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Mechanism of Meerwein Arylation of Furan Derivatives

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Abstract—Catalytic arylation of furan-2-carbaldehyde with arenediazonium salts was studied. The yields of 5-arylfuran-2-carbaldehydes were found to depend on the solvent, catalyst, and anion in the arenediazonium salt. Redox catalysis and generation of aryl radicals are not sufficient conditions for the reaction to occur. The reaction is successful only under conditions ensuring formation of complex intermediates. A mechanism involving two $Cu^{2+} \leftrightarrow Cu^{+}$ catalytic series and generation of furan-2-carbaldehyde was proposed.

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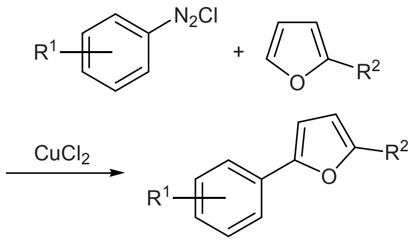
Interest in arylation of furan derivatives is largely determined by prospects in searching for biologically active substances among compounds of the furan series. Many furan derivatives are used as medicines [1, 2]. Such medicines as Nitrafudan, Dantrolene, Clodanolene, and Azimilide contain an arylfuran fragment. Numerous arylfuran compounds exhibit versatile biological activity [2–5]. A convenient method for the synthesis of arylfurans is copper-catalyzed arylation of furan derivatives with arenediazonium salts according to Meerwein [4, 6–12]. These reactions were reported mainly for 2-substitued furans which underwent arylation at the 5-position (Scheme 1).

Scheme 1.



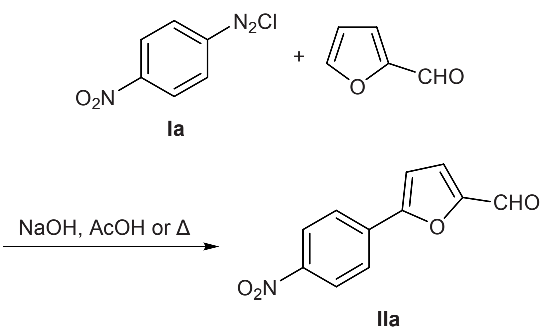
R^2 = CHO, COOH, COOR, CH_2OH, COMe, CN, COCHO, COCOOH.

Arylation of furfurol was reported most commonly. Reactions of furan compounds with diazonium salts are usually carried out under conditions similar to Meerwein reaction which is most typical of unsaturated compounds. Homolytic arylation of furan ring as an aromatic system (Gomberg reaction) is also known [7, 13]. Presumably, copper-catalyzed arylation of furan derivatives follows a mechanism similar to one of the above reactions. In the first case, the reaction is redox catalytic, and it involves intermediate copper complexes [14, 15], while in the second radical arylation occurs [7, 13]. The ESR and polarographic data indicated generation of a radical adduct (arylfuryl radical) [16, 17], and radical mechanism of the process was proposed.

We performed a series of experiments on the arylation of furfurol with a view to elucidate in detail mechanism of this reaction. The following modes of generation of aryl radicals were tried: decomposition of *N*-nitrosoacetanilide, decomposition of diazonium salts in alkaline medium, on heating, and in the presence of potassium iodide, thermal and catalytic decomposition of diaryliodonium salts, reduction of diazonium salts with ascorbic acid, and their electrochemical reduction. The reagents and conditions were selected in such a way that the formation of intermediate complexes by the catalyst [Cu(I) or Cu(II)] with furfurol and diazonium salt be either favored or completely excluded.

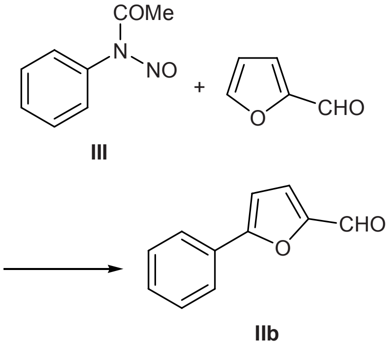
Using 4-nitrobenzenediazonium chloride (**Ia**) as an example we examined decomposition of diazonium salt in the presence of furfurol in alkaline medium (Gomberg reaction conditions) and on heating (Scheme 2). In the first case, 5-(4-nitrophenyl)furan-2-carbaldehyde (**IIa**) was obtained in 9% yield, and in the second case the yield of **IIa** was 11.5%. In both cases, the reactions were accompanied by considerable tarring. Standard Meerwein reaction conditions ensure 50–60% yield of aldehyde **IIa**. In the reaction of fur-

Scheme 2.



furol with *N*-nitrosoacetanilide (**III**), which is known as a good radical arylation reagent [18, 19], 5-phenylfuran-2-carbaldehyde (**IIb**) was formed in as poor as 10% yield (Scheme 3).

