

SYNTHESIS OF PYRIDYL(TRICHLOROMETHYL)CARBINOLS UNDER  
INTERPHASE-CATALYSIS CONDITIONS

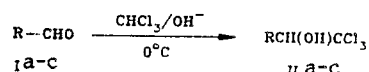
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UDC 547.821.2:541.128

The corresponding pyridyl(trichloromethyl)carbinols were obtained by reactions of 2- and 3-formylpyridine and 6-methyl-2-formylpyridine with chloroform in the presence of aqueous or solid alkali and an interphase catalyst. It is shown that carrying out the reaction in a liquid-solid system is more efficient than in a liquid-liquid system.

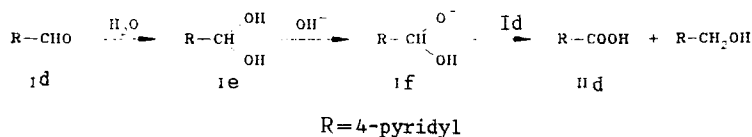
The two-phase  $\text{CHCl}_3$ -50% aqueous NaOH system in the presence of an interphase catalyst is a source of both dichlorocarbene and the trichloromethyl anion. Depending on the nucleophilicity of the substrate and the reaction conditions, the reacting particle is:  $\text{CCl}_2$  or  $\text{CCl}_3^-$  [1]. Aryl(trichloromethyl)carbinols or aryl( $\alpha$ -hydroxy)acetic acids can be obtained by the action of these particles on aromatic aldehydes; the direction of the process depends on the reaction conditions [2]. The behavior of formylpyridines in such systems has not been studied.

In the present research we investigated the transformations of 2-, 3-, and 4-formylpyridine (Ia, b, d) and 6-methyl-2-formylpyridine (Ic) in  $\text{CHCl}_3$ -50% aqueous NaOH solution and  $\text{CHCl}_3$ -solid NaOH in the presence of an interphase catalyst - triethylbenzylammonium chloride (TEBAC).



I, II a R=2-pyridyl; b R=3-pyridyl, c R=6-methyl-2-pyridyl

The corresponding pyridyl(trichloromethyl)carbinols IIa-c, which were isolated in 20-30% yields (Table 1), are formed in the reaction of  $\alpha$ - and  $\beta$ -formylpyridines Ia-c with the  $\text{CHCl}_3$ -50% aqueous NaOH system in the presence of TEBAC at  $0^\circ\text{C}$  for 2-3 h. A similar compound cannot be obtained from  $\gamma$ -aldehyde Id; the corresponding alcohol and acid are formed via the Cannizzaro reaction (the acid was obtained in 41% yield). The difference in the behavior of  $\gamma$ -aldehyde Id from the  $\alpha$  and  $\beta$  isomers is probably due to its ability to readily undergo conversion to hydrate Ie [3, 4], the deprotonation of which in the presence of alkali gives anion If, which is postulated [5] as the key intermediate in the Cannizzaro reaction.



Aldehydes Ia,b are considerably less inclined to undergo conversion to hydrates [3, 4], and the formation of anions of the If type as a result of nucleophilic addition of the  $\text{OH}^-$  anion to the carbonyl group of aldehydes Ia,b under interphase-catalysis conditions is un-

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Translated from Khimiya Geterotsiklicheskih Soedinenii, No. 1, pp. 46-49, January, 1990.  
Original article submitted July 11, 1988.

TABLE 1. Results of the Synthesis of Pyridyl(trichloromethyl)carbinols in Interphase Systems from Formylpyridines with  $\text{CHCl}_3\text{-OH}^-$  in the Presence of TEBAC

Starting aldehyde	Carbinol	mp, * °C	Yield, %	
			liq.-liq.	liq.-solid
Ia	IIa	110 (110 [8])	25	50
Ib	IIb	140 (141 [9])	20	28
Ic	IIc	132	30**	—

\*Compounds Ia, c were recrystallized from ether- $\text{CH}_2\text{Cl}_2$  (1:1), while Ib was recrystallized from  $\text{MeOH-H}_2\text{O}$  (1:1).

