SYNTHESIS OF FUNCTIONALLY SUBSTITUTED PYRIDINES AND DIPYRIDYL-SUBSTITUTED COMPOUNDS WITH THE AID OF LOW-VALENCE COBALT COMPLEXES

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UDC 547.824'825'829'239.2'212'314.
2.07:542.97:543.422'51

The possibility of the preparation of oxygen, nitrogen, and sulfur-containing pyridines and dipyridyl-substituted compounds by the cyclocotrimerization of substituted propionitriles with acetylene under the influence of a Co(2-ethylhexanoate)$_2$—Al$(C_2H_5)_3$ catalyst was demonstrated. It was established that the nature of the heteroatom in substituted propionitriles has virtually no effect on the direction of the reaction.

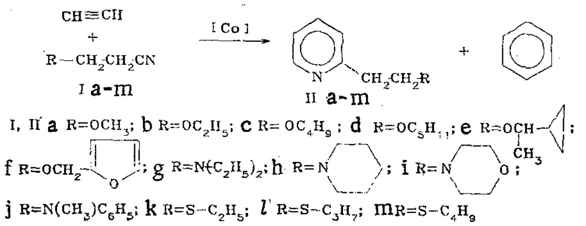
One of the promising and efficient methods for the synthesis of pyridines with various structures is a method based on the cyclocotrimerization of nitriles with acetylenes under the influence of cobalt complexes [1, 2]. This reaction has been studied primarily in the case of the simplest alkanenitriles and acetylenes.

In order to investigate the possibility of the use of nitriles with more complex structures in the indicated reaction and to obtain 2-substituted oxygen-, nitrogen-, and sulfur-containing pyridines and dipyridyl-substituted compounds of practical importance we studied the reaction of γ-alkoxy-, γ-alkylthio-, γ-dialkyl-, and γ-cycloalkylaminopropionitriles and α,ω-dinitriles with acetylene catalyzed by low-valence cobalt complexes. In addition, it was of interest to ascertain the effect of the structure of propionitriles that are bi- and tridentate ligands on the direction of cyclocotrimerization and the activity and selectivity of the action of cobalt catalysts.

In the course of our study of cyclocotrimerization we established that the highest yields of pyridines can be obtained when a catalyst prepared by the reduction of cobalt bis(ethylhexanoate) with triethylaluminum is used. In this connection, all of the subsequent experiments on the synthesis of pyridines were carried out with the aid of this catalytic system.

The cyclocotrimerization of alkoxy- and cycloalkoxypropionitriles Ia-d with acetylene in a ratio of 1:2 in toluene at 150°C for 10 h leads to the corresponding 2-alkoxyethylpyridines IIa-d in rather high yields. Benzene, the percentage of which in the reaction mixture amounts to ∿30%, is formed in each experiment along with pyridines IIa-d. Propionitriles Ie,f (obtained from cyclopropylmethylcarbinol, furfuryl alcohol, and acrylonitrile) react with acetylene to give pyridines IIe, f in yields that do not exceed 65% and 60%, respectively.

It is apparent from Table 1 that the structure of the radical in the ether residue of the propionitrile has an appreciable effect on the overall yields of the cyclooligomers and the amounts of pyridines in the reaction mixtures.



Institute of Chemistry, Bashkir Branch, Academy of Sciences of the USSR, Ufa 450054. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 360-365, March, 1984. Original article submitted April 27, 1983; revision submitted July 27, 1983.

0009-3122/84/2003-0290$08.50

TABLE 1. Cyclocotrimerization of Mono- (Ia-m) and Dinitriles (IIIa-c) with Acetylene under the Influence of a Co(2-Ethylhexanoate)$_2$—Al(C_2H_5)$_3$ Catalyst

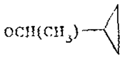
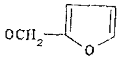
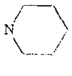
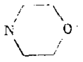
Compound	R	Overall yield, %	Ratio of the reaction products, %	
			II a-m	benzene
Ia	OCH_3	90	80	20
Ib	OC_2H_5	90	79	21
Ic	OC_4H_9	85	70	30
Id	OC_6H_{11}	80	73	27
Ie		50	65	35
If		30	60	40
Ig	$N(C_2H_5)_2$	55	90	10
Ih		70	95	5
Ii		75	98	2
Ij	$N(CH_3)C_6H_5$	60	89	11
Ik	$S—C_2H_5$	33	60	40
Il	$S—C_3H_7$	35	43	57
Im	$S—C_4H_9$	40	30	70

TABLE 1 (continued)

