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O.A. Nurkenov[1,3], T.M. Seilkhanov[2], S.D. Fazylov[1], G.Zh. Karipova[1], D.M. Ermek[3], D.E. Tishtykbayeva[3]

[1]Institute of Organic Synthesis and Coal Chemistry of the Republic of Kazakhstan, Karaganda;
[2] Sh. Ualikhanov Kokshetau State University, Kokshetau;
[3]Karaganda State Technical University MES RK, Karaganda
nurkenov_oral@mail.ru, tseilkhanov@mail.ru,
iosu8990@mail.ru, gulja_1708@mail.ru

SYNTHESIS AND STRUCTURE OF DIETHYL-2,6-DIMETHYL-PYRIDIN-3,5-DICARBOXYLATE

Abstract. The article is devoted to the development of a preparatively convenient method for the synthesis of diethyl-2,6-dimethylpyridin-3,5-dicarboxylate. The data on the synthesis of diethyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate obtained by three-component cyclocondensation of two equimolar amounts of acetoacetic ester, urotropine and ammonium acetate by the Ganch method are presented. It was shown that when ethanol was boiled for 2 h, diethyl 2,6-dimethyl-1,4-dihydropyridin-3,5-dicarboxylate with sodium nitrite in acetic acid led to the formation of the corresponding aromatic pyridine. The structures of the synthesized compounds were studied by ^{1}H and ^{13}C NMR spectroscopy, as well as by the data of two-dimensional spectra of COSY (^{1}H-^{1}H) and HMQC (^{1}H-^{13}C). The values of chemical shifts, multiplicity, and integrated intensity of 1H and 13C signals in one-dimensional NMR spectra were determined. Using spectra in the formats COSY (^{1}H-^{1}H) and HMQC (^{1}H-^{13}C), homo- and heteronuclear interactions were established, confirming the structure of the studied compounds.

Keywords: Ganch reaction, 1,4-dihydropyridines, ^{1}H and ^{13}C NMR spectra, diethyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate.

Introduction

It is known that the derivatives of the Ganch reaction - 1,4-dihydropyridines, are of great interest not only in terms of their possible preparative modification and possessing a wide range of pharmacological activity, but also the constant detection and identification of derivatives of new forms of biological activity among this class of derivatives [1-12]. The chemical oxidation reaction of 1,4-dihydropyridines has been well studied; a number of both organic and inorganic reagents are used as oxidizing agents [13-19].

Methods

^{1}H and ^{13}C NMR spectra of compounds **1, 2** were recorded in DMSO-d_6 on a JNM-ECA 400 spectrometer (399.78 and 100.53 MHz on ^{1}H and ^{13}C nuclei, respectively) of the Jeol company from Japan. The survey was carried out at room temperature using a DMSO-d_6 solvent. Chemical shifts are measured relative to the signals of residual protons or carbon atoms of a deuterated solvent.

Experimental part

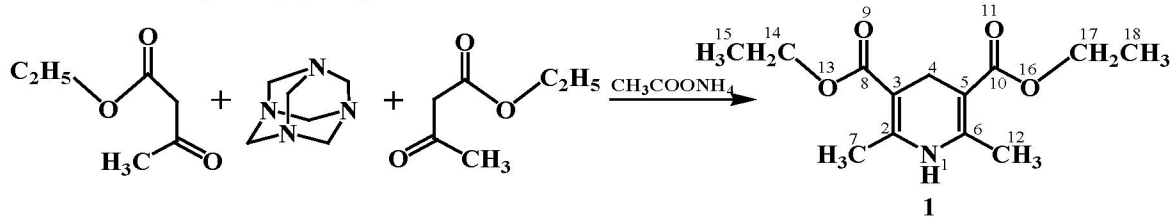
Diethyl-2,6-dimethyl-1,4-dihydropyridin-3,5-dicarboxylate (1). A mixture of 15.6 g (0.12 mol) of acetoacetic ester, 1.54 g (0.01 mol) of urotropin and 4.62 g (0.06 mol) of ammonium acetate in 60 ml of ethanol is boiled for 1 hour. The solution is cooled, the precipitate is filtered off. Yield 2.50 g (90.0%), temperature melting 189-190°C.