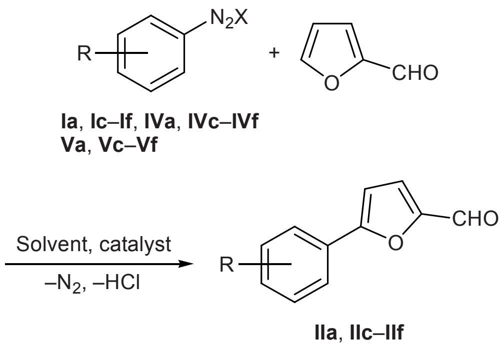
Scheme 3.



Aryl radicals can also be generated by decomposition of diaryliodonium salts [20, 21]. However, we failed to synthesize aldehydes **IIa** and **IIb** from furfurol and diaryliodonium chloride according to Meerwein (water, acetone, $CuCl_2$). Iodine-induced dediazonation [21, 22] of 4-nitrobenzene- and benzenediazonium tetrafluoroborates **IVa** and **IVb** (ArN_2BF_4 + KI) in the presence of furfurol gave only ~5% of arylfurans **IIa** and **IIb**, though aliphatic unsaturated compounds are known to readily undergo arylation under analogous conditions [22, 23]. Ascorbic acid was reported to effectively reduce diazonium salts to aryl radicals [24]. The reaction of 4-nitrobenzenediazonium chloride (**Ia**) with furfurol in the presence of an equimolar amount of ascorbic acid afforded only 15% of aldehyde **IIa**. We also examined reactions of furfurol with electrochemically generated aryl radicals. The latter were generated in two modes using an "inert" platinum electrode and a copper anode [25]. Electrochemical reduction of 4-nitrobenzenediazonium chloride (**Ia**) in the presence of furfurol using a copper plate as anode produced aldehyde **IIa** in 35% yield. Copper dissolved to give cations which catalyzed the reaction. When analogous experiment was performed in the absence of chloride ion (4-nitrobenzenediazonium tetrafluoroborate was used as starting compound), the yield of aldehyde **IIa** decreased to 7%. Only traces of **IIa** were formed from $4\text{-}O_2NC_6H_4N_2Cl$ and furfurol in the presence of copper when no electric current was passed through the system. Insignificant amounts of aldehyde **IIa** (3–5%) were obtained by electrochemical reduction of 4-nitrobenzenediazonium tetrafluoroborate (**IVa**) at a platinum electrode in the presence of furfurol, regardless of the potential applied. Thus, in all experiments described above the yields of 5-arylfuran-2-carbaldehydes **IIa** and **IIb** were considerably lower than in copper-catalyzed reactions of furfurol with diazonium salts or these compounds were not formed at all. These data suggest that the reaction of furfurol with arenediazonium salts follows a more complicated mechanism than radical arylation. Redox catalysis is not a sufficient condition, and it is not confined to reduction of diazonium ion. Insofar as electrochemical version with arenediazonium chlorides is characterized by a satisfactory yield, while arenediazonium tetrafluoroborates give rise to insignificant amounts of 5-arylfuran-2-carbaldehydes, chloride ion is likely to be involved in complex formation as a ligand [14, 15].

Taking into account that arylation with diazonium salts is usually carried out in aqueous acetone in the presence of $CuCl_2$, it was presumed [10, 26] that such reactions are catalyzed by CuCl generated by reaction of $CuCl_2$ with acetone. However, this statement cannot be regarded as indisputable [14, 15]; therefore, we examined in more detail the conditions for arylation of furfurol with a view to optimize the yield and elucidate effects of different factors on the reaction course. For this purpose, the arylation of furfurol was performed

Scheme 4.



