DETAILS OF PYRIDINE SYNTHESIS BY THE SIMULTANEOUS CYCLOTRIMERIZATION REACTIONS OF SUBSTITUTED ACETYLENES AND NITRILES IN THE PRESENCE OF COBALTOCENE

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The simultaneous cyclotrimerization reaction of acetylenes and nitriles makes it possible to prepare various pyridine derivatives in one step. Cobalt catalysts are generally used as catalysts in these reactions [1, 2]; one of the most readily available cobalt catalysts is cobaltocene (Cc) [3]. The principles of this reaction process, especially in the case of substituted acetylenes and nitriles, have not been adequately investigated.

In the present paper we have examined the simultaneous cyclotrimerization of phenylacetylene (I) and 3-phenoxypropyne (II) with benzonitrile (III) in the presence of Cc. The reaction was carried out in toluene solvent at reflux in the presence of 1-2 mole % Cc.

Reaction products were obtained in up to 97% yields upon the simultaneous cyclotrimerization of (I) or (II) with (III) (Table 1). Trisubstituted isomeric pyridine and benzene derivatives were isolated by preparative chromatography; their structures were established on the basis of IR, PMR, and mass spectral data, as well as the results of elemental analysis. Cyclotrimers derived from (II): 4,6-bis(phenoxymethyl)-2-phenylpyridine, 3,6-bis-(phenoxymethyl)-2-phenylpyridine, and tris(phenoxymethyl)benzene (mixtures of 1,3,5- and 1,2,4-isomers) were prepared first.

As can be seen from the data in Table 1, at a (I):(III) ratio = 2:1 the yield of triphenylpyridines is 43.0%, while at a 1:2 ratio the yield is 53.0%, i.e., a fourfold increase in the concentration of (III) in the reaction mixture does not substantially increase the yield of pyridine derivatives. During the cyclotrimerization of (II) and (III) at a ratio of 1:2 the yield of substituted pyridines is 73.3%. At the same time, the yield of substituted benzenes formed as a result of homocyclotrimerization of (II) is 14.8%, while for (I) it was 30.0%. The symmetrical product predominates in the mixture of pyridine isomers, while in the case of the benzene derivatives the unsymmetrical product predominates. In Table 2 we have shown the ratios of isomeric products obtained in the cyclotrimerization reactions of (I) and (II) with (III), as well as in their homocyclotrimerization reactions in the absence of (III).

Compound	RC₂H: PhCN ratio	Yield, %						
		pyridine isomers			benzene isomers			
		2.4.6-	2,3,6-	total	1,2,4-	1,3.5-	total	
(I) (I) (II)	2:1 1:2 1:2	35,5 37,6 47,0	7,5 15,4 26,3	43,0 53,0 73,3	50,6 28,6 11,9	4,0 1,4 2,9	54,6 30,0 14,8	

TABLE 1. Product Yields in the Simultaneous Cyclotrimerization of Phenylacetylene and 3-Phenoxypropyne with Benzonitrile in the Presence of Cobaltocene

*Deceased.

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Compound	RC ₂ H : PhCN	2,4,6- :2,3,6-py-	1,2,4-:1,3,5-benzene isomers		
Compound	ratio	ridine isomers	in the presence of (III)	in the absence of (III)	
(I) (I) (II)	2:1 1:2 1:2	4,7 2,4 1,8	12,6 20,4 4,1	2,1 2,2	

TABLE 2. Isomer Ratios of Benzene and Pyridine Derivatives Prepared via the Cyclotrimerization of Acetylenes and Their Cyclotrimerization with Benzonitrile

The data in Table 2 indicate that the ratio of symmetrical and unsymmetrical isomers depends on the RC_2H :PhCN ratio and on the structure of the acetylene. An increase in the amount of (III) present in the starting material mixture leads to an increase in the relative amount of unsymmetrical pyridine and benzene isomers.

The following reaction scheme can be postulated, based on the mechanism proposed in [4]:



In the first stage of the reaction intermediates A and B are formed, which contain cobaltacyclopentadiene rings (Co-CPD). These intermediates subsequently coordinate with a molecule of (III), to give pyridine derivatives, or with a molecule of RC₂H to give benzene derivatives. An increase in the concentration of (III) in the reaction medium leads to an increase in the yield of pyridines. The reactivity of the triple bond in acetylene compounds with respect to coordination is determined by the electronic properties of the substituent attached to the triple bond. The reactivity is greater for Ph than for PhOCH2, which explains the higher yield of benzenes and lower yield of pyridines in the case of compound (I), and, conversely, also rationalizes the increased yield of pyridines and reduction in the yield of benzenes in the case of compound (II). Two possible isomers A and B can be obtained in the formation of Co-CPD from unsymmetric acetylenes. The structure of the Co-CPD is influenced apparently by both electronic [5] and steric [6] substituent effects in the acetylene. It has been shown [6] that the reactions of monosubstituted acetylenes are expected to result in a greater probability of formation of intermediate A, which should produce the unsymmetric pyridine isomer upon subsequent reaction with (III). The nitrile apparently coordinates preferentially, however, with the more "accessible" cobalt atom in intermediate metallacycle B, which leads to the formation of the symmetrical pyridine derivative; the Co-cycle A, on the other hand, is consumed primarily in the formation of 1,2,4-substituted benzene. As the concentration of (III) in the reaction medium is increased. the amount of the more polar intermediate A apparently increases as well. This results in enhanced probability for its coordination with both (III) and RC₂H; this explains the increase in the amount of unsymmetric pyridine and benzene isomers as the concentration of (III) is raised. In the absence of (III) in a weakly polar medium, the formation of Co-CPD of the type A and B in the cyclotrimerization of acetylenes is apparently statistical in nature, which leads to the observed statistical distribution of 1,2,4- and 1,3,5-benzene isomers (2:1) upon further reaction of the intermediate Co-CPD with another molecule of RC₂H.

EXPERIMENTAL

IR spectra were recorded on a UR-20 spectrophotometer using KBr pellets, while PMR spectra were obtained on a Bruker WP-200SY spectrometer (in acetone- d_{ϵ} as solvent). Mass spectra were measured on an MS-30 spectrometer. GLC analyses were performed on a Chrom-4 chromatograph equipped with a flame ionization detector, using a 3 × 1000 mm column filled with 3% OV-17 on N-super chromatone, with N_2 as carrier gas, and at 240°C.

<u>Cocyclotrimerization of Phenylacetylene and Benzonitrile</u>. A solution of 29.7 g (0.271 mole) phenylacetylene, 55.3 g (0.542 mole) benzonitrile, and 0.512 g (2.71 mmoles) cobaltocene in 30 ml toluene under an Ar atmosphere was heated with stirring at 110°C for 7 h. The toluene was distilled from the reaction mixture, followed by unreacted starting materials at 100°C (10 mm Hg); the residue (30.2 g) was chromatographed on silica gel. The triphenyl-benzenes were eluted with hexane, the triphenylpyridines with benzene. Yield 7.90 g (28.6%) of 1,2,4-triphenylbenzene, mp 119-120°C (from hexane) (120-121°C [7]); 0.40 g (1.4%) 1,3,5-triphenylbenzene, mp 171-172°C (from AcOH) (172°C [8]); 15.64 g (37.6%) 2,4,6-triphenylpyridine, mp 137-138°C (from ethanol) (137.5°C [9]), picrate mp 192-193°C (192.5°C [10]); 6.26 g (15.4%) 2,3,6-triphenylpyridine, mp 114-115°C (from ethanol) (115°C [11]); picrate mp 169-170°C (163°C [11]), 2,3,6-triphenylpyridine picrate. Found, %: C 64.2; H 3.9; N 10.7. $C_{2,3}H_{17}N\cdot C_{6}H_{3}N_{3}O_{7}$. Calculated, %: C 64.9; H 3.7; N 10.4.

In an analogous manner, reaction of 1.76 g (17.2 mmoles) phenylacetylene, 0.89 g (8.6 mmoles) benzonitrile, and 0.049 g (0.258 mmole) cobaltocene in 6 ml toluene gave 2.1 g of product. Based on GLC analysis the mixture contained 44.8% 2,4,6-triphenylpyridine, 9.4% 2,3,6-triphenylpyridine, 42.4% 1,2,4-triphenylbenzene, and 3.4% 1,3,5-triphenylbenzene, in yields equal to 35.5, 7.5, 50.6, and 4.0%, respectively.

