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SYNTHESIS BASED ON ETHYL CYANOACETATE

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Abstract: It has been shown that self-condensation ethyl cyanoacetate under conditions of excess potash in DMSO undergoes an intermolecular Claisen-type condensation involving three substrate molecules to form ethyl 2,4-dicyano-2-[2-cyanoacetyl-3-oxo]-butanoate. Self-condensation ethyl cyanoacetate takes place in the presence of triethyl phosphite and zinc acetate with the participation of three reagent molecules resulting in triethyl 3-cyano-2,4-diiminopentane-1,3,5-tricarboxylate. Alkylation ethyl cyanoacetate with 1,2-dichloroethane, cycloalkylation products were obtained: cyclopropane and cyclohexane derivatives, as well as a polymer product. The reaction of ethyl cyanoacetate with 1,2,3-trichloropropane occurs in a 2:3 ratio giving ethyl 7-chloro-2-(2-chloroallyl)-2,5-dicyano-3-methylene-7-enoate and 2,5-bis(2-chloroallyl)-3-methylenehexanedinitrile.

Keywords: self-condensation, ethylcyanoacetate, triethyl phosphite, dichloroethane, trichloropropane

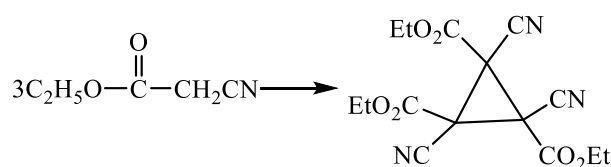
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Introduction

Systematic studies of the alkylation of compounds with an active methylene group with haloalkanes have shown wide possibilities for creating the most diverse organic compounds of practical importance on their basis [1,2].

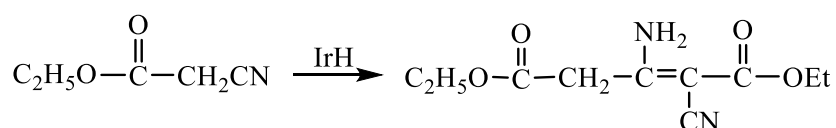
One of the interesting objects of research is ethyl cyanoacetate, on the basis of which

various classes and types of compounds are synthesized. Nitrogen- and sulfur-containing heterocycles are obtained by condensation of ethyl cyanoacetate with carbonyl compounds [3,4]. Cyclotrimerization of ethyl cyanoacetate, tricyanocyclopropane – 1,2,3-tricarboxylate was obtained [5]



In the presence of iridium hydride as a catalyst, C–H addition occurs at the triple bond

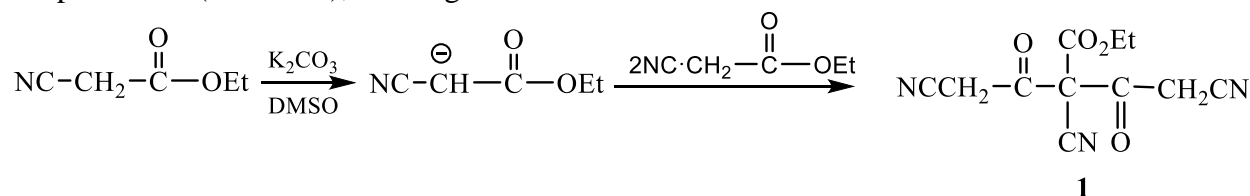
of the nitrile group with the formation of an unsaturated amine [6]