R = 4-O_2N (**a**), 3-O_2N (**c**), 4-Cl (**d**), 4-Br (**e**), 3-Cl (**f**);
I, X = Cl; **IV**, X = BF_4; **V**, X = HSO_4.

using various solvents and catalysts and arenediazonium salts with different anions (Scheme 4).

The arylation of furfurol with arenediazonium salts **Ia** and **Ic**–**If** in aqueous chloroform, diethylene glycol dimethyl ether, and acetonitrile afforded the corresponding aldehydes **II** in poor yield, and the process was accompanied by considerable tarring. The yield of **II** increased in going to aqueous acetone, while the most appropriate solvent systems (see table) were DMF–water (1 : 1) and DMSO–water (1 : 1). In the latter system the yields of 5-arylfuran-2-carbaldehydes increased on the average to 60%. Analogous yields were obtained in water, but the reaction was very slow: the conversion of initial diazonium salt was complete in 3 days at room temperature.

As catalyst we tried copper(II) acetate and copper(II) sulfate in addition to commonly used $CuCl_2$. The catalyst strongly affected the arylation of furfurol with arenediazonium chlorides **Ia** and **Ic**–**If**. The arylation efficiency was considerably lower when freshly prepared copper(I) chloride was used as catalyst (run nos. 9, 10). These findings contradict a scheme according to which the initial step is electron transfer from Cu(I) to diazonium ion to form aryl radical [26].

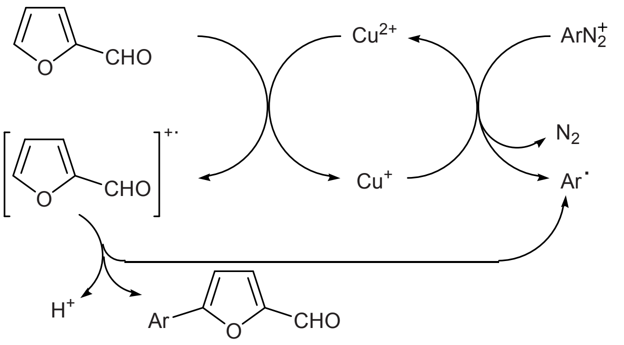
In order to estimate the effect of counterion in arenediazonium salt, the arylation of furfurol with arenediazonium hydrogen sulfates **Va** and **Vc**–**Vf** and tetrafluoroborates **IVa** and **IVc**–**IVf** was examined. Arenediazonium hydrogen sulfates **Va** and **Vc**–**Vf** failed to react with furfurol (run nos. 11–13). The reactions of furfurol with arenediazonium tetrafluoroborates **IVa** and **IVc**–**IVf** were carried out in aqueous acetone (1 : 1), anhydrous DMSO, and aqueous DMSO (1 : 1) in the presence of CuCl, $CuSO_4$, $Cu(OAc)_2$, and $CuCl_2$. Copper(I) chloride, copper(II) sulfate, and copper(II) acetate did not catalyze the process (run nos. 14–16). The reaction was fast and efficient in aqueous DMSO (1 : 1) in the presence of $CuCl_2$ (run no. 1): the yields of arylfurancarabaldehydes **II** attained 75–80%. The reaction in anhydrous DMSO (run no. 5) occurred at a considerably lower rate (3–4 days), and the yields were smaller.

It should be emphasized that the best results are obtained with $CuCl_2$ as catalyst, while CuCl does not catalyze the reaction at all, other conditions being equal (cf. run nos. 1 and 15). Obviously, the role of DMSO is important: in going from DMSO to acetone (run nos. 7, 9), the difference in the catalytic activity of $CuCl_2$ and CuCl becomes less significant. The presence of chloride ion (even in a catalytic rather than equimolar amount) is crucial. In the reaction under study chloride ion is not necessary for oxidation of radical (radical adduct) with ligand transfer in the final step, as in the classical Meerwein chloroarylation of unsaturated compounds [15]. Presumably, chloride ion behaves as an active ligand capable of being replaced by diazonium ion or furfurol molecule in the copper coordination sphere in the course of formation and subsequent transformations of intermediate mixed-ligand complexes. Probably, as in the arylation of unsaturated compounds, such intermediate complexes are arenediazonium tetrachlorocuprates(II) [14, 15, 27]. While studying the reaction of arenediazonium sulfate (**IIc**) with furfurol in the presence of $CuSO_4$, different amounts of NaCl were added to the reaction mixture. When the ArN_2HSO_4–$CuSO_4$–NaCl ratio attained a value of 2 : 1 : 4, the yield of aldehyde **IIc** was the same as in the reaction with ArN_2Cl and $CuCl_2$. The above ratio conforms to the arenediazonium tetrachlorocuprate(II) stoichiometry, $(ArN_2^+)_2CuCl_4^{2-}$.