Diethyl-2,6-dimethylpyridin-3,5-dicarboxylate (2). To a suspension of 1.27 g (0.005 mol) of diethyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate in 15 ml of acetic acid at room temperature, 0.69 g (0.01 mol) of sodium nitrite was added in portions. After all sodium nitrite was added, the reaction mixture was stirred for 2 hours at room temperature. Then it is poured onto ice, neutralized with ammonia

and the precipitated product 2 is filtered off, washed with water. Yield 1.13 g (89.7%), temperature melting 74-75°C.

Results and discussions

In order to obtain and further modify the new derivatives of symmetric 1,4-dihydropyridines, a three-component cyclocondensation of two equimolar amounts of acetoacetic ester was carried out by the Ganch method. Instead of formaldehyde and ammonia in the classic version of the Ganch synthesis, it used urotropine and ammonium acetate. Ethanol was chosen as a solvent. The reaction time was monitored by TLC. As a result of the reaction, after 1 h of boiling the mixture, a light yellow precipitate formed, which after filtration did not require additional purification, since According to the ^{1}H and ^{13}C NMR spectra, it turned out to be analytically pure product **1**.



1

In the ^{1}H NMR spectrum of compound **1**, the equivalent methyl protons H-15, 15, 15, 18, 18, 18 of the ethyl carboxylate groups appeared as a six-proton triplet at 1.14 ppm with ^{3}J 7.2 Hz. The neighboring equivalent methylene protons H-14, 14, 17, 17 of the ethyl carboxylate substituent resonated with a four-proton quadruplet signal at 4.01 ppm, respectively with ^{3}J 6.8 Hz. Equivalent methyl protons H-7, 7, 7, 12, 12, 12, which do not have protons splitting them in the neighborhood, were manifested by the expected six-proton singlet at 2.02 ppm. At 3.06 ppm atoms of H-4, 4 of the dihydropyridine fragment were resonated by a two-proton singlet. In the weakest field at 8.25 ppm single-proton singlet protons H-1 of the dihydro-pyridine nucleus appeared.

In the ^{13}C NMR spectrum of compound **1**, signals of equivalent ethyl carboxylate groups appeared at 14.92 (C-15, 18), 59.46 (C-14, 17) and 167.65 (C-8, 10) ppm. The carbon atoms of the equivalent methyl substituents C-7, 12 resonated at 18.47 ppm. The carbon atoms of the dihydropyridine fragment are observed at 25.23 (C-4), 97.52 (C-3, 5) and 147.09 (C-2, 6) ppm.