Compound	X	Overall yield, %	Ratio of the reaction products, %	
			IVa-c	Va-c
IIIa	O	90	80	20
IIIb	S	15	98	2
IIIc	NH	65	75	25

A slight decrease in the overall yields of the cyclooligomers is observed when the alkoxy groupings in nitriles Ia-f are replaced by aminoalkyl radicals (Ig-j) however, the selectivity with respect to pyridines IIg-j in these experiments reaches ∿98%. On the other hand, not only the overall yields of the cyclooligomers but also the percentages of 2-alkylthioethylpyridines IIk-m decrease significantly in the cyclocotrimerization of 3-alkylthiopropionitriles Ik-m. The overall yields of cyclooligomers increase somewhat as the length of the hydrocarbon chain in the thioalkyl radical of γ-substituted propionitriles increases, but the selectivity with respect to pyridines IIk-m decreases substantially in this case. In these experiments a significant amount of the acetylene used in the reaction is converted to benzene, the yield of which reaches ∿70% in the experiment with Im.

It may be assumed that alkylthiopropionitriles Ik-m or cyclocotrimerization products IIk-m, which, in contrast to Ia-j, are "hard" electron-donor bidentate ligands, form stable complexes with the central atom of the catalyst, thereby hindering the approach and activation of acetylene molecules. To verify this assumption we investigated the cyclocotrimerization of propionitriles Ia, d, h with acetylene in the presence of catalytic amounts (80 mmole) of added alkylthiopropionitriles Il, m or pyridines IIl, m.

We found that the indicated additives markedly decrease the yields of pyridines IIa, d, h and that the yields of the latter do not exceed ∿25%.

We then investigated the cyclocotrimerization of acetylene with oxygen-, nitrogen-, and sulfur-containing dinitriles IIIa-c under the influence of the Co(ethylhexanoate)$_2$—Al(C_2H_5)$_3$ two-component catalytic system.

Thus dintrile IIIa reacts readily with excess acetylene in the presence of this catalyst under the conditions described above to give 1-pyridyl-5-cyano-3-oxapentane (IVa) and 1,5-dipyridyl-3-oxapentane (Va) in ∿90% yield in a ratio of 8:2. Similar results were obtained in experiments with bis(β-cyanoethyl)sulfide (IIIb), which forms pyridines IVb and Vb

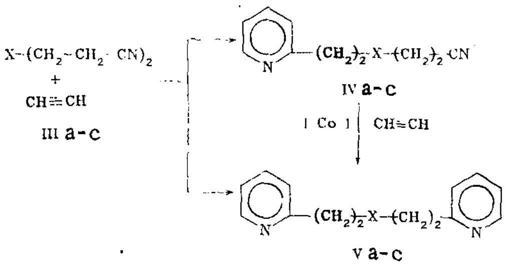
TABLE 2. Constants of IIa-m, IVa-c, and Va-c

