HOMOLYTIC AMINATION OF BENZO-1,4-DIOXANE

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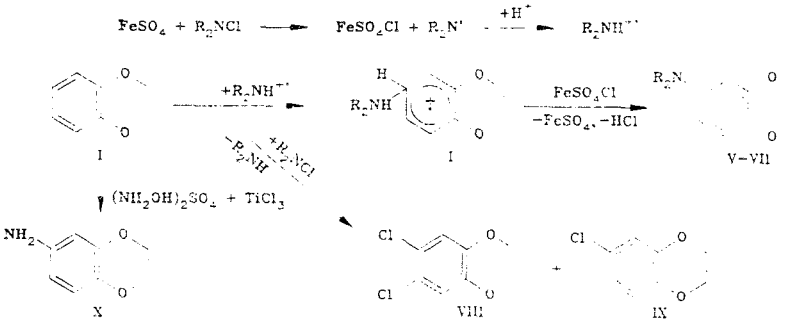
UDC 547.841'565:542.958.3

When 5,6-benzo-1,4-dioxane was reacted with N,N-dialkylchloramines in the presence of $FeSO_4$ at 10-20°C in a solution of acetic and sulfuric acids, 6-(N,N-dialkylamino)benzo-1,4-dioxanes and 6-chloro- and 6,7-dichlorobenzo-1,4-dioxanes were obtained. Under the conditions used in the study mainly chlorination products were synthesized. Reaction of 5,6-benzo-1,4-dioxane with the system $(NH_3OH)_2SO_4$–$TiCl_3$ resulted in the formation of 6-aminobenzo-1,4-dioxane.

Amination of aromatic compounds by treatment with N-alkyl- and N,N-dialkyl-chloramines in the presence of bivalent iron salts results in the formation of the corresponding aromatic N-alkyl- and N,N-dialkyl-amino derivatives [1, 2]. However, in the case of aromatic compounds that contain electron-donating substituents the process is accompanied by an electrophilic chlorination reaction and corresponding chlorinated derivatives are formed together with the amination products [1, 2].

In the present work we have studied the possibility of obtaining amino derivatives of 5,6-benzo-1,4-dioxane by aminating it using the systems N,N-dialkylchloramine–$FeSO_4$ and $(NH_3OH)_2SO_4$–$TiCl_3$. It was established that when 5,6-benzo-1,4-dioxane (I) is reacted with N,N-dimethyl-, N,N-diethyl-, and N,N-dipropyl-chloramines (II-IV) in the presence of $FeSO_4$ in a solution of acetic and sulfuric acids (CH_3COOH:H_2SO_4 = 1:5 by volume) at 10-20°C and with an equimolar ratio of reactants I-II (or III, IV) to $FeSO_4$, 6-(N,N-dimethylamino)-, 6-(N,N-diethylamino)-, and 6-(N,N-dipropylamino)-benzo-1,4-dioxanes (V-VII) are formed with yields of 15, 30, and 9%, respectively, and in all cases dialkylamines and 6,7-dichlorobenzo-1,4-dioxane (VIII) are formed in 30-50% yield with approximately 70-80% conversion of the initial compound I.

According to the accepted mechanism [1, 2] for homolytic amination of aromatic compounds, formation of products (V-VII) occurs via a stage involving an intermediate radical cation σ-complex (Ia).



II, V R=CH_3; III, VI R=C_2H_5, IV, VII R=C_3C_7

The selective formation of 6-(N,N-dialkylamino) derivatives and the absence of other positional isomers is most likely due to the greater probability of forming the thermodynamically most favorable σ-complex Ia compared to its isomers. When the concentration of the N,N-dialkylchloramine is reduced by a factor of 2-5, the yields of products V-VIII and the degree of conversion of the initial compound I decrease and 6-chlorobenzo-1,4-dioxane

Ufa Petroleum Institute, Ufa 450062. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 316-318, March, 1989. Original article submitted July 13, 1987; revision submitted December 15, 1987.

0009-3122/89/2503- 0261$12.50

(IX) – the product derived from monochlorination of the initial compound – is mainly formed. The formation of products VIII and IX evidently occurs as a result of electrophilic chlorination [1] of compound I on treatment with N,N-dialkylchloramines II-IV.