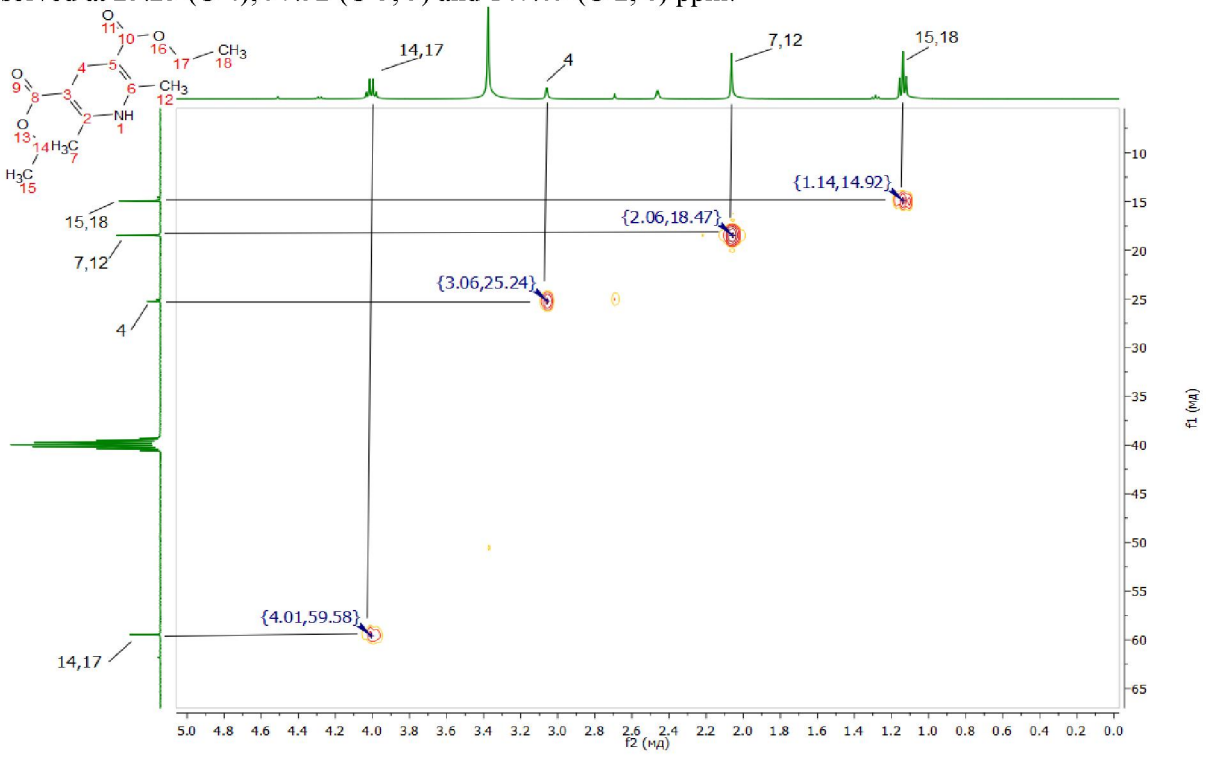


Figure 1 – Spectrum survey of HMQC compound **1** in DMSO

The structure of compound **1** was also confirmed by the methods of two-dimensional NMR spectroscopy COSY (^{1}H-^{1}H) and HMQC (^{1}H-^{13}C), which allows one to establish spin-spin interactions of a homo- and heteronuclear nature (Figs. 1 and 2). The observed correlations in the molecule are presented in the diagrams. In the spectra of ^{1}H-^{1}H COSY compounds, spin-spin correlations are observed through three bonds of the neighboring methyl and methylene protons of the ethyl carboxylate fragments $H^{15,18}$-$H^{14,17}$ with coordinates at 1.11, 4.01 and 4.00, 1.14 ppm. Heteronuclear interactions of protons with carbon atoms through one bond were established using ^{1}H-^{13}C HMQC spectroscopy for all pairs present in the compound: $H^{15,18}$-$C^{15,18}$ (1.14, 14.92), $H^{7,12}$-$C^{7,12}$ (2.06, 18.47) , H^4-C^4 (3.06, 25.24) and $H^{14,17}$-$C^{14,17}$ (4.01, 59.58).

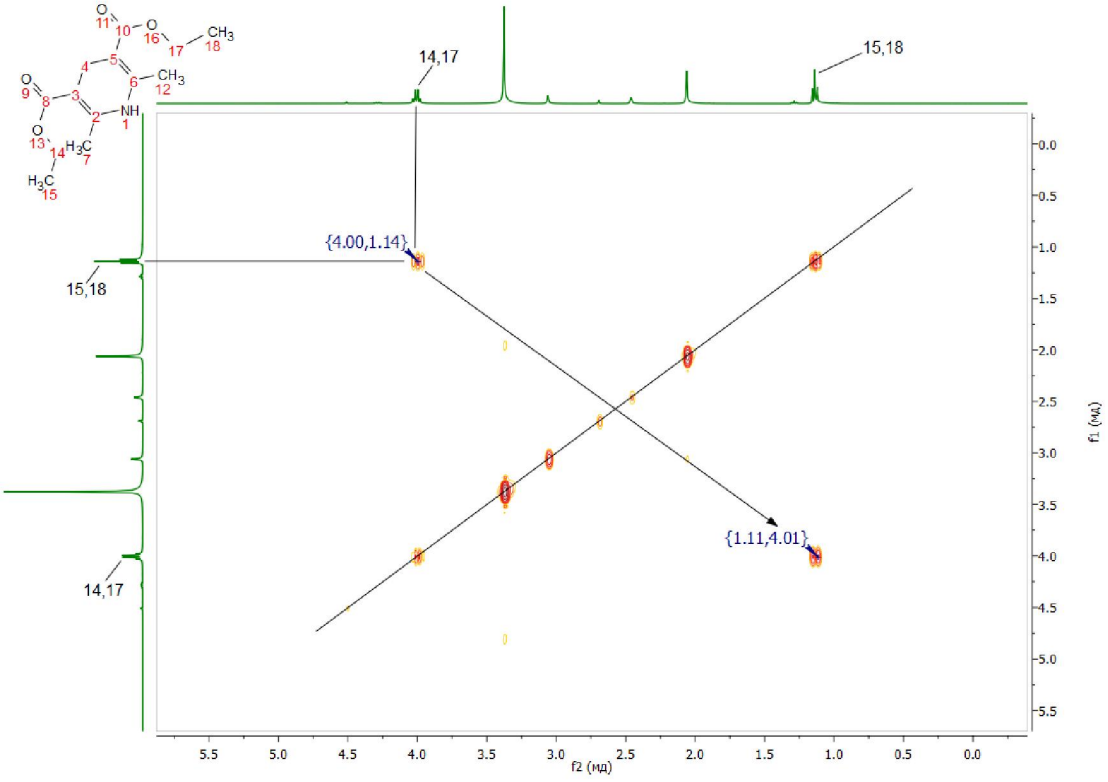
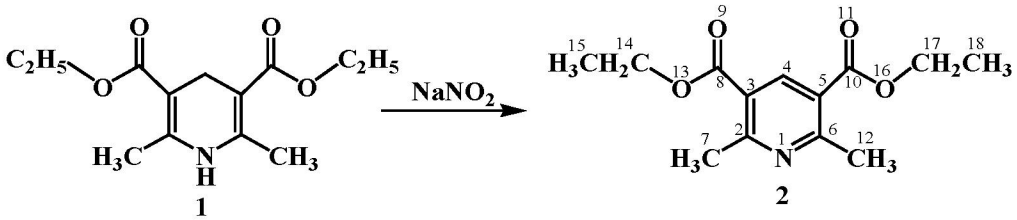