Arylation of furfurol with arenediazonium salts

Run no.	X in ArN_2X	Solvent	Catalyst	Yield, %
1	BF_4	DMSO–water, 1 : 1	$CuCl_2$	75–80
2	Cl	DMSO–water, 1 : 1.25	$Cu(OAc)_2$	61–66
3	Cl	Water	$CuCl_2$	55–60
4	Cl	DMSO–water, 1 : 1	$CuCl_2$	50–60
5	BF_4	Anhydrous DMSO	$CuCl_2$	44–48
6	Cl	DMSO–water, 1 : 1.25	$CuSO_4$	40–46
7	BF_4	Acetone–water, 1 : 1	$CuCl_2$	32–40
8	Cl	Acetone–water, 1 : 1	$CuCl_2$	25–40
9	Cl	Acetone–water, 1 : 1	CuCl	15–20
10	Cl	DMSO–water, 3 : 4	CuCl	8–11
11	HSO_4	DMSO–water, 1 : 1	$CuCl_2$	–
12	HSO_4	DMSO–water, 1 : 1	$CuSO_4$	–
13	HSO_4	Water	$CuCl_2$	–
14	BF_4	DMSO–water, 1 : 1	$CuSO_4$	–
15	BF_4	DMSO–water, 1 : 1	CuCl	–
16	BF_4	DMSO–water, 1 : 1	$Cu(OAc)_2$	–
17	HSO_4	DMSO–water, 1 : 1	$CuSO_4$–NaCl, 1:4	55–58

Scheme 5.



We can conclude that the arylation of furfurol involves intermediate formation of copper coordination compounds. The complexation of $CuCl_2$ with furfurol was confirmed experimentally. The complex was isolated in the reaction of $CuCl_2$ with furfurol in acetone or acetonitrile. The complex is stable; it decomposes at 140°C. Presumably, copper(II) ion coordinates furfurol molecule at the carbonyl oxygen atom: the IR spectrum of the complex contained an absorption band at 1610 cm^{-1} (C=O; 1680 cm^{-1} in the IR spectrum of furfurol). In addition, the C=C stretching vibration band was displaced from 1560 to 1525 cm^{-1} upon complex formation.