When the concentration of N,N-dialkylchloramines is increased by a factor of 3-5, there is no increase in the yield of products V-VII.

As the concentration of ferrous sulfate increases, the conversion of substrate I decreases substantially. The latter is most likely due to an increase in the rate of reduction of aminyl radical cations formed during the reaction by $FeSO_4$ [1], which reduces the proportion of radical cations taking part in the reaction with benzodioxane I. Thus, under the conditions used in the study it was not possible to obtain the required products V-VII in high yield.

In contrast to the reactions reported above, when 5,6-benzo-1,4-dioxane (I) is reacted with hydroxylamine sulfate in the presence of titanium trichloride in a water–acetic acid solution (H_2O:CH_3COOH = 1:2.5 by volume) at 20°C and with a molar ratio of reactants I: $(NH_3OH)_2SO_4$:$TiCl_3$ = 1:3:3, 6-aminobenzo-1,4-dioxane (X) is formed in 58% yield with approximately 70% conversion of the initial compound I. A threefold excess of hydroxylamine sulfate and titanium trichloride relative to the substrate is necessary to achieve about 70% conversion of the initial compound I. When there is an equimolar ratio of the reactants the conversion of benzodioxane I does not exceed 40%. Apparently, in this case, as in the reaction of N,N-dialkylchloramines with $FeSO_4$, some of the aminyl radicals ($NH_3^{+\cdot}$) formed decompose by reduction with $TiCl_3$ and do not participate in the amination of dioxane I.

It is possible to obtain products V-VII in 70-90% yield by N-alkylation of compound X with methyl iodide, ethyl bromide, or propyl bromide in the presence of NaOH.

EXPERIMENTAL

Homolytic Amination of 5,6-Benzo-1,4-dioxane (I) with N,N-Dialkylchloramines II-IV. This was carried out in a glass reaction vessel placed in an ice bath and fitted with a mechanical stirrer. A solution of compound I (20 mmole) in a mixture of acetic and sulfuric acids and the required quantity of N,N-dialkylchloramine were added to the vessel and the mixture was cooled to 10°C. A calculated quantity of $FeSO_4 \cdot 7H_2O$ was then added with agitation over a period of 30 min, the temperature of the reaction mixture increased to 20°C as this took place. The mixture was agitated for a further 30 min, poured into ice-cold water, treated with a 30% solution of NaOH until pH 10 was reached, and extracted with ether (3 × 100 ml). The ether extracts were dried over Na_2SO_4, the ether was evaporated, and the reaction mixture was separated by means of liquid chromatography on a 20 cm column of Al_2O_3 (40-250 μm). The eluent used was a mixture of ether and hexane in the ratio 1:5.

The elemental analysis data for C, H, and N corresponded to the calculated figures.

Reaction of 5,6-Benzo-1,4-dioxane (I) with the System $(NH_3OH)_2SO_4$–$TiCl_3$. This was carried out in a glass reaction flask fitted with a magnetic stirrer. To the flask was added 20 mmole of dioxane I in a water–acetic acid solution, 60 mmole of hydroxylamine sulfate, and 60 mmole of a 15% solution of $TiCl_3$ was added dropwise with agitation over a period of 15-20 min. The mixture was agitated for a further 30 min at room temperature. Unreacted substrate I was extracted with ether, the ether was evaporated, and the residue weighed (~30% of the initial compound had not reacted). The aqueous layer was treated with a 30% solution of NaOH until it gave an alkali reaction and was then extracted with ether (3 × 100 ml). The ether extracts were dried over Na_2SO_4, the ether was evaporated, and the extract was analyzed by GLC. Yield of compound X was 58% with conversion of the initial compound I of approximately 70%. An LKhM18 MD chromatograph was used with a thermal conductivity detector. The chromatographic system used for analysis was: 2 m column, 20% SKTFT, 50Kh on Chromaton NAW, programmed temperature regime 100-250°C, 6°C/min. Helium carrier gas was used, with a throughput of 2.0 liters/h. Dioxane X was isolated by liquid chromatography on a column as described above.