Figure 2 – Survey of the spectrum of COSY compound **1** in DMSO

Oxidative dehydrogenation of diethyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **1** to the corresponding aromatic pyridine **2** was carried out with sodium nitrite in acetic acid. As a result of the reaction, diethyl-2,6-dimethylpyridin-3,5-dicarboxylate **2** was isolated in analytically pure form with a yield of 89.7%.



1 **2**

In the ^{1}H NMR spectrum of compound **2**, the equivalent methyl protons H-15, 15, 15, 18, 18, 18, 18 of the ethyl carboxylate groups showed a six-proton triplet at 1.28 ppm with ^{3}J 6.8 Hz (Fig. 3). The neighboring equivalent methylene protons H-14, 14, 17, 17 of the ethyl carboxylate substituent resonated with a four-proton quadruplet signal, respectively, at 4.27 ppm with ^{3}J 6.8 Hz. Equivalent methyl protons H-7, 7, 7, 12, 12, 12, which do not have protons splitting them in the neighborhood, were manifested by the expected six-proton singlet at 2.67 ppm. In the aromatic region, a single-proton singlet at 8.44 ppm. the pyridine proton H-4 resonated.

In the ^{13}C NMR spectrum of compound **2**, signals of equivalent ethyl carboxylate groups appeared at 14.53 (C-15, 18), 61.77 (C-14, 17) and 165.65 (C-8, 10) ppm (fig. 4). The carbon atoms of the equivalent methyl substituents C-7, 12 resonated at 25.00 ppm. The carbon atoms of the pyridine fragment are observed at 123.11 (C-3, 5), 140.43 (C-4) and 161.83 (C-2, 6) ppm.