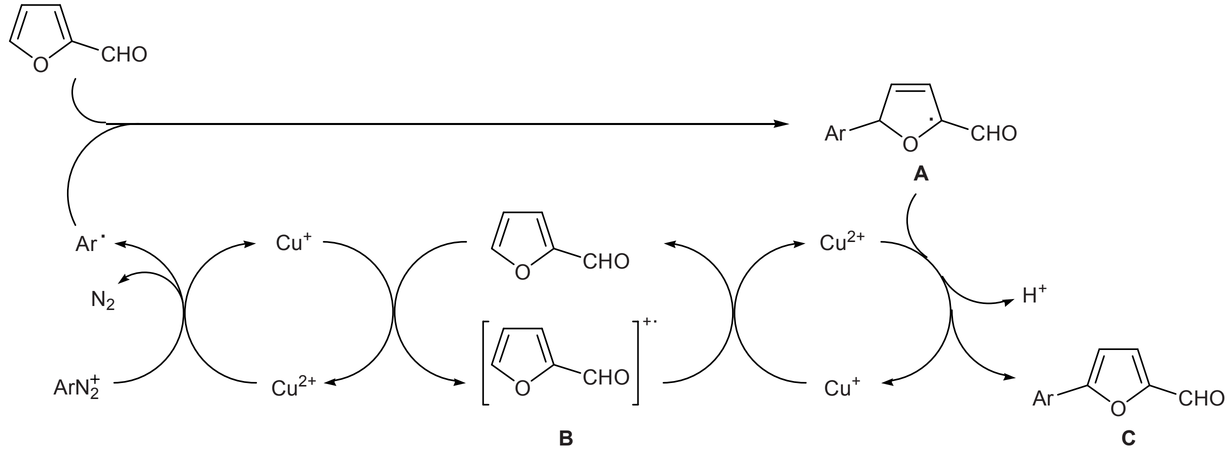
Our results indicate that the reaction is not initiated according to the scheme $ArN_2^+ + Cu^+ \rightarrow Ar^{\cdot} + N_2 + Cu^{2+}$, for the best results were obtained with copper(II) salts under conditions that do not favor their reduction. Then the initial step is copper(II)-mediated electron transfer from the substrate molecule (furfurol) to diazonium ion, as in conventional Meerwein arylation [13, 14, 28]. As a result, furfurol radical cation is formed (Scheme 5), which is fairly typical for heterocyclic compounds [29–31]. Some heterocyclic compounds are capable of undergoing one-electron oxidation with diazonium ions to give radical cations [29]. Obviously, strong furfurol–$CuCl_2$ complexation favors electron transfer. The transformations shown in Scheme 5 may be regarded as ligand interactions inside mixed-ligand copper complexes. If the reaction coordinate involves formation of radical adduct **A** (such adducts were detected by ESR for both furfurol [17] and unsaturated compounds [32]), the reaction scheme should comprise two catalytic cycles with participation of two substrate molecules [14, 15] (Scheme 6).

The catalytic system $Cu^+ \leftrightarrow Cu^{2+}$ mediates electron transfer from furfurol to diazonium ion. Aryl radical thus formed inside activated complex [arenediazonium tetrachlorocuprate(II)–furfurol or arenediazonium salt–catalyst–furfurol] reacts with the second furfurol molecule to give radical adduct **A**. The latter donates an electron through copper(II) ion to radical cation **B** generated in the first cycle with formation of product **C**.

EXPERIMENTAL

Arylation of furfurol according to Gomberg. A solution of 1 g of sodium hydroxide and 16 g of sodium acetate trihydrate in 50 ml of water was added to a mixture of 12.4 ml (0.15 mol) of furfurol and 60 ml of acetone, and an aqueous solution of 4-nitrobenzenediazonium chloride (**Ia**) (prepared by diazotization of 0.1 mol of 4-nitroaniline) was added dropwise under stirring, maintaining the pH value at 5–6 with the aid of acetate buffer. When nitrogen no longer evolved (5 h at 25°C), the mixture was diluted with water, and the oily material was separated and washed with water, alcohol, and diethyl ether. The product

Scheme 6.



solidified and was additionally purified by column chromatography on Al_2O_3 using benzene as eluent. Yield of aldehyde **IIa** 2 g (9%), mp 209–210°C.

The reaction with thermal decomposition of diazonium salt was carried out in a similar way at 35–40°C without addition of NaOH and AcONa. The product was isolated as described above. Yield of compound **IIa** 2.5 g (12%).

Reaction of *N*-nitrosoacetanilide with furfurol. A mixture of 16.4 g (0.1 mol) of *N*-nitrosoacetanilide (**III**), 12.4 ml (0.15 mol) of furfurol, and 120 ml of acetone was stirred at 18–20°C (~4 h). When nitrogen no longer evolved, the mixture was diluted with water and extracted with diethyl ether. The extract was dried over $MgSO_4$, the solvent was distilled off, and the residue was distilled under reduced pressure. Yield of 5-phenylfuran-2-carbaldehyde 1.7 g (10%), bp 132–135°C (2 mm).

Decomposition of diphenyliodonium chloride in the presence of furfurol. A mixture of 12 g (0.038 mol) of diphenyliodonium chloride, 6.6 ml (0.08 mol) of furfurol, 1.5 g of copper(II) chloride dihydrate, 50 ml of acetone, and 50 ml of water was heated for 8 h under reflux with stirring. The mixture was extracted with diethyl ether, the extract was dried over $MgSO_4$, the solvent was distilled off, and the residue was distilled under reduced pressure. We thus isolated iodobenzene and unreacted furfurol. No 5-phenylfuran-2-carbaldehyde (**IIb**) was formed when the reaction was carried out in aqueous dioxane with no catalyst or in the presence of CuCl.