Compound	bp, °C (mm)	n_D^{20}	IR spectrum, cm^{-1}	PMR spectrum, ppm	M^+	Found, %			Empirical formula	Calc., %		
						C	H	N		C	H	N
Ia	67 (2)	1,4830	760, 1115, 1580, 2980	2,6 (2H, q, CH_2—C_5H_4N); 3,21 (3H, m, O—CH_3); 3,63 (2H, q, O—CH_2); 6,65—7,2 (4H, C_5H_4N)	137	70,2	7,8	10,0	$C_8H_{11}ON$	70,1	8,0	10,2
Ib	73—74 (2)	1,4850	760, 1120, 1585, 2990	0,92 (3H, m, CH_3); 2,93—3,8 [6H, O$(CH_2)_2$, CH_2—C_5H_4N]; 6,87—8,5 (4H, C_5H_4N)	151	71,4	8,3	9,6	$C_9H_{13}NO$	71,5	8,6	9,3
Ic	102—104 (2)	1,4775	755, 1120, 1590, 2980	0,86 (3H, m, CH_3); 1,38 [4H, t, $(CH_2)_2$]; 2,93—3,8 [6H, O$(CH_2)_2$, CH_2—C_5H_4N]; 6,87—8,5 (4H, C_5H_4N)	179	73,5	9,4	7,8	$C_{11}H_{17}NO$	73,7	9,5	7,8
Id	118—120 (1)	1,5080	760, 1120, 1580, 2820, 2980	1,2 [6H, m, $(CH_2)_3$]; 1,6 [4H, d $(CH_2)_2$—C<]; 2,88 (3H, t, CH_2—C_5H_4N, >CH—O); 3,6 (2H, t, CH_2—O); 6,9—8,26 (4H, C_5H_4N)	205	76,3	9,1	6,9	$C_{13}H_{19}NO$	76,1	9,3	6,8
Ie	140—145 (20)	1,4961	760, 1112, 1590, 2980, 3015	0,33 [5H, d, $(CH_2)_2$CH]; 1,1 (3H, d, CH_3); 2,83 (3H, m, CH_2—O, O—C—H); 3,67 (2H, m CH_2—C_5H_4N); 7,0—8,4 (4H, C_5H_4N)	191	75,2	9,1	7,2	$C_{12}H_{17}NO$	75,4	8,9	7,3
If	60—64 (20)	1,5800	760, 1120, 1560, 3000	2,9—3,78 (4H, O—CH_2, —CH_2—C_5H_4N); 4,4 (2, m, CH_2); 6,5 (2H, d, =CH—CH=); 7,7 (1H, t, O—CH=); 7,2—8,4 (4H, C_5H_4N)	203	71,0	6,5	6,7	$C_{12}H_{13}NO_2$	70,9	6,4	6,9
Ig	74—76 (2)	1,5010	756, 1590, 2810, 2375	0,93 (6H, t, CH_3); 2,4 [4H, d, N$(CH_2)_2$]; 2,73 (4H, m, >N—CH_2, CH_2—C_5H_4N); 6,5—8,12 (4H, C_5H_4N)	178	73,9	10,2	15,6	$C_{11}H_{18}N_2$	74,2	10,1	15,7
Ih	83—85 (1)	1,5255	760, 1560, 2810, 2940	1,56 (6H, m, CH_2); 2,7 (2H, m, —CH_2—N<); 2,54 [4H, d, N$(CH_2)_2$]; 3,0 (2H; m, CH_2—C_5H_4N); 7,14—8,52 (4H, C_5H_4N)	190	75,6	9,6	14,3	$C_{12}H_{18}N_2$	75,8	9,5	14,7
Ii	106—110 (1—2)	1,5200	760, 1595, 3000	2,36 t [4H, t, N$(CH_2)_2$]; 2,73 (4H, d, CH_2—N<, —CH_2—C_5H_4N); 3,86 [4H, t, O$(CH_2)_2$]; 6,01—8,4 (4H, C_5H_4N)	192	67,3	8,5	15,0	$C_{11}H_{16}N_2O$	68,8	8,3	14,6

Ij	148—150 (2)	1,5730	700, 755, 1510, 1605	2,73 (4H, m, >N—CH_2—; CH_2—C_5H_4N); 3,63 (3H, t, CH_3); 6,4—7,08 (5H, C_6H_5); 7,1—8,4 (4H, C_5H_4N)	212	79,3	7,4	13,0	$C_{14}H_{16}N_2$	79,2	7,6	13,2
Ik	70—73 (1—2)	1,5019	750, 1595, 2810, 2970	0,93 (3H, t, CH_3); 2,35 (2H, q, CH_2); 2,53 (4H, d, S—CH_2; CH_2—C_5H_4N); 6,9—8,4 (4H, C_5H_4N)	167	64,6	7,9	8,2	$C_9H_{13}NS$	64,7	7,8	8,4
Il	87—88 (1—2)	1,5025	750, 1580, 2820, 2980	0,88 (3H, d, CH_3); 1,11—1,33 (2H, CH_2); 2,48 [4H, m, $S(CH_2)_2$]; 2,58 (2H, m, CH_2—C_5H_4N); 6,63—8,4 (4H, C_5H_4N)	181	66,1	8,4	7,9	$C_{10}H_{15}NS$	66,3	8,3	7,7
Im	106—108 (1)	1,5120	745, 1580, 2820, 2980	0,83 (3H, t, CH_3); 1,48 d, [4H, d, $(CH_2)_2$]; 2,33 [4H, t, $S(CH_2)_2$]; 2,83 (2H, m, CH_2—C_5H_4N); 6,8—8,3 (4H, C_5H_4N)	195	67,3	8,9	7,4	$C_{11}H_{17}NS$	67,7	8,7	7,2
IVa	132—133 (1)	1,4985	770, 1120, 1590, 2275, 2900	2,73 (2H, t, CH_2—CN); 3,13 (2H, t, CH_2—C_5H_4N); 3,73 q [4H, q, $(CH_2)_2$—O]; 7,17—8,47 (4H, C_5H_4N)	176	68,0	7,1	15,8	$C_{10}H_{12}N_2O$	68,2	6,8	15,9
Va	141—143 (1)	1,5285	760, 1110, 1590, 2900	2,5—3,0 [4H, $(CH_2—C_5H_4N)_2$]; 3,83 [4H, t., $O(CH_2)_2$]; 7,17—8,47 [8H, $(C_5H_4N)_2$]	228	73,9	7,2	12,3	$C_{14}H_{16}N_2O$	73,7	7,0	12,3
IVb	136 (1)	1,5200	730, 1430, 1590, 2270, 2930	2,6 (4H, t, CH_2—CN, CH_2—C_5—H_4N); 2,9 [4H, d, $(CH_2)_2S$]; 7,06—8,4 (4H, C_5H_4N)	192	62,8	6,40	14,5	$C_{10}H_{12}N_2S$	62,5	6,3	14,6
Vb	150—152 (1)	1,5430	780, 1435, 1590, 1710, 2930	2,0 (4H, d, CH_2—$C_5H_4N)_2$; 2,9 [4H, m, $(CH_2)_2S$]; 7,17—8,33 [4H, $(C_5H_4N)_2$]	244	69,0	6,3	11,4	$C_{14}H_{16}N_2S$	68,9	6,6	11,5
IVc	153—155 (1—2)	1,5310	770, 1470, 1510, 2260, 2930, 3400	1,8 (1H, m, >N—H); 2,83 [8H, t, CH_2—C_5H_4N, >$N(CH_2)_2$, CH_2—CN]; 7,17—8,5 (4H, C_5H_4N)	175	68,8	7,4	23,5	$C_{10}H_{13}N_3$	68,6	7,4	24
Vc	180—185 (1—2)	1,5500	765, 1480, 1500, 2930, 3400	1,8 (1H, m, >N—H); 2,83 [8H, t, $(CH_2—C_5H_4N)_2$, CH_2—N—CH_2]; 7,17—8,5 [8H, $C_5H_4N)_2$]	227	74,1	7,6	18,4	$C_{14}H_{17}N_3$	74,0	7,5	18,5