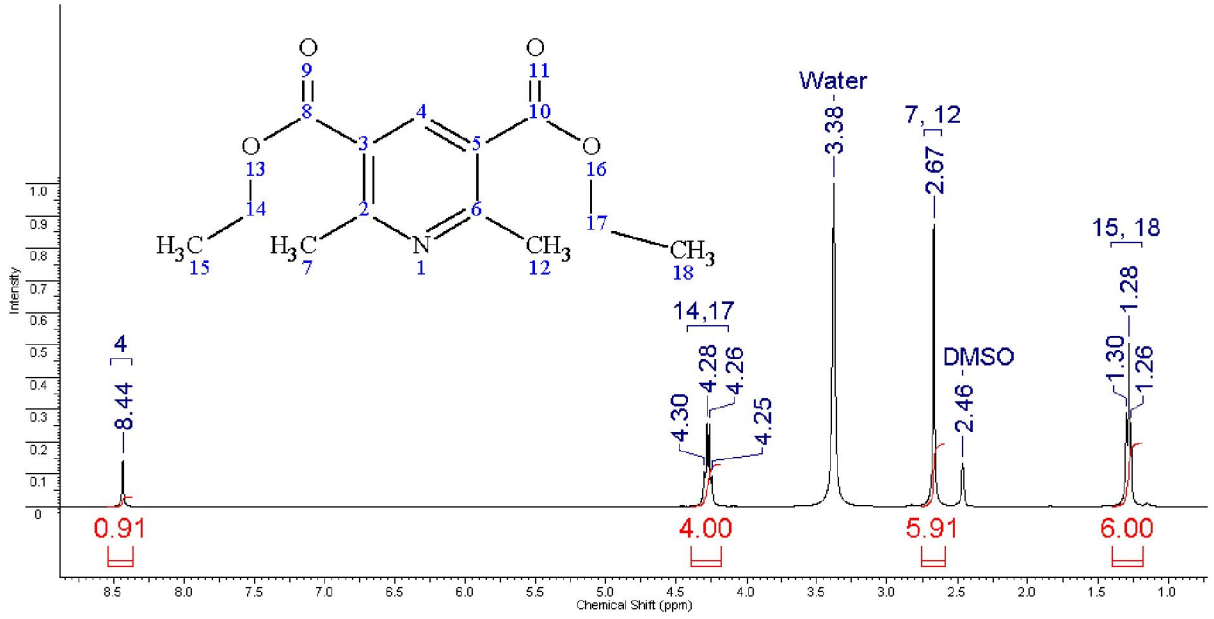


Figure 3 – Survey of the NMR ^{1}H spectrum of compound **2** in DMSO

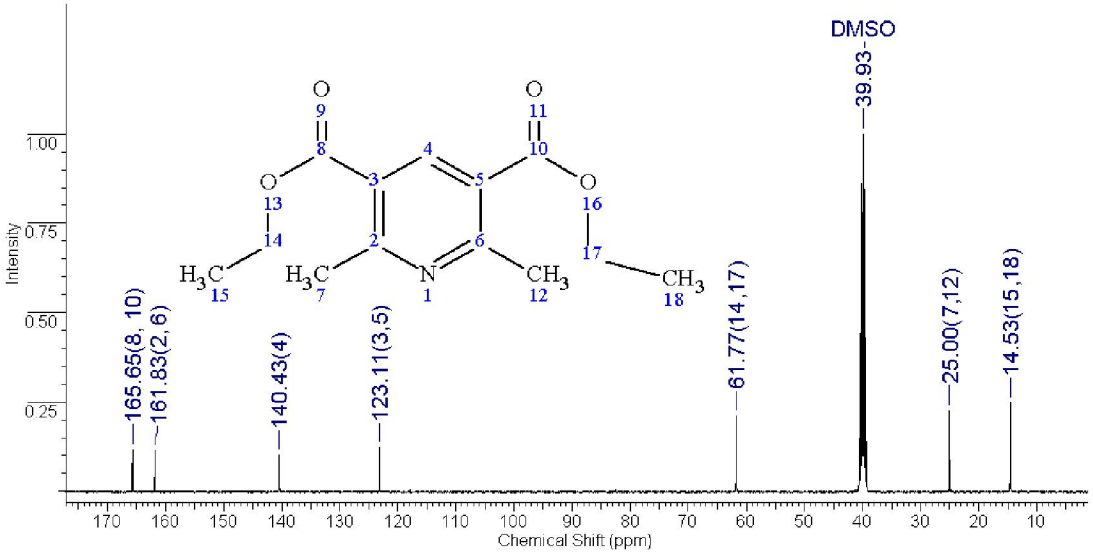
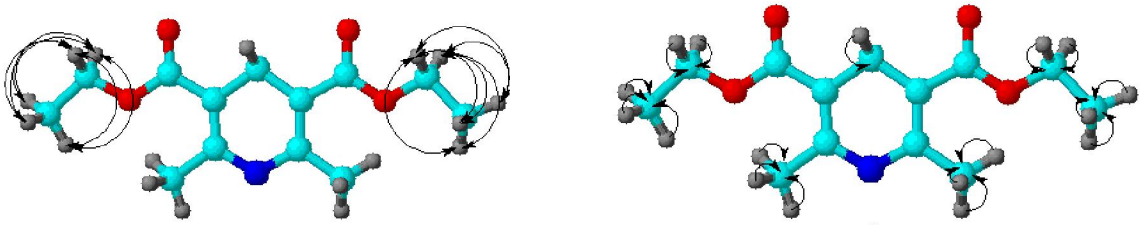