Reaction of benzenediazonium tetrafluoroborate with furfurol in the presence of potassium iodide. Benzenediazonium tetrafluoroborate (**IVb**), 13.7 g (0.07 mol), was added in portions to a mixture of 11.6 ml (0.14 mol) of furfurol, 11.6 g of potassium iodide, 45 ml of acetone and 15 ml of water. Vigorous evolution of nitrogen was observed at 0–10°C. The mixture was treated with sodium thiosulfate until the aqueous phase turned colorless and was then extracted with diethyl ether. The extract was dried over $MgSO_4$ and evaporated, and the residue was distilled under reduced pressure to isolate iodobenzene and 0.6 g (5%) of 5-phenylfuran-2-carbaldehyde (**IIb**), bp 120–123°C (2 mm). The reaction of 4-nitrobenzenediazonium tetrafluoroborate with furfurol was carried out in a similar way. After treatment with sodium thiosulfate, the precipitate was filtered off, washed with water, and purified by column chromatography on Al_2O_3 using benzene as eluent. Yield of aldehyde **IIa** 0.6 g (4%).

Reaction of 4-nitrobenzenediazonium chloride with furfurol in the presence of ascorbic acid. A cold solution of diazonium salt **Ia** prepared by diazotization of 0.05 mol of 4-nitroaniline was added dropwise to a mixture of 7.5 ml (0.09 mol) of furfurol, 8.8 g (0.05 mol) of ascorbic acid, 70 ml of acetone, and 35 ml of water. The mixture was stirred at 20–25°C until nitrogen no longer evolved. The oily material was separated and washed with several portions of water and then with alcohol and diethyl ether. The solid residue was purified by column chromatography on Al_2O_3 using benzene as eluent to isolate 1.6 g (15%) of 5-(4-nitrophenyl)furan-2-carbaldehyde (**IIa**).

Arylation of furfurol with 4-nitrobenzenediazonium salts under conditions of electrochemical reduction. The reaction was carried out in a four-necked reactor equipped with a thermometer, bubble counter, and two electrodes connected to a P5827M potentiostat. A copper plate was used as a working electrode, and a platinum electrode served as an auxiliary electrode. The reaction mixture was stirred with a magnetic stirrer.

The reactor was charged with 50 ml of acetone and 12.5 ml (0.15 mol) furfurol, approximately a half (0.1 mol) of a solution of 4-nitrobenzenediazonium chloride (**Ia**) was added, and a required voltage was supplied to the electrodes. In all cases the current density was 7 mA/cm^2. Nitrogen evolved at 20–30°C. The addition of diazonium solution lasted 1 h. The mixture was stirred until nitrogen no longer evolved (~6 h). The organic layer was separated, washed with water, and evaporated, and the residue was subjected to column chromatography on Al_2O_3 using benzene as eluent to isolate 3.8 g (35%) of 5-(4-nitrophenyl)furan-2-carbaldehyde (**IIa**).

The reaction of 11.8 g (0.05 mol) of 4-nitrobenzenediazonium tetrafluoroborate (**IVa**) with 6.6 ml (0.08 mol) of furfurol in a mixture of 50 ml of acetone and 50 ml of water was carried out for 5 h at 30–35°C, and the process was accompanied by strong tarring. The organic layer was separated, washed with water, and evaporated, and the residue was subjected to column chromatography on Al_2O_3 using benzene as eluent to isolate 0.8 g (7%) of aldehyde **IIa** and 0.35 g (5%) of 4-nitrophenol.

In experiments with inert electrodes, 11.8 g (0.05 mol) of 4-nitrobenzenediazonium tetrafluoroborate (**IVa**) reacted with 6.6 ml (0.08 mol) of furfurol, the working electrode (cathode) being a platinum plate. The reaction was carried out for 8 h at 30–36°C. By column chromatography on Al_2O_3 using benzene as eluent we isolated 0.6 g (5%) of aldehyde **IIa**.