in ∿65% overall yield with acetylene. The cyclocotrimerization of amino nitrile IIIc with acetylene, which leads primarily to 1-pyridyl-5-cyano-3-azapentane (IVc), proceeds with high selectivity. In addition to IVc, the reaction mixture contained ∿2% 1,5-dipyridyl-3-azapentane (Vc). The overall yield of IVc and Vc was ∿15%. All of our attempts to increase the yields of these compounds through changing the nature and structure of the components of the catalyst, the ratio of the monomers, and the reaction conditions were unsuccessful.

Compounds Va-c can be obtained in 95, 80, and 40% yields, respectively, in the cyclocotrimerization of pyridines IVa-c in the presence of the catalyst indicated above and excess acetylene.



III—Va X=O; b X=S; c X=NH

The results obtained in this research made it possible to conclude that the investigated propionitriles Ia-m and IIIa-c have approximately identical reactivities in the reaction with acetylene and that their structures do not affect the direction of the cyclocotrimerization. In addition, the investigation of the indicated reaction made it possible to develop convenient and simple methods for the synthesis of difficult-to-obtain functionally substituted pyridines and dipyridyl-substituted compounds that are of promise as polydentate ligands, complexing agents, and biologically active substances.

EXPERIMENTAL

Monomers with 99% purity were used in the research. Gas-liquid chromatography (GLC) was carried out with a Khrom-41 chromatograph with a flame-ionization detector and a 1.2-m-long column packed with 15% Apiezon on Cyolit-545 with nitrogen as the carrier gas. The PMR spectra of solutions in CCl_4 were recorded with a Tesla BS-467 spectrometer. The IR spectra of mineral oil suspensions were recorded with a UR-20 spectrometer. The mass spectra were obtained with an MKh-1303 spectrometer at an ionizing-electron energy of 70 eV and an ionization-chamber temperature of 200°C.

Cyclocotrimerization of Acetylene with Nitriles Ia-m (general method). A 90-mmole sample of $Al(C_2H_5)_3$ was added in a stream of argon at 0°C to a solution of 30 mmole of Co-(2-ethylhexanoate)$_2$ in 10 ml of toluene, the mixture was stirred for 15 min, and the resulting solution of the catalyst was transferred to a steel autoclave of the C type with a capacity of 1 liter, to which 0.15 mole of nitrile Ia-m and 100 ml of toluene had been previously added, after which 0.3 mole of acetylene was fed into the autoclave (the pressure in the autoclave rose to 13 atm). The autoclave was heated at 150°C for 10 h, after which it was cooled, and the reaction mixture was treated with methanol and filtered. The solution was distilled in vacuo with a Widmer column to give the corresponding pyridine IIa-m and benzene. The yields of pyridines IIa-m and benzene are presented in Table 1, and the constants of the compounds obtained are given in Table 2. The percentages of pyridines IIa-m and benzene were determined from GLC data.