Figure 4 – Survey of the NMR ^{13}C spectrum of compound **2** in DMSO

The structure of compound **2** was also confirmed by two-dimensional NMR spectroscopy COSY (^{1}H-^{1}H) and HMQC (^{1}H-^{13}C), which allows one to establish spin-spin interactions of a homo- and heteronuclear nature (Fig. 5). The observed correlations in the molecule are presented in the diagrams. In the spectra of the ^{1}H-^{1}H COSY compound, spin-spin correlations are observed through three bonds of the neighboring methyl and methylene protons of the ethyl carboxylate fragments $H^{15,18}$-$H^{14,17}$ with coordinates at 1.26, 4.27 and 4.26, 1.28 ppm. Heteronuclear interactions of protons with carbon atoms through one bond were established using ^{1}H-^{13}C HMQC spectroscopy for all pairs present in the compound: $H^{15,18}$-$C^{15,18}$ (1.27, 14.63), $H^{7,12}$-$C^{7,12}$ (2.66, 25.04) $H^{14,17}$-$C^{14,17}$ (4.28, 61.57); and H^{4}-C^{4} (8.42, 140.33).



a b

Figure 5 – Correlation scheme in the spectra of COSY (a) and HMQC (b) of compound **2**

Thus, we synthesized diethyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate and developed a fairly simple and effective method for producing diethyl-2,6-dimethylpyridin-3,5-dicarboxylate, the structure of which is proved ^{1}H and ^{13}C NMR spectroscopy, as well as the data of two-dimensional spectra of COSY (^{1}H-^{1}H) and HMQC (^{1}H-^{13}C).

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О.А. Нүркенов[1,3], Т.М. Сейлханов[2], С.Д. Фазылов[1], Г.Ж. Кэріпова[1], Д.М. Ермек[3], Д.Э. Тыштыкбаева[3]

[1]ҚР Органикалық синтез және көмірхимиясы институты, Қарағанды қ.;
[2]Ш. Уәлиханов атындағы Көкшетау мемлекеттік университеті, Көкшетау қ.;
[3]Қарағанды мемлекеттік техникалық университеті, Қарағанды қ.