\*\*The yield was 21% when chiral catalyst III was used.

likely, since the concentration of  $\text{OH}^-$  ions in chloroform (where the aldehydes are localized) is negligible: extraction of  $\text{OH}^-$  ions into the organic phase by the  $\text{Et}_3\text{N}^+\text{CH}_2\text{Ph}$  quaternary cation does not occur even in the absence of competing more-lipophilic anions, and it is virtually excluded when  $\text{CCl}_3^-$  ions are present [6]. Thus in the  $\text{CHCl}_3\text{-50\% aqueous NaOH}$  system containing TEBAC formylpyridines Ia-c add the trichloromethyl anion, which leads to the formation of the corresponding carbinols IIa-c. 4-Pyridyl(trichloromethyl)carbinol can be synthesized only in an acidic medium by the reaction of aldehyde Id with trichloroacetic acid in dimethyl sulfoxide [7].

Merz and Tomahogh [2] have proposed that the interphase catalyst extracts  $\text{OH}^-$  ions into the organic phase, where deprotonation of chloroform and generation of the  $\text{CCl}_3^-$  anion occur. Subsequently, however, it was established that an "interphase" mechanism rather than an "extraction" mechanism is realized in the  $\text{CHCl}_3\text{-aqueous NaOH}$  system, i.e., deprotonation of chloroform occurs on the interphase boundary, and the catalyst transfers the  $\text{CCl}_3^-$  anion into the volume of the organic phase in the form of an ion pair with the quaternary ammonium cation [1].

The use of solid NaOH in place of 50% aqueous NaOH made it possible to increase the yield of alcohol IIa from 25% to 50% and the yield of alcohol IIb from 20% to 28% (Table 1). 4-Pyridyl(trichloromethyl)carbinol also is not formed from aldehyde Id when solid alkali is used. As in the  $\text{CHCl}_3\text{-50\% aqueous NaOH}$  system, only products of the Cannizzaro reaction were obtained from aldehyde Id. This is evidently due to the presence of a sufficient amount of moisture in the sodium hydroxide.

The literature contains little information (published in recent years) regarding the synthesis of IIa, b. Thus carbinol IIa was obtained only by the reaction of 2-trimethylsilylpyridine with chloral [8], and IIb was obtained by the action of potassium tert-butoxide on aldehyde Ib in chloroform-tert-butyl alcohol [9] and by electrochemical reduction of aldehyde Ib in  $\text{CCl}_4\text{-CHCl}_3$  [10]. Carbinol IIc has not been described in the literature and was obtained by us for the first time. The structures of carbinols IIa-c were confirmed by data from the PMR and mass spectra (Table 2); the parameters of the PMR spectrum of IIa are close to those described in the literature [8].

It is known that benzaldehyde in the  $\text{CHCl}_3\text{-50\% aqueous NaOH}$  system in the presence of TEBAC at an elevated temperature (56°C) is converted to mandelic acid; this is evidently a consequence of a change in the mechanism of the reaction, which takes place under such conditions with the participation of dichlorocarbene [2]. The corresponding pyridyl( $\alpha$ -hydroxy)-acetic acids cannot be obtained via this method from aldehydes Ia-d.

