

Synthesis of Difurfuryl Diamines by the Acidic Condensation of Furfurylamine with Aldehydes and Their Mechanism of Formation

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Difurfuryl diamino compounds can be obtained via single-step reactions of furfurylamine with formaldehyde and other aldehydes in 2.5-5.2 M hydrochloric acid at 20-50 °C. Yields for the single step reaction (30-50%) are comparable to those for three-step procedures involving protection and deprotection of the amino group.

Introduction

In search for renewable replacements for petroleum-based compounds, difurfuryl diamines (see Figure 1) have attracted interest.¹ These compounds, which are based on a difurylalkane moiety, are ultimately derived from furfural, which is potentially available in vast quantities from agricultural waste materials and byproducts of solvent wood-pulping operations.² Difurfuryl diamines can serve as curing agents for epoxy resins.³ In addition, they are readily converted to the corresponding difurfuryl diisocyanates, which can be used as substitutes for the petroleum-based compound diphenylmethane diisocyanate (MDI). Difurfuryl diisocyanates can replace MDI in polyurethane systems⁴ and in adhesives for the production of composite wood products.⁵

Numerous descriptions of the synthesis of difuryl and difurfuryl compounds by the acidic condensation of a furanic compound with an aldehyde or ketone have appeared in the literature. However, most of the reported results have been limited to the reactions of esters of furoic acid⁶⁻⁹ or of furan and/or 2-methylfuran.¹⁰⁻¹⁸ Reasoning based on analogies with the reactions of these

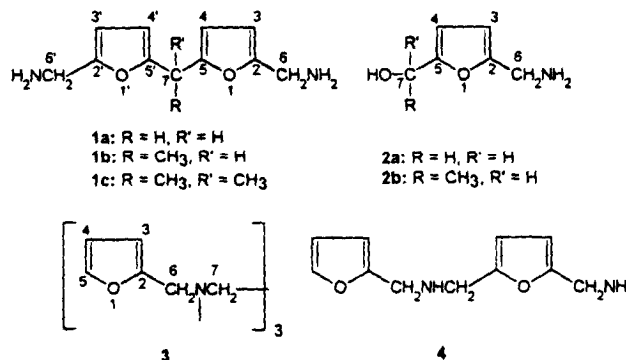


Figure 1. Products of the acid-catalyzed reactions of furfurylamine with aldehydes.

compounds indicates that it should be possible to obtain difurfuryl diamines by the acidic condensation of furfurylamine with an aldehyde. However, the facility with which amino groups react with carbonyl compounds presents a significant complication in reactions with furfurylamine. An earlier attempt to prepare difurfuryl diamines directly from furfurylamine was unsuccessful, and until now, difurfuryl diamines have been obtained only by protecting the amino group as the *N*-formyl derivative during reaction.⁷ We describe here a direct preparation of difurfuryl diamines by the reaction of stoichiometric quantities (2:1) of furfurylamine and an aldehyde in 2.5-5.2 M hydrochloric acid at temperatures from 20 to 50 °C. For the reactions of furfurylamine with formaldehyde

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and acetaldehyde, the putative intermediate 5-(hydroxyalkyl)furfurylamines have been isolated and identified.

Experimental Section

Equipment. $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra were recorded on a Bruker WM250 250 MHz spectrometer. IR spectra were obtained with a Nicolet Model 6000 IR spectrometer. Gas chromatograms of reactants and products were obtained with an HP 7600A gas chromatograph. Low resolution electron impact mass spectra (EIMS) and GC-mass spectra (EIGC) were recorded on a Finnigan Model 4500 mass spectrometer. High resolution electron impact mass spectra (HRMS) were obtained by the Chemistry Instrumentation Center, Department of Chemistry, University of Wisconsin-Madison using a Kratos MS-80RFA with DS55/DS90. Microdistillations were carried out in a Perkin Elmer Model 131T microstill.

Materials. Furfurylamine (QO Chemicals; Memphis, TN) was purified by vacuum distillation. Its identity was verified by $^1\text{H-NMR}$, $^{13}\text{C-NMR}$, and IR spectroscopies and its purity (>99%) by HPLC and GLC. Acetaldehyde (Fluka, Switzerland), 35 wt % formaldehyde solution (Fischer; Fairlawn, NJ), hydrochloric acid (Baker; Phillipsburg, NJ), sodium hydroxide (Mallinckrodt; Paris, KY), and hydroxylamine hydrochloride (Aldrich; Milwaukee, WI) were used without additional purification.