ДИЭТИЛ-2,6-ДИМЕТИЛПИРИДИН-3,5-ДИКАРБОКСИЛАТ СИНТЕЗІ ЖӘНЕ ҚҰРЫЛЫСЫ

Аннотация. Мақала диэтил-2,6-диметилпиридин-3,5-дикарбоксилат синтезінің қолайлы әдісін іздестіруге арналған. Ганч әдісі бойынша ацетоуксус эфирі, уротропин және аммоний ацетатының екі эквимольді мөлшерінде үшкомпонентті циклоконденсациямен алынған диэтил-2,6-диметил-1,4-дигидропиридин-3,5-дикарбоксилатты синтездеу бойынша зерттеу деректері қарастырылған. Конденсация процесінің еріткіші ретінде этанол таңдалды. Реакция уақыты ЖҚХ көмегімен бақыланды. Реакцияның нәтижесінде қоспаны 1 сағат қайнатқаннан кейін ашық-сары тұнба түзілді, ол сүзуден кейін қосымша тазартуды талап етпеді, өйткені ЯМР ^{1}H және ^{13}C спектріне сәйкес ол аналитикалық таза өнім болып шықты. Диэтил-2,6-диметил-1,4-дигидропиридин-3,5-дикарбоксилаттың тотығу дегидрленуі тиісті ароматты пиридинге дейін сірке қышқылында натрий нитриті қатысуы арқылы жүргізіледі. Реакция нәтижесінде диэтил-2,6-диметилпиридин-3,5-дикарбоксилат 89,7% шығымымен аналитикалық таза түрде бөлінді. Синтезделген қосылыстардың құрылысы ЯМР ^{1}H - және ^{13}C-спектроскопия әдістерімен, сондай-ақ COSY (^{1}H-^{1}H) және HMQC (^{1}H-^{13}C) екі өлшемді спектрлерінің деректерімен зерттелді. Бірөлшемді ЯМР спектрлерінде ^{1}H және ^{13}C сигналдардың интегралдық қарқындылығы, мультиплеттілігі және химиялық ығысу мәндері анықталды. COSY (^{1}H-^{1}H) және HMQC (^{1}H-^{13}C) форматтарында спектрлер көмегімен зерттелетін қосылыстардың құрылымын растайтын гомо - және гетероядролық өзара әрекеттесулер орнатылды. Диэтил-2,6-диметил-1,4-дигидропиридин-3,5-дикарбоксилат қосылысының ^{1}H ЯМР спектрінде метильді протондар H-15, 15, 15, 18, 18, 18 этилкарбоксилатты топтар 1.14 м.б. ^{3}J 7.2 Гц кезінде алты триплетпен пайда болатындығы айқындалды. ^{13}C спектрінде диэтил-2,6-диметил-1,4-дигидропиридин-3,5-дикарбоксилат қосындысының этилкарбоксилат топтарының эквиваленттi сигналдары 14.92 (C-15, 18), 59.46 (C-14, 17) және 167.65 (C-8, 10) м.б. кезінде айқын көрінген. C-7, 12 эквиваленттi метильді орынбасарларының көміртекті атомдары 18.47 м.б. кезінде резонацияланған. Дигидропиридинді фрагменттің көміртегі атомдары 25.23 (C-4), 97.52 (C-3, 5) және 147.09 (C-2, 6) м.б. аймағында анықталды. Сондай-ақ диэтил-2,6-диметилпиридин-3,5-дикарбоксилаттың ЯМР ^{1}H спектрінде эквиваленттi метильді протондары H-15, 15, 15, 18, 18, 18 этилкарбоксилатты топтар 1.28 м.б. ^{3}I 6.8 Гц кезінде алты триплетпен көрінетіні анықталған, ал ЯМР ^{13}C спектрінде карбоксилатты топтардың эквиваленттi этил сигналдары 14.53 (C-15, 18), 61.77 (C-14, 17) және 165.65 (C-8, 10) м.б. кезінде байқалды. C-7, 12 эквиваленттi метильді орынбасарларының көміртекті атомдары 25.00 м.б. кезінде резонацияланды. Пиридинді фрагменттің көміртегі атомдары 123.11 (C-3, 5), 140.43 (C-4) және 161.83 (C-2, 6) м.б. байқалған.

Түйін сөздер: Ганч реакциясы, 1,4-дигидропиридиндер, ЯМР ^{1}H - және ^{13}C-спектрлер, диэтил-2,6-диметил-1,4-дигидропиридин-3,5-дикарбоксилат.

О.А. Нуркенов[1,3], Т.М. Сейлханов[2], С.Д. Фазылов[1], Г.Ж. Карипова[1], Д.М. Ермек[3], Д.Э. Тиштыкбаева[3]

[1]Институт органического синтеза и углехимии РК, г. Караганда;
[2]Кокшетауский государственный университет им. Ш. Уалиханова, г. Кокшетау;
[3]Карагандинский государственный технический университет, г. Караганда