Results and discussion

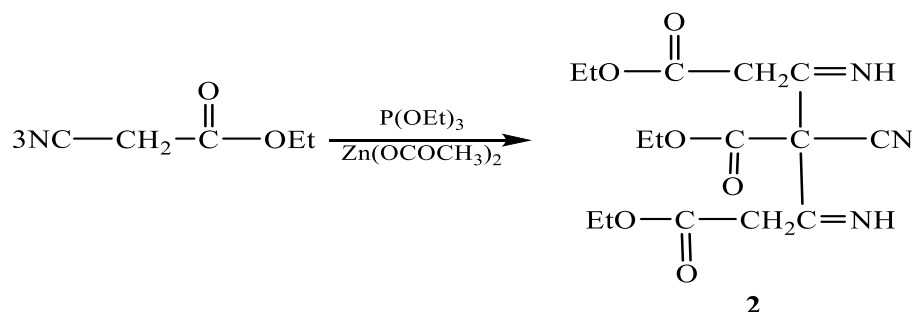
In contrast to the above scheme, we have found that ethyl cyanoacetate, under conditions of excess potash in DMSO at elevated temperatures (90-100°C), undergoes Claisen-

type intermolecular condensation with the participation of three molecules of ethyl cyanoacetate to form compound **1**.



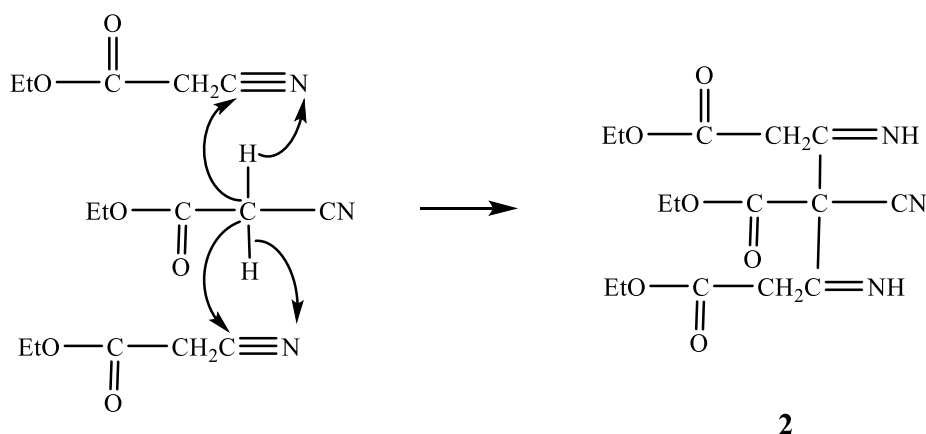
It also revealed that ethyl cyanoacetate in the presence of triethyl phosphite and zinc acetate enters into self-condensation, where three moles

of ethyl cyanoacetate simultaneously participate.



A distinctive feature of this reaction from the previous study [7] is that the active methylene group of one molecule joins two nitrile fragments of the second and third

molecules of ethyl cyanoacetate, forming diiminoderivative **2** according to the trend as follows:

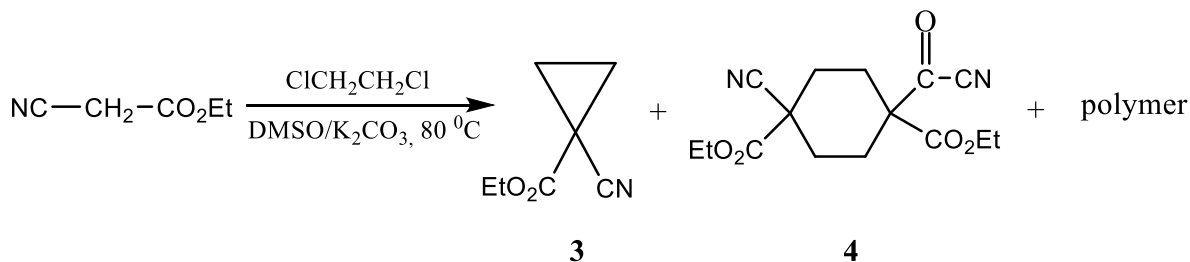


The ¹H NMR spectrum of compound **2** contains triplets at 1.15 (3H) and 1.25 (6H) ppm, as well as quartets at 4.05 (2H, CH₂O) and 4.15 ppm. (4H, 2CH₂O) which confirm the presence of three ethoxy groups. Integral intensities confirm the ratio of these groups (1:2). Singlet at 3.35 ppm characterizes

methylene units. Broadened signal in a weak field 6.25 ppm should be classified as imino groups (C=NH).