The reaction of benzaldehyde with chloroform in the presence of 50% aqueous NaOH and a chiral interphase catalyst, viz., N-benzylquininium chloride, gives optically active phenyl-(trichloromethyl)carbinol (optical purity 0.84%) [11]. We studied the transformations of aldehyde Ic in the  $\text{CHCl}_3\text{-50\% aqueous NaOH}$  system using chiral ammonium salts, viz., (8S,9R)-N-benzylcinchonidinium chloride (III) and (+)-tubocurarine chloride (IV). In the presence of catalyst III carbinol IIc is formed in 21% yield and displays small optical rotation

TABLE 2. Spectral Characteristics of Pyridyl(trichloromethyl)-carbinols

Compound	PMR spectrum (CDCl <sub>3</sub> /TMS), δ, chemical shifts, ppm							Mass-spectrum,* m/z (I <sub>rel</sub> , %)				
	2-H. m	3-H	4-H. m	5-H. m	6-H. m	CH. s	OH. br.s	CH. s	M <sup>+</sup>	[M-Cl] <sup>+</sup>	[M-CCl <sub>3</sub> ] <sup>+</sup>	[M-CH(OH)] <sup>+</sup> × [CCl <sub>3</sub> ] <sup>+</sup>
IIa	—	7,23...7.84 (m)			8,59	5,20	5,91	—	—	190 (0,3)	108 (100)	78(30)
IIb	8,78	—	7,98	7,31	8,60	5,24	—	—	225 (0,5)	—	108 (100)	78(12)
IIc	—	7,11...7,71 (m)			—	5,15	—	2,59	—	204 (1,2)	122 (100)	92(47)

\*The peaks of the characteristic ions containing the <sup>35</sup>Cl isotope are presented.

([α]<sub>546</sub><sup>21</sup> + 1.5°; c = 1.7, CHCl<sub>3</sub>). Quaternary salt IV does not catalyze the reaction of aldehyde Ic with CHCl<sub>3</sub>-NaOH.

#### EXPERIMENTAL

The PMR spectra of solutions of the compounds in CDCl<sub>3</sub> or D<sub>6</sub>-DMSO were recorded with a Bruker WH-90/DS spectrometer (90 MGz) with tetramethylsilane as the internal standard. The mass spectra were recorded with a Kratos MS-25 chromatographic mass spectrometer (70 eV) and an MS-50 mass spectrometer (70 eV). Analysis of the reaction mixtures by GLC was carried out with a Chrom-4 chromatograph with a flame-ionization detector and a glass column (1.2 m by 3 mm) packed with 5% OV-17 on Chromosorb W/AW (60-80 mesh). The carrier gas was helium (60 ml/min), and the column temperature was 200°C.

In the research we used 2-, 3-, and 4-formylpyridines, triethylbenzylammonium chloride (TEBAC). Fluka (8S,9R)-N-benzylcinchonidinium chloride (III) ([α]<sub>D</sub><sup>20</sup> - 163.3° (c = 1.0, CHCl<sub>3</sub>)), Fluka (+)-tubocurarine chloride pentahydrate (IV) ([α]<sub>D</sub><sup>20</sup> +195 ± 5° (c = 0.5 water)), Aldrich 6-methyl-2-formylpyridine and Chemapol sodium hydroxide.

The results of elementary analysis for the previously undescribed carbinol IIc (C<sub>8</sub>H<sub>8</sub>Cl<sub>3</sub>NO) for C, H, and N were in agreement with the calculated values.

Synthesis of Pyridyl(trichloromethyl)carbinols (general method). A 0.64-ml sample of a 50% aqueous solution of NaOH (12 mmole) or 0.48 g (12 mmole) of solid pulverized sodium hydroxide was added to a cooled (to 0°C) solution of 19 mmole of aldehyde Ia-c and 0.023 g (0.1 mmole) of TEBAC (or 0.1 mmole of III or IV) in 25 ml of chloroform (30 mmole) at such a rate that the temperature did not exceed 0-5°C, after which the mixture was stirred for another 2-3 h at 0°C with periodic selection of a sample with a microsyringe and analysis of GLC until the starting aldehydes had vanished from the reaction mixtures. After this, 5 g of ice was added, the mixture was neutralized with concentrated HCl (1.2 ml), and the organic phase was separated. The aqueous phase was extracted with chloroform, the chloroform extracts were combined and washed with 5% NaHCO<sub>3</sub> solution and dried over MgSO<sub>4</sub>, and the chloroform was removed by distillation. The residue was recrystallized from ether-methylene chloride or methanol-water (1:1). The results of the experiments are presented in Table 1; data from the PMR and mass spectra of pyridyl(trichloromethyl)carbinols IIa-c are presented in Table 2.