Cocyclotrimerization of 3-Phenoxypropyne and Benzonitrile. A solution of 18.9 g (0.143 mole) 3-phenoxypropyne, 29.5 g (0.296 mole) benzonitrile, and 0.383 g (2 mmoles) cobaltocene in 20 ml toluene was heated with stirring at 110°C for 7 h, under an Ar atmosphere. The toluene was distilled under vacuum [100°C (10 mm Hg)], followed by unreacted starting materials; the residue (22.5 g) was chromatographed on a column with silica gel with CCl₄ as eluent. The first substance to elute was 2.8 g (14.8%) tris(phenoxymethyl)benzene (mixture of 1,2,4- and 1,3,5-isomers, in a ratio of 4.1:1.0, according to PMR spectral data), mp 55-73°C. Found, %: C 82.2; H 6.2. C₂₇H₂₄O₃. Calculated, %: C 81.8; H 6.1. IR spectrum (ν, cm⁻¹): 815, 880 (C₆H₃), 2870, 2930 (CH₂), 1240, 1050 (PhOCH₂). PMR spectrum (δ, ppm): 5.12 s (6H, 1,3,5-isomer, 2H, 1,2,4-isomer, CH₂), 5.28 s (4H, CH₂), 7.31 t (6H, C₆H₅), 6.88-7.12 m (9H, $C_{6}H_{5}$), 7.61, 7.49 q (2H, $C_{6}H_{3}$, J = 8 Hz), 7.56 s (3H, $C_{6}H_{3}$), 7.71 s (1H, $C_{6}H_{3}$). Mass spectrum, m/z: 396 (M⁺), 303 (M⁺-C₆H₅O), 209 (M⁺-C₆H₅O-C₆H₅OH). Eluted next was 12.4 g (47%) of 4,6-bis(phenoxymethyl)-2-phenylpyridine, mp 93-94°C (from hexane). Found, 7: C 81.68; H 5.55; N 3.87. C₂₅H₂₁NO₂. Calculated, %: C 81.74; H 5.72; N 3.81. IR spectrum (v, cm⁻¹): 1050, 1250 ($C_6H_5OCH_2$), 1560 (C=N), 2870, 2930 (CH₂). PMR spectrum (δ , ppm, J, Hz): 5.22 s (2H, CH₂), 5.28 s (2H, CH₂), 6.90-7.50 m (13H, C_6H_5), 7.61 s (1H, C_5H_2N), 7.91 s $(1H, C_5H_2N), 8.18 q (2H, C_6H_5, J = 2).$ Mass spectrum, m/z: 367 (M⁺), 290 (M⁺-C_6H_5), 274 (M⁺-C_6H_5O), 180 (M⁺-C₆H₅O-C₆H₅OH). Further elution with benzene gave 6.9 g (26.3%) 2-phenyl-3,6-bis(phenoxymethyl)pyridine, mp 62-64°C (from hexane). Found, %: C 82.31; H 5.67; N 3.68. C₂₅H₂₁NO₂. Calculated, %: C 81.74; H 5.72; N 3.81. PMR spectrum (δ, ppm, J, Hz): 5.10 s (2H, CH₂), 5.25 s (2H, CH₂), 6.90-7.70 m (15H, C₆H₅), 7.58, 8.04 q (2H, C₅H₂N, J = 8). Mass spectrum, m/z: 367 (M⁺), 290 (M⁺-C₆H₅), 274 (M⁺-C₆H₅O), 180 (M⁺-C₆H₅O-C₆H₅OH).

CONCLUSIONS

The simultaneous cyclotrimerization process of phenylacetylene and 3-phenoxypropyne with benzonitrile has been studied in the presence of cobaltocene. An increase in the amount of nitrile in the starting material mixture increases the concentration of unsymmetrical pyridine and benzene isomers in the reaction products. 3,6- and 4,6-bis(phenoxymethyl)-2-phenylpyridines and tris(phenoxymethyl)benzenes have been prepared and characterized for the first time.

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SULFUR HETEROCYCLES.

12.* REACTIONS OF CYCLIC ANHYDRIDES OF $\beta\text{-SULFINOCARBOXYLIC}$ ACIDS WITH NUCLEOPHILES

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We have recently [2] reported the synthesis of a new class of heterocyclic compounds, namely the internal anhydrides of β -sulfinoalkanoic and o-sulfinobenzoic acids. We here report an examination of the chemical properties of these compounds.

It has been found that both the aliphatic and aromatic mixed anhydrides are hydrolytically unstable, and in air or moist ether they are converted into the sulfinic acids (I)-(IV), which readily disproportionate [3-5]. Treatment of the anhydrides with sodium bicarbonate gives the more stable bis-sodium salts of β -(hydroxysulfinyl)carboxylic acids (V) and (VI).



These same salts (V) and (VI) have been obtained previously from β -sulfinocarboxylic bis-acid chlorides and sodium bicarbonate, but in admixture with sodium chloride [2].

Aminolysis of the aliphatic anhydrides with primary or secondary amines proceeds exothermically with cleavage of the 0-acyl bond to give β -hydroxysulfinylalkanoic acid amides as salts with the amine at the sulfinyl group (Table 1).



o-Sulfinobenzoic acid reacts with amines in a similar way [6]. The structures of the aminolysis products (VII)-(XII) were confirmed by their IR spectra (Table 2), the vSO_2^{\odot} absorption being seen as two bands at 945-970 (symm) and 980-1030 cm⁻¹ (asymm).

Alcoholysis of 1,2-oxathiolan-5-one-2-oxides with equimolar amounts of alcohols also results in O-CO bond fission to give monoesters of β -hydroxysulfinylalkanoic acids at the

*For previous communication, see [1].

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