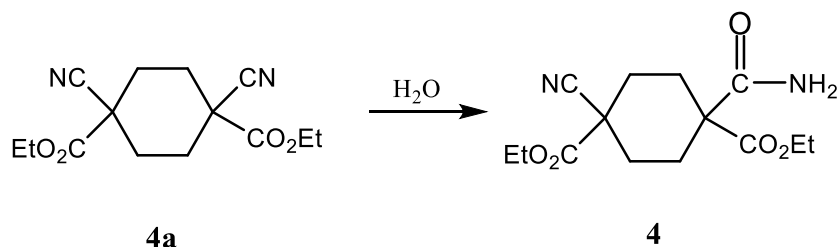
It established that ethyl cyanoacetate is alkylated with 1,2-dichloroethane in the presence of potash in DMSO with the formation of three products: C,C-dialkylation with the

formation of a cyclopropane derivative - gemnitrilethoxycarbonylcyclopropane (**3**); a product of intermolecular tetra-C-alkylation with the participation of two moles of substrate and two moles of reagent (dichloroethane) -



The formation of amide **4** should be considered as a product of hydrolysis of the primary

tetralkylation of **4a** at the nitrile group.



The resulting polymer is practically insoluble in organic solvents, which makes easy to isolate it from the mixture.

The phosphorus analogue of ethyl cyanoacetate, diethoxyphosphorylcyanomethyl phosphonate, under identical conditions is alkylated with 1,2-dichloroethane, forming only

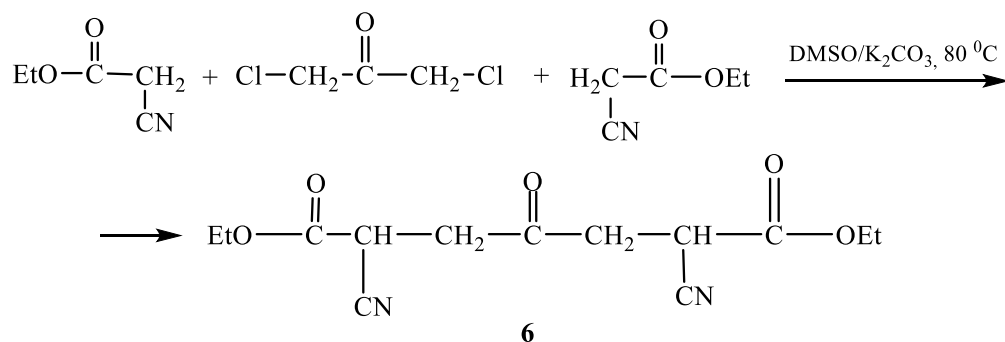
the C,C-cyclodialkylation product - gem-cyanodiethoxyphosphoryl-cyclopropane (**5**), the structure of which is confirmed by ^1H , ^{13}C and ^{31}P NMR. Previously, compound **5** was obtained using 1,2-dibromoethane using various catalysts [8-10].



Doublet in the region of 1.7 ppm corresponding to four protons with $^3J_{\text{HP}}$ 12 Hz characterizes the hydrogens of the cyclopropane nucleus. The chemical shift of phosphorus is 22 ppm, which confirms the phosphonate structure. It ought to be noted that the condensation of ethyl cyanoacetate with 1,2-dibromoethane also