Methods. The final product distributions were determined by gas chromatographic analyses of reaction samples, using methyl stearate as an internal standard. The analyses were performed on a methyl silicone gum capillary column (Hewlett-Packard HP-1, 0.53 mm i.d., 5 m length, 2.65 μm film thickness). Helium (17 mL/min, 9:1 split ratio) was the carrier gas, and detection was by flame ionization. After 1.5 min at 40 $^\circ\text{C}$, the column temperature was brought to 200 $^\circ\text{C}$ at a programmed rate of 30 $^\circ\text{C}/\text{min}$, and then held at that temperature for the remainder of the analysis. This GC method is fully described in an earlier publication.¹⁹

5,5'-Methylenedifurfurylamine (1a; Figure 1). a. **Method One.** Synthesis was carried out as previously described in the literature.¹ IR and $^1\text{H-NMR}$ spectra were consistent with those previously reported.¹ $^{13}\text{C-NMR}$ [CDCl_3]: δ 155.8 (C^2 , C^2), 150.8 (C^5 , C^5), 107.1 (C^4 , C^4), 106.0 (C^3 , C^3), 39.4 (C^6 , C^6), 27.6 (C^7). EIMS, m/e (relative intensity): 206 (M^+ , 0.1), 190 (12), 189 (100), 188 (11), 161 (5), 131 (5), 109 (10), 96 (43), 94 (10), 80 (10), 78 (10), 68 (12).

b. **Method Two.** Furfurylamine (22.5 g) was added to a 500 mL round-bottom flask and cooled in an ice bath to 25 $^\circ\text{C}$. 6 M Hydrochloric acid (165 mL) was added slowly, using the ice bath to maintain the temperature at or near 25 $^\circ\text{C}$. The reaction flask was removed from the ice bath, and a 35 wt % formaldehyde solution (9.2 mL) was added dropwise. After 70 min the reaction mixture was neutralized by the addition of 6 M sodium hydroxide (166 mL) and extracted with chloroform (2 \times 110 mL). The combined chloroform layers were washed with distilled water (100 mL) and evaporated to yield an oil. The oil was distilled (132.5 $^\circ\text{C}$, 0.27 mmHg) to give 3.9 g of 5,5'-methylenedifurfurylamine that was 99% pure as determined by GC. $^1\text{H-NMR}$, $^{13}\text{C-NMR}$, and EIGC were consistent with those of the material obtained in method one. HRMS: m/e 206.1051 (M^+); $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_2$ requires m/e 206.1055.

5,5'-Ethylidenedifurfurylamine (1b; Figure 1). Furfurylamine (50 g) and 6 M hydrochloric acid (172 mL) were combined in a 500 mL round-bottom flask. This solution was cooled to 4 $^\circ\text{C}$, and acetaldehyde (15.8 mL) was quickly added. The mixture was removed from the ice bath and heated to 40 $^\circ\text{C}$. After 50 min, the reaction mixture was cooled in an ice bath, neutralized with 6 M sodium hydroxide (172 mL), and extracted with chloroform (3 \times 100 mL). The chloroform layer was dried over MgSO_4 and evaporated to yield 55.2 g of an amber-colored oil from which 26.7 g (47%) of pure 5,5'-ethylidenedifurfurylamine was obtained by vacuum distillation of the crude product. IR and $^1\text{H-NMR}$ spectra were consistent with those previously reported.¹ $^{13}\text{C-NMR}$ [CDCl_3]: δ 155.6

and 155.4 (C^2 , C^2 , C^5 , C^5), 105.6 and 105.5 (C^3 , C^3 , C^4 , C^4), 39.4 (CH_2), 33.2 (CH), 18.1 (CH_3); EIMS, m/e (relative intensity): 220 (M^+ , 1), 204 (13), 203 (100), 188 (27), 161 (21), 96 (30), 68 (8). HRMS: m/e 220.1206 (M^+); $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_2$ requires m/e 220.1212.

5-(Hydroxymethyl)furfurylamine (2a; Figure 1). Furfurylamine (18 g) and 6 M hydrochloric acid were combined in a 500 mL round-bottom flask. The solution was cooled to