Pyridine-4-carboxylic Acid (IIId). A 0.64-ml sample of a 50% aqueous solution of NaOH (12 mmole) was added dropwise at 0°C in the course of 1 h to a solution of 1.07 g (10 mmole) of 4-formylpyridine and 0.023 g (0.1 mmole) of TEBAC in CHCl<sub>3</sub>, and the mixture was stirred for another 2 h. Ice and chloroform were added. Analysis by GLC provided evidence that the organic layer contained the 4-pyridylcarbinol (~ 45% yield according to GLC). The aqueous layer was separated and acidified with concentrated HCl to pH 3.6 (the isoelectric point of acid IIId [5]). The precipitate was recrystallized from water to give 0.5 g of colorless crystals of acid IIId (41% yield) with mp 315°C (mp 311°C [5]). The PMR spectrum of a solution in D<sub>6</sub>-DMSO and the mass spectrum coincided with the data for acid IIb in catalogs [12, 13].

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SYNTHESIS OF TRICHLOROMETHYL-SUBSTITUTED AZINES FROM DICHLOROMETHYL-SUBSTITUTED AZINES AND CARBON TETRACHLORIDE UNDER INTERPHASE CATALYSIS CONDITIONS

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UDC 547.861.2'821.411'  
412.133.541.128.13

The reactions of 2- and 3-dichloromethylpyridines and dichloromethylpyrazine with carbon tetrachloride in the presence of aqueous or solid alkali and an interphase catalyst lead to the corresponding trichloromethyl-substituted azines. The  $\text{CCl}_4$ -solid KOH-18-crown-6 system, in the use of which trichloromethyl-substituted heterocycles were obtained in preparative yields, was the most effective.

Among the diverse reactions with the participation of carbanions generated by the action of alkali hydroxides on CH acids in two-phase systems in the presence of interphase catalysts, halogenation processes with the participation of perhaloalkanes are of particular interest. These compounds, particularly carbon tetrachloride, are strong electrophiles that react with the carbanions with the formation of halogenated products that, depending on the structure, may be final products or may undergo successive transformations [1, 2]. It was recently shown that benzal chlorides that contain electron-donor (Me, Et) or electron-acceptor ( $\text{NO}_2$ , Cl) substituents in the ring are converted to the corresponding substituted benzotrichlorides in good yields in the system  $\text{CCl}_4$ -50% aqueous NaOH solution in the presence of (n-dodecyl)trimethylammonium chloride [3, 4].

In a continuation of our research on the synthesis of polychloromethyl-substituted azines [5] in our present research we studied the reactions of dichloromethyl derivatives of pyridine and pyrazine with  $\text{CCl}_4$  in the presence of alkali under interphase-catalysis conditions in order to obtain the corresponding trichloromethyl-substituted azines. The starting 2-dichloromethylpyridine (I) and dichloromethylpyrazine (III) were obtained by free-radical chlorination of, respectively,  $\alpha$ -picoline and methylpyrazine with N-chlorosuccinimide; 3-dichloromethylpyridine (II) was synthesized by the reaction of 3-formylpyridine with phosphorus pentachloride [5]. The reactions of dichloromethyl-substituted azines I-III with  $\text{CCl}_4$  were carried out using a 50% aqueous solution of NaOH in the presence of catalytic amounts of a quaternary ammonium salt (system A: liquid-liquid) or solid KOH in the presence of 18-crown-6

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Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga 226006.  
Translated from *Khimiya Geterotsiklicheskikh Soedinenii*, No. 1, pp. 50-53, January, 1990.  
Original article submitted July 12, 1988.