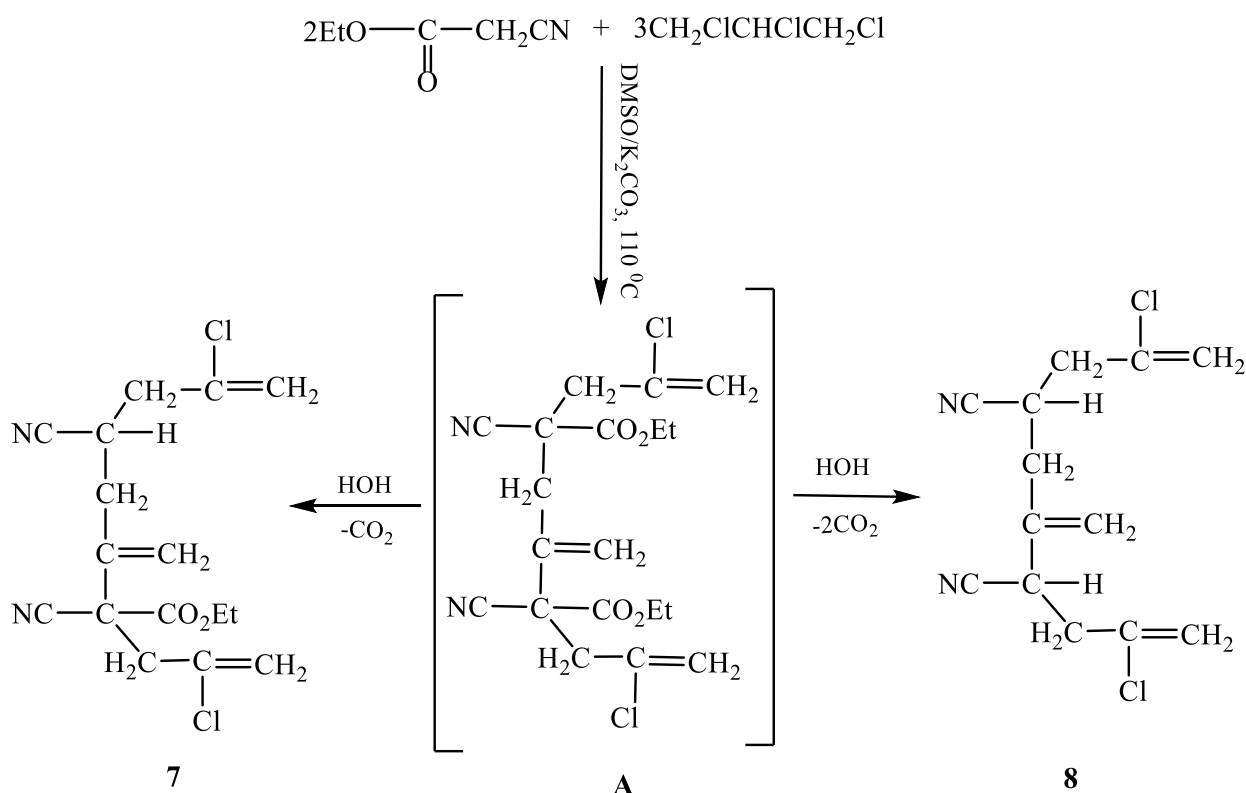
produces **5**.

When ethyl cyanoacetate is alkylated with 1,3-dichloroacetone under identical conditions in a 2:1 ratio, 1,3-di(ethoxycarbonylcyanomethyl) acetone is formed



Alkylation of ethyl cyanoacetate with 1,2,3-trichloropropane under the above conditions takes place with the participation of two moles of substrate and three moles of reagent simultaneously. Along with alkylation,

dehydrochlorination also occurs. Alkylation product **A** under the reaction conditions undergoes partial or complete hydrolysis of the ester fragment with further decarboxylation to form the appropriate products **7** and **8**.



