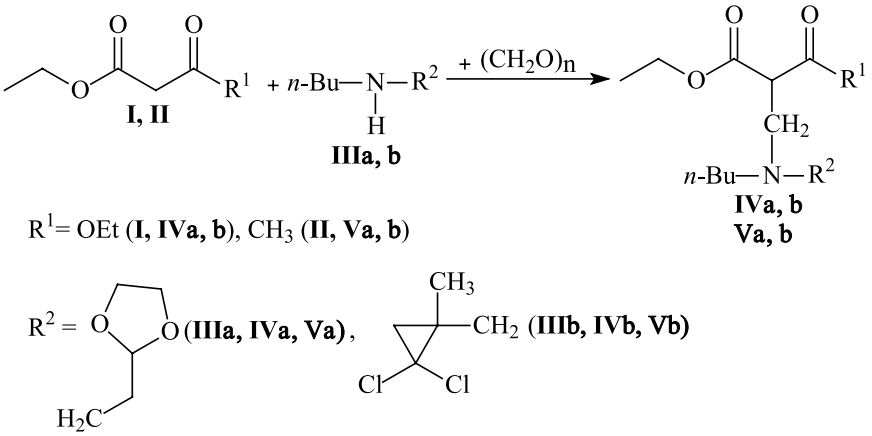
From the obtainedresults, it is apparent that the selectivity of formation of *tert*-amines **IVa**, **IVb**, **Va**, and **Vb** decreasesupon going from diethylmalonate **I** to acetoacetic ester **II**.

The initial secondary amines **IIIa**, **IIIb** containing the *gem*-dichlorocyclopropane and cyclo-acetal fragmentsdo not significantly differ interms of their activity in this reaction.

The replacement of the aprotic solvent (benzene) by organic acids (acetic or propionic) or their esters led to a sharp decrease in the selectivity for the formation of *tert*-amines **IVa**, **IVb**, **Va**, and **Vb**.

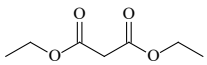
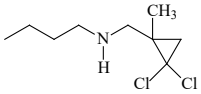
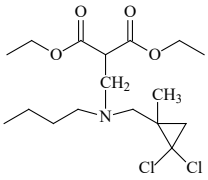
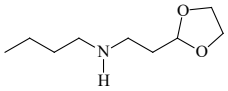
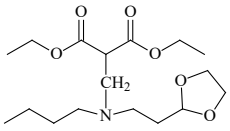
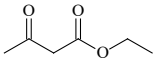
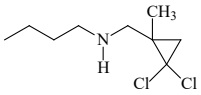
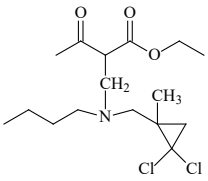
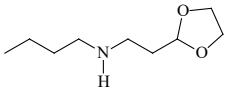
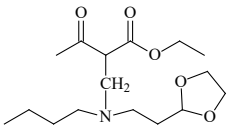
The adduct **IVa** obtained from diester **I** and secondary amine **IIIa** was decarboxylated (Scheme 2) according to the previously described procedure [14, 15].

Ethyl ester of β-aminopropionic acid **VI** was isolated in 88% yield.

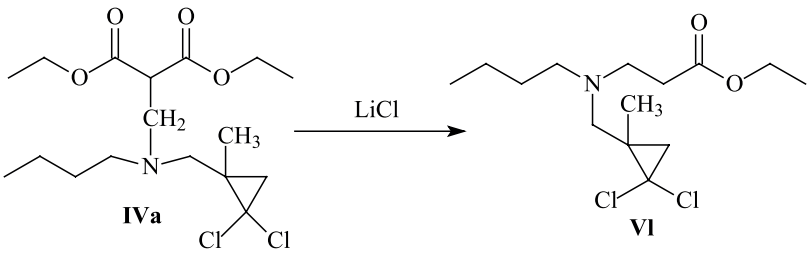


Scheme 1. Condensation of CH-acids, secondary amines, and paraformaldehyde.

Table. Condensation of secondary amines with formaldehyde and CH-acids under the action of thermal heating and MWR

Reagents		Product	Reaction product yield	
CH-acid	Secondary amine		Duration of thermal heating, h	Duration of MWR, min
 **I**	 **IIIa**	 **IVa**	3–5	90
	 **IIIb**	 **IVb**	3–5	88
 **II**	 **IIIa**	 **Va**	≤3	85
	 **IIIb**	 **Vb**		83

Note: CH-acid : amine : paraformaldehyde ratio = 2 : 1 : 1; duration (h) of thermal heating/MWR = 20–25 : 2–6; process temperature (°C) thermal heating/MWR = 100 : 60; amine conversion (%) following thermal heating/MWR = ≤5 : 90.



Scheme 2. Decarboxylation of *tert*-amine **IVa**.

CONCLUSIONS

In contrast to thermal heating, at which this reaction is only feasible with an extremely low yield of the target product, secondary amines containing *gem*-dichlorocyclopropane and cycloacetal fragments condense under the action of MWR with paraformaldehyde and CH-acids to form the corresponding *tert*-amines. Decarboxylation of a *tert*-amine with two ester groups and containing a *gem*-dichlorocyclopropane moiety leads to β-aminopropionic acid ethyl ester.

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Authors' contributions

A.I. Musin – conducting research;

D.S. Sultanova – reviewing publications on the topic of the article;

Yu.G. Borisova – collection and processing of the material and writing the text of the article;

T.P. Mudrik – consultation on planning;

R.R. Daminev – development of the concept of scientific work, critical revision with the introduction of valuable intellectual content.

The authors declare no conflicts of interest.

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