5-(3-Nitrophenyl)furan-2-carbaldehyde (IIc). *Run no. 1.* A mixture of 0.35 g of $CuCl_2 \cdot 2H_2O$, 2.5 ml (0.03 mol) of furfurol, 20 ml DMSO, and 20 ml of water was stirred at 24–26°C. 3-Nitrobenzenediazonium tetrafluoroborate (**IVc**), 7.1 g (0.03 mol), was added in portions, and the mixture was stirred until nitrogen no longer evolved and was left to stand for 24 h. The organic phase was separated, washed with water, and evaporated, and the residue was recrystallized from carbon tetrachloride. Yield 5.0 g (77%), mp 158–159°C. Run nos. 5, 7, and 14–16 followed an analogous procedure.

Run no. 3. A solution of 3-nitrobenzenediazonium chloride (**Ic**), prepared from 3.45 g (0.025 mol) of 3-nitroaniline, 6.5 ml of concentrated hydrochloric acid, 10 ml of water, and 1.8 g (0.026 mol) of sodium nitrite, was added dropwise to a mixture of 0.7 g of $CuCl_2 \cdot 2H_2O$, 2.5 ml (0.03 mol) of furfurol, and 25 ml of water. The mixture was left to stand for two days and diluted with water, and the precipitate was filtered off, washed with water, alcohol, and diethyl ether, and recrystallized from CCl_4. Yield 3.0 g (55%).

Run no. 4. A solution of 3-nitrobenzenediazonium chloride (**Ic**), prepared from 6.9 g (0.05 mol) of 3-nitroaniline, 13 ml of concentrated hydrochloric acid, 10 ml of water, and 3.6 g (0.052 mol) of sodium nitrite, was added dropwise under stirring at 23–26°C to a mixture of 0.7 g of $CuCl_2 \cdot 2H_2O$, 5 ml (0.06 mol) of furfurol, and 50 ml of DMSO. The mixture was stirred until nitrogen no longer evolved and diluted with water, and the precipitate was filtered off, washed with water, alcohol, and diethyl ether, and recrystallized from carbon tetrachloride. Yield 5.6 g (52%). Run nos. 2, 6, and 8–10 were carried out following an analogous procedure.

Reaction of 3-nitrobenzenediazonium hydrogen sulfate with furfurol. *Run no. 12.* A solution of 3-nitrobenzenediazonium hydrogen sulfate (**Ic**), prepared from 6.9 g (0.05 mol) of 3-nitroaniline, 6 ml of concentrated sulfuric acid, 35 ml of water, and 3.6 g (0.052 mol) of sodium nitrite in 15 ml of water, was cooled and added dropwise under stirring to a mixture of 0.8 g of $CuSO_4$, 5 ml (0.06 mol) of furfurol, and 55 ml of DMSO. The mixture was stirred for 3–4 h (slow evolution of nitrogen was observed), left overnight, and dilted with water, and the precipitate was filtered off and washed with water, alcohol, and diethyl ether. The product contained no aldehyde **IIc**. Run nos. 11 and 13 followed an analogous procedure.

Reaction of 3-nitrobenzenediazonium hydrogen sulfate with furfurol in the presence of $CuSO_4$ and NaCl (*run no. 17*). A solution of 3-nitrobenzenediazonium hydrogen sulfate, prepared from 6.9 g (0.05 mol) of 3-nitroaniline, 6 ml of concentrated sulfuric acid, 25 ml of water, and 3.6 g (0.052 mol) of sodium nitrite in 15 ml of water, was added dropwise under stirring at 23–26°C to a mixture of 2 g (0.0125 mol) of $CuSO_4$, 3 g (0.05 mol) of NaCl, 5 ml of (0.06 mol) furfurol, and 40 ml of DMSO. The mixture was left to stand for 24 h and diluted with water, and the precipitate was filtered off, washed with water, alcohol, and diethyl ether, and recrystallized from carbon tetrachloride. Yield of aldehyde **IIc** 6.2 g (57%). At **Vc**–$CuSO_4$–NaCl ratios of 0.05 : 0.0125 : 0.025 and 0.05 : 0.0125 : 0.006 the yield was 5.2 g (48%) and 2.2 g (20%), respectively.

The reactions of diazonium salts **Ia**, **Id–If**, **IVa**, **IVd–IVf**, **Va**, and **Vd–Vf** with furfurol were carried out according to analogous procedures.

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