СИНТЕЗ И СТРОЕНИЕ ДИЭТИЛ-2,6-ДИМЕТИЛПИРИДИН-3,5-ДИКАРБОКСИЛАТА

Аннотация. Статья посвящена разработке препаративно удобного способа синтеза диэтил-2,6-диметилпиридин-3,5-дикарбоксилата. Приведены данные по синтезу диэтил-2,6-диметил-1,4-дигидропиридин-3,5-дикарбоксилата, полученного трехкомпонентной циклоконденсацией двух эквимольных количеств ацетоуксусного эфира, уротропина и ацетата аммония по методу Ганча. В качестве растворителя процесса конденсации был выбран этанол. Время реакции контролировали с помощью ТСХ. В результате реакции после 1 ч кипячения смеси образовывался светло-желтый осадок, который после фильтрации не требовал дополнительной очистки, поскольку, согласно спектрам ЯМР ^{1}H и ^{13}C, он оказался аналитически чистым продуктом. Окислительное дегидрирование диэтил-2,6-диметил-1,4-дигидропиридин-3,5-дикарбоксилата до соответствующего ароматического пиридина проведено в присутствии нитрита натрия в уксусной кислоте. В результате реакции был выделен диэтил-2,6-диметилпиридин-3,5-дикарбоксилат в аналитически чистом виде с выходом 89,7 %. Исследованы строения синтезированных соединений методами ЯМР ^{1}H- и ^{13}C-спектроскопии, а также данными двумерных спектров COSY (^{1}H-^{1}H) и HMQC (^{1}H-^{13}C). Определены значения химических сдвигов, мультиплетность и интегральная интенсивность сигналов ^{1}H и ^{13}C в одномерных спектрах ЯМР. С помощью спектров в форматах COSY (^{1}H-^{1}H) и HMQC (^{1}H-^{13}C) установлены гомо- и гетероядерные взаимодействия, подтверждающие структуру исследуемых соединений. Зафиксировано, что в спектре ЯМР ^{1}H диэтил-2,6-диметил-1,4-дигидропиридин-3,5-дикарбоксилата метильные протоны H-15, 15, 15, 18, 18, 18 этилкарбоксилатных групп проявились шестипротонным триплетом при 1.14 м.д. с ^{3}J 7.2 Гц. В спектре ЯМР ^{13}C диэтил-2,6-диметил-1,4-дигидропиридин-3,5-дикарбоксилата сигналы эквивалентных этилкарбоксилатных групп обнаружено при 14.92 (C-15, 18), 59.46 (C-14, 17) и 167.65 (C-8, 10) м.д. Углеродные атомы эквивалентных метильных заместителей C-7, 12 резонировано при 18.47 м.д. Атомы углерода дигидропиридинового фрагмента наблюдено при 25.23 (C-4), 97.52 (C-3, 5) и 147.09 (C-2, 6) м.д. Также выяснено, что в спектре ЯМР ^{1}H диэтил-2,6-диметилпиридин-3,5-дикарбоксилата эквивалентные метильные протоны H-15, 15, 15, 18, 18, 18 этилкарбоксилатных групп проявляются шестипротонным триплетом при 1.28 м.д. с ^{3}J 6.8 Гц, а в спектре ЯМР ^{13}C сигналы эквивалентных этилкарбоксилатных групп резонируют при 14.53 (C-15, 18), 61.77 (C-14, 17) и 165.65 (C-8, 10) м.д. Углеродные атомы эквивалентных метильных заместителей C-7, 12 резонировались при 25.00 м.д. Атомы углерода пиридинового фрагмента наблюдено при 123.11 (C-3, 5), 140.43 (C-4) и 161.83 (C-2, 6) м.д.

Ключевые слова: реакция Ганча, 1,4-дигидропиридины, ЯМР ^{1}H- и ^{13}C-спектры, диэтил-2,6-диметил-1,4-дигидропиридин-3,5-дикарбоксилат.

Information about authors:

Nurkenov O.A. – Doctor of chemical sciences, Professor, Institute of Organic Synthesis and Coal Chemistry of the Republic of Kazakhstan, e-mail: nurkenov_oral@mail.ru;

Seilkhanov T.M. – Candidate of Chemical Sciences, Sh. Ualikhanov Kokshetau State University, e-mail: tseilkhanov@mail.ru, https://orcid.org/0000-0003-0079-4755;

Fazylov S.D. – corresponding member of NAS RK, Doctor of chemical sciences, Professor, Institute of Organic Synthesis and Coal Chemistry of the Republic of Kazakhstan. e-mail: iosu8990@mail.ru, https://orcid.org/0000-0002-4240-6450;

Karipova G.Zh. – researcher, master, Institute of Organic Synthesis and Coal Chemistry of the Republic of Kazakhstan. e-mail: gulja_1708@mail.ru, https://orcid.org/0000-0002-3896-6156;

Ermek D.M. – master, Karaganda State Technical University. e-mail: dark_han_-96@list.ru, https://orcid.org/0000-0002-6964-8599;

Tishtykbayeva D.E. – master, Karaganda State Technical University. e-mail: dana_9605@mail.ru, https://orcid.org/0000-0003-1796-2276

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