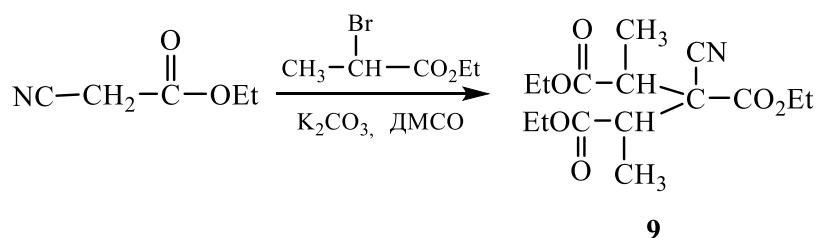
The structure of the obtained products **7** and **8** was confirmed by ^1H and ^{13}C NMR spectroscopy data. The NMR spectrum of compound **8** completely lacks resonance signals of ethoxy groups. Multiplets in the region of 2.6-2.8 and 3.3-3.4 ppm characterize the methylene and methine hydrogen atoms, respectively. Resonance signals in a weak field 5.35-5.5 ppm should be classified as vinyl protons.

The NMR spectrum of compound **7** contains a signal of the ethoxy group with a

chemical shift of 1.15 ppm. (triplet) and 4.0 ppm (quartet) (2H, CH_2O). The difference in boiling points of products **7** and **8** allows them to be identified by vacuum distillation.

Of interest was the use of α -halopropionate in the alkylation reaction of ethyl cyanoacetate, where the activity of the halogen is significantly higher than their activity in alkyl halides.

When ethyl cyanoacetate is alkylated with ethyl α -bromopropionate, only the C,C-dialkylation product is formed.



In this case, the monoalkylation product was not obtained, in contrast to the results given

in [11], where the formation of C-mono and C,C-dialkylation products was noted.

Experimental part

^1H and ^{13}C NMR spectrum was recorded on a Bruker spectrometer AV-300 [300 (^1H) and 75 (^{13}C) MHz, respectively], internal standard – TMS. The melting point was determined on an SMP 30 Stuart instrument. Elemental analysis was carried out on a Carlo instrument Erba 1106. The purity of the obtained compounds was monitored by TLC on Silufol plates UV - 254, eluent – acetone-hexane (1:1).

General procedure for self-condensation of ethyl cyanoacetate in the presence of K_2CO_3 and DMSO. A mixture consisting of 0.12 mol of ethyl cyanoacetate, 0.25 mol of K_2CO_3 in 50 ml of DMSO was stirred for 12 hours at 80°C . The mixture was stirred for 12 hours at 80°C . Cooled, treated with water and extracted with ethyl ether. The extract was dried with MgSO_4 , the solvent was distilled off, and the residue was distilled under vacuum.

Ethyl 2,4-dicyano-2-(2-cyanoacetyl)-3-oxobutanoate (1). From 14 g of ethyl cyanoacetate we obtained **1**. Yield 22.80 g (76%), bp $154\text{--}157^\circ\text{C}$ (2 mm Hg), n_D^{20} 1.4652. Found, %: C 53.87; H 4.32; N 17.65. $\text{C}_{11}\text{H}_9\text{N}_3\text{O}_4$. Calculated, %: C 53.44; H 3.64; N 17.00. ^1H NMR (DMSO- d_6), δ ppm: 1.15 t (3H, CH_3), 4.0–4.2 m (6H, 3OCH_2). ^{13}C NMR (DMSO- d_6), δC ppm: 16.44 (CH_3), 24.88 (CH_2), 60.65 (OCH_2), 118.66 ($\text{C} \equiv \text{N}$), 164.95, 165.86 (COO), ($\text{C}=\text{O}$), ($-\text{C}-\text{C}-\text{C}-$).

Self-condensation of ethyl cyanoacetate in the presence of triethyl phosphite and zinc acetate. Under similar conditions, triethyl 3-cyano-2,4-diiminopentane-1,3,5-tricarboxylate (2) was obtained from 42 g of ethyl cyanoacetate, 20 g of $\text{P}(\text{OC}_2\text{H}_5)_3$ and 18 g of zinc acetate. Yield 28.86 g (64.65%), bp $121\text{--}123^\circ\text{C}$ (2 mm Hg), n_D^{20} 1.4573. ^1H NMR (DMSO- d_6), δ ppm: 1.15 t (3H, CH_3), 1.25 t (6H, 2CH_3), 4.05 k (2H, CH_2O), 4.15 k (4H,