Cyclocotrimerization of Dinitriles IIIa-c with Acetylene. A 120-ml sample of $Al(C_2H_5)_3$ was added to 0°C in a stream of argon to a solution of 40 mmole of Co(2-ethylhexanoate)$_2$ in 15 ml of toluene, and the mixture was stirred for 15 min. The resulting solution of the catalyst was transferred to a 1-liter steel autoclave of the C type, to which 0.1 mole of dinitrile IIIa-c and 100 ml of toluene had been previously added, after which 0.4 mole of acetylene was fed in. The autoclave was heated at 150°C for 10 h, after which it was cooled. The reaction mixture was treated with methanol, and the mixture was filtered and distilled in vacuo to give the corresponding nitriles IVa-c and dipyridyl-substituted compounds Va-c. The yields of nitriles IVa-c and dipyridyl-substituted compounds Va-c and their constants are presented in Tables 1 and 2.

Cyclocotrimerization of Pyridyl Nitriles IVa-c with Acetylene. A solution of the catalyst obtained as indicated above was added to a steel autoclave of the C type, to which 0.1 mole of pyridyl nitrile IVa-c and 100 ml of toluene had been previously added, after which 0.3 mole of acetylene was fed in. The autoclave was heated at 150°C for 15 h, after which it was cooled. The reaction mixture was treated with methanol, and the mixture was filtered and distilled in vacuo to give the corresponding dipyridyl-substituted Va-c.

Cyclocotrimerization of Propionitriles with Acetylene in the Presence of Added Alkylthiopropionitriles. A 120-mmole sample of $Al(C_2H_5)_2$ was added at 0°C in a stream of argon to a solution of 40 mmole of $Co(2\text{-ethylhexanoate})_2$ in 15 ml of toluene, and the mixture was stirred for 15 min. An 80-mmole sample of the corresponding nitrile I*l*, m or pyridine II*l*, m was added, and the mixture was stirred for 20 min. The resulting solution of the catalyst was transferred to a 1-liter steel autoclave, to which 0.1 mole of nitrile Ia and 100 ml of toluene had been previously added, and 0.3 mole of acetylene was fed in. The autoclave was heated at 150°C for 10 h, after which it was cooled. The reaction mixture was decomposed with methanol, and the mixture was filtered in vacuo. Depending on the additive used, the yield of pyridine IIa was 23, 20, 19, or 20%, respectively.

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CONDENSATION OF AZOMETHINES WITH DIMETHYL ACETYLENEDICARBOXYLATE

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UDC 547.462.8'26'551.2'592.12.2'
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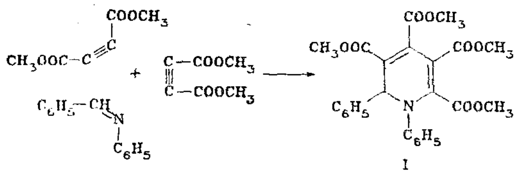
The condensation of dimethyl acetylenedicarboxylate with benzylidene- and cyclohexylideneaniline, as well as with cyclohexylidene-p-toluidine and cyclohexylidene-p-anisidine, under various conditions gave 1:1, 1:2, and 1:3 adducts. The structures of the isolated substances, which are formed as a result of the addition of the ester to the azomethines with subsequent 1,5-prototropic rearrangement (arylcyclohexenylvinylamines), as well as by cycloaddition (substituted dihydropyridines and spiro-cyclohexanedihydropyridines), are discussed.

Information regarding reactions involving the cycloaddition of dimethyl acetylenedicarboxylate (DMAD) to azomethines, which are promising methods for the synthesis of various heterocyclic compounds, is limited. It has been reported [1] that DMAD reacts with benzylidenebenzylamine but does not react with benzylideneaniline. We have studied the latter reaction in absolute ether at room temperature or at 0°C, as well as in hot toluene. It all cases we isolated an adduct of cycloaddition of two molecules of DMAD to benzylideneaniline, viz., 1,2-diphenyl-3,4,5,6-tetramethoxycarbonyl-1,2-dihydropyridine (I), in low yield by means of chromatographic separation of the reaction products. Its structure was confirmed by analytical and spectral (Table 1) data.



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