Synthesis of Compounds (V-VII). This was carried out in a glass tube at 100°C by alkylation of 6-aminobenzo-1,4-dioxane with methyl iodide, ethyl bromide, and propyl bromide, respectively, in the presence of alkali. For this purpose a benzene solution of 6.6 mmole of 6-aminobenzo-1,4-dioxane, 15 mmole of alkyl halide, and 10 mmole of NaOH were added to the glass tube. The tube was sealed and thermostated on a water bath for 6 h at 100°C.

When the reaction was complete, the benzene was evaporated and the required product separated on a column as described above. Yields of products V-VII were 1.07, 1.1, and 1.1 g, respectively.

Compounds V-X were identified from their PMR spectra and elemental analysis data. PMR spectra were recorded at 20°C on a Tesla BS-497 spectrometer (100 MHz) in $(CD_3)_2CO$, with HMDS as internal standard.

6-(N,N-Dimethylamino)benzo-1,4-dioxane (V, $C_{10}H_{13}NO_2$): n_D^{20} 1.5685. PMR spectrum: 2.64 [6 H, m, $(CH_3)_2N$]; 4.03 (4 H, s, $2CH_2O$); 6.04-6.22, 6.46-6.68 ppm (3 H, m, C_6H_3).

6-(N,N-Diethylamino)benzo-1,4-dioxane (VI, $C_{12}H_{17}NO_2$): n_D^{20} 1.5518. PMR spectrum: 0.88 (6 H, t, $2CH_3$), 3.1 [4 H, q, $(CH_2)_2$]; 3.96 (4 H, s, $2CH_2O$); 5.95-6.16, 6.46-6.60 ppm (3 H, m, C_6H_3).

6-(N,N-Dipropylamino)benzo-1,4-dioxane (VII, $C_{14}H_{21}NO_2$): n_D^{20} 1.5430. PMR spectrum: 0.76 (6 H, t, $2CH_3$); 1.4 (4 H, m, $2CH_2$); 3.0 [4 H, t, $(CH_2)_2N$]; 4.0 (4 H, s, $2CH_2O$); 6.0-6.16, 6.48-6.62 ppm (3 H, m, C_6H_3).

6,7-Dichlorobenzo-1,4-dioxane (VIII, $C_8H_6Cl_2O_2$): mp 150°C. PMR spectrum: 4.23 (8 H, s, $2CH_2O$); 6.94 ppm (2 H, s, $C_6H_2Cl_2O_2$).

6-Chlorobenzo-1,4-dioxane (IX, $C_8H_7ClO_2$): bp 253-255°C. n_D^{20} 1.5620. PMR spectrum: 4.08 (4 H, s, $2CH_2O$); 6.62-6.78 ppm (3 H, m, C_6H_3).

6-Aminobenzo-1,4-dioxane (X, $C_8H_9NO_2$): n_D^{20} 1.5998. PMR spectrum (in CCl_4): 3.56 (2 H, s, NH_2); 3.98 (4 H, s, $2CH_2O$); 5.98 s, 6.32-6.48 ppm (3 H, m, C_6H_3).

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CHEMISTRY OF ISOFLAVONE HETEROANALOGS.

12.* BENZODIOXANE ANALOGS OF FLAVANONE AND ISOFLAVONE

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UDC 547.814.5'841.07:543.422.25:615.272.4

Benzodioxane analogs of chalcones were isomerized to the corresponding flavanones and isoflavones. The PMR and IR spectra of these compounds were discussed.

Silibine [2, 3] and some of its derivatives [4, 5] are well-known natural complex flavanoids, which possess considerable biological activity, for example, antihepatotoxic activity. Since silibine contains the benzodioxane fragment and such compounds with a different oxidation state have not been obtained, we undertook to synthesize and study the properties of benzodioxane analogs of some flavonoids, which are simpler than silibine, (2R,3R)-3,5,7-trihydroxy-2-[(2R*,3R*)-3-(4-hydroxy-3-methoxyphenyl)-2-hydroxymethyl-6-benzodioxane-1,4-yl]-4-chromanone. We have recently reported the synthesis of various analogs of silibine such as chalcones, flavones, and isoflavones containing the 1,4-benzodioxan-6-yl group [1]. The present communication gives further results in this study.

*For Communication 11, see [1].

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 319-323, March, 1989. Original article submitted November 4, 1987.