$2\text{CH}_2\text{O}$), 3.35 s (4H, 2CH_2), 6.25 br.s. (2H, $\text{C}=\text{NH}$). ^{13}C NMR (DMSO- d_6) δC ppm: 14.24; 16.44 (CH_3), 24.85 (CH_2), 60.58, 60.65, 61.66 (OCH_2), 115.36 ($\text{C}=\text{NH}$), 118.63 ($\text{C} \equiv \text{N}$), 164.70, 165.95 (2 COO). Found, %: C 53.87; H 6.21; N 12.36. $\text{C}_{15}\text{H}_{20}\text{O}_6\text{N}_3$. Calculated, %: C 53.25; H 5.91; N 12.42.

Method for alkylation of ethyl cyanoacetate with mono- and polyhaloalkanes. To a mixture of 14 g of ethyl cyanoacetate and 0.25 mol of K_2CO_3 in 50 ml of DMSO, 0.12 mol of 1,2-dichloroethane was added dropwise with stirring. The mixture was stirred for 12 hours at 80°C , cooled, treated with water and extracted with ethyl ether. The extract was dried with MgSO_4 , the solvent was distilled off, and a residue was formed in the form of a viscous mass. The residue was treated with toluene and kept for 36 hours. The crystals that formed were **ethyl 1-cyanocyclopropane-1-carboxylate (3)**. Yield 18.68 g (33.57%), mp 172°C . Found, %: C 60.76, H 6.12, N 10.54. $\text{C}_7\text{H}_9\text{NO}_2$. Calculated, %: C 60.43; H 6.47; N 10.07. ^1H NMR (CDCl_3), δ ppm: 1.15 t (6H, 2CH_3), 1.74–2.00 m (4H, $\text{CH}_2\text{-CH}_2$), 4.25 m (4H, 2OCH_2). ^{13}C NMR (CDCl_3), δC ppm: 17.28, 32.21, 48.00, 62.00, 118.12, 166.02.

Diethyl 1-cyano-4-(cyanocarbonyl)cyclohexane-1,4-dicarboxylate (4). The residue not dissolved in toluene was treated with hot ethanol. After cooling, crystals **4** fell out. Yield 14.85 g (27%), mp 127°C . Found, %: C 56.21; H 7.13; N 10.23. $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_5$. Calculated, %: C 56.75; H 6.75; N 9.45. ^1H NMR (CDCl_3), δ ppm: 1.15 t (6H, 2CH_3), 1.85–2.36 m (8H, 4CH_2), 4.02 m (4H, 2OCH_2), 6.8–7.0 us.s. (2H, NH_2). ^{13}C NMR (DMSO- d_6), δC ppm: 14, 27, 28, 37, 59.95, 94.20, 118.20, 157.40, 164.12, 166.30.

Diethyl (1-cyanocyclopropyl)phosphonate (5).

Under similar conditions, from 22 g of diethylcyanomethylphosphonate and 12 g of dichloroethane, a residue was formed, distilled under vacuum to obtain **5**. Yield 18.32 g (66%), bp 70-73⁰C (2 mm Hg), n_D^{20} 1.4464. Found, %: C 47.64; H 7.21; N 6.45; P 15.87. C₈H₁₄NPO₃. Calculated, %: C 47.29; H 6.89; N 6.89; P 15.27. ¹H NMR (CDCl₃), δ ppm: 1.08 t (6 H, 2CH₃, ³J_{HH} 7.2 Hz), 1.34 d (4H, CH₂CH₂), 3.95 m (4H, 2OCH₂). ¹³C NMR (CDCl₃) δ C ppm: 13.5, 15.6, 62, 119.2.

Diethyl 2,6-dicyano-4-oxoheptanedioate (6). Under similar conditions, a thick mass in the form of syrup **6** was formed from 4.6 g of ethyl cyanoacetate and 2.4 g of 1,3-dichloropropan-2-one. Yield 7.3 g (72%). Found, %: C 53.44; H 5.45; N 9.43. C₁₃H₁₆N₂O₅. Calculated, %: C 55.71; H 5.71; N 10.00. ¹H NMR (CDCl₃), δ ppm: 1.1-1.3 t (6H, 2CH₃), 2.3 d (4H, 2CH₂=O), 3.3 t (2H, CH-CH₂), 4.15-4.30 m (4H, 2CH₂O). ¹H NMR (CDCl₃), δ C ppm: 15.59, 22.58, 31.61, 40.22, 60.22, 61.54, 63.40, 115.87, 118.26, 123.79, 147.81, 160.84, 163.43, 165.01, 200.56.

Method of alkylation of ethyl cyanoacetate with trichloropropane in the presence of K₂CO₃ and DMSO. A mixture of 26 g of ethyl cyanoacetate, 50 g of potash in 70 ml of DMSO was added with stirring to 32 g of 1,2,3-trichloropropane. The mixture was stirred for 8-10 hours at 110-120⁰C. Cooled, treated with water and extracted with ethyl ether. The extract was dried with MgSO₄, the solvent was distilled off, and the residue was distilled under vacuum.

Ethyl 7-chloro-2-(2-chloroallyl)-2,5-dicyano-3-methyleneoct-7-enoate (7). Yield 14 g (54%), bp 90-93⁰C (2 mm Hg). Found, %: C 56.21; H 5.88; N 8.65; Cl 21.23. C₁₆H₁₈N₂O₂Cl₂. Calculated, %: C 56.30; H 5.27; N 8.21; Cl 20.82. ¹H NMR (CDCl₃), δ

ppm: 1.25 t (3H, CH₃), 2.65-2.80 m (4H, 2CH₂), 3.05 s (2H, -CH₂-), 3.35 m (1H, CH), 4.24 m (2H, OCH₂), 5.45 d.d. (4H, 2CH=C). ¹³C NMR (CDCl₃), δ C ppm: 12, 19.18, 43.50, 48.7, 62.4, 117, 119, 137.

2,5-bis(2-chloroallyl)-3-methylenehexanedinitrile (8). Yield 9.8 g (38%), bp. 115-117⁰C (2 mm Hg). Found, %: C 60.24; H 5.87; N 10.12; Cl 26.97. C₁₃H₁₄N₂Cl₂. Calculated, %: C 57.99; H 5.20; N 10.40; Cl 26.97. ¹H NMR (CDCl₃), δ ppm: 2.62-2.84 m (4H, 2CH₂), 3.45 m (1H, CH), 5.35 d.d. (4H, 2CH₂=C). ¹³C NMR (CDCl₃), δ C ppm: 12, 19.18, 43.50, 48.7, 62.4, 117, 119, 137.

Method for alkylation of ethyl cyanoacetate with ethyl 2-bromopropionate. A mixture of 5.1 g of ethyl cyanoacetate, 12 g of potash in 50 ml of DMSO was stirred for 1-2 hours at room temperature and 8.3 g of ethyl 2-bromopropionate was added dropwise. The temperature was gradually brought to 80⁰C and stirred for 8-10 hours. Cooled, treated with water and extracted with ethyl ether. The extract was dried with MgSO₄, the solvent was distilled off, and the residue was distilled under vacuum. The resulting product is **tri-3-cyanopentane-2,3,4-tricarboxylate (9)**. Yield 4.6 g (58%), bp 72-175⁰C (2 mm Hg), n_D^{20} 1.4580. Found, %: C 57.13; H 7.86; N 4.97. C₁₅H₂₃NO₆. Calculated, %: C 57.50; H 7.34; N 4.47. ¹H NMR (CDCl₃), δ ppm: 1.15-1.23 m (9H, 3CH₃), 1.37 d.d. (3H, CH₃), 3.15 k, 3.20 k and 3.35 k (4H, 4CH), 3.95-4.25 m (6H, 3OCH₂). ¹³C NMR (CDCl₃), δ C ppm: 13.45, 13.87, 14.20, 39.28, 40.21, 42.63, 43.64, 53.19, 53.94, 61.35, 61.48, 62.39, 77.24, 77.78, 166.10, 166.16, 171.08, 171.25, 172.09.

Conclusion

It was established that self-condensation ethyl cyanoacetate under conditions of excess potash in DMSO undergoes an intermolecular Claisen-type condensation involving three substrate molecules to form ethyl 2,4-dicyano-2-[2-cyanoacetyl-3-oxo]-butanoate. Self condensation ethyl cyanoacetate in the presence of triethyl phosphite and zinc acetate also takes place with the participation of three reagent

molecules giving triethyl 3-cyano-2,4-diiminopentane-1,3,5-tricarboxylate. Alkylation ethyl cyanoacetate with 1,2-dichloroethane, cycloalkylation products were obtained: cyclopropane and cyclohexane derivatives, as well as a polymer product. The reaction of ethyl cyanoacetate with 1,2,3-trichloropropane occurs in a 2:3 ratio giving ethyl 7-chloro-2-(2-chloroallyl)-2,5-dicyano-3-methyleneoct-7-

enoate and 2,5-bis(2-chloroallyl)-3-methylenehexanedinitrile.

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ETİL SİANOASETAT ƏSASINDA SİNTEZ

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Xülasə: Etil siyanoasetat DMSO-da artıq kalium şəraitində üç substrat molekulunun iştirakı ilə öz-özünə kondensləşərək molekullararası Claisen tipli kondensasiyaya məruz qalır və etil 2,4-disiyano-2-[2-siyanoasetil-3-okso]butanoat əmələ gətirir. Trietilfosfit və sink asetatın iştirakı ilə etil siyanoasetatın öz-özünün kondensləşməsi də üç reagent molekulunun iştirakı ilə trietil 3-siano-2,4-diiminopentan-1,3,5-trikarboksilat verir. Etil siyanoasetatın 1,2-dixloretran ilə alkülləşməsi nəticəsində tsikloalkülləşmə məhsulları əldə edilmişdir: tsiklopropan və tsikloheksan törəmələri, həmçinin polimer xarakterli birləşmələr alınmışdır. Etil siyanoasetatın 1,2,3-trixloropropan ilə reaksiyası 2:3 nisbətində baş verir və etil 7-xloro-2-(2-xloroalil)-2,5-disiyano-3-metilenat-7-enoat və 2,5-bis(2-xloroalil)-3-metilenheksan dinitril alınır.

Açar sözlər: öz-özünə kondensləşmə, trietilfosfit, dixloretran, trixloropropan

СИНТЕЗ НА ОСНОВЕ ЭТИЛЦИАНОАЦЕТАТА

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Аннотация: Показано, что самоконденсация этилцианоацетата в условиях избытка поташа в ДМСО подвергается межмолекулярной конденсации типа Кляйзена с участием трех молекул субстрата с образованием этил 2,4-дициано-2-[2-цианоацетил-3-оксо]бутаноата. Сококонденсация этилцианоацетата в присутствии триэтилфосфита и ацетата цинка протекает также с участием трех молекул реагента, давая триэтил-3-циано-2,4-дииминопентан-1,3,5-трикарбоксилат. Алкилированием этилцианоацетата с 1,2-дихлорэтаном получены продукты циклоалкилирования: циклопропановые и циклогексановые производные, а также продукт полимерного характера. Реакция этилцианоацетата с 1,2,3-трихлорпропаном протекает в соотношении 2:3, давая этил 7-хлор-2-(2-хлораллил)-2,5-дициано-3-метиленаат-7-еноат и 2,5-бис(2-хлораллил)-3-метилгександинитрил.

Ключевые слова: самоконденсация, триэтилфосфит, дихлорэтан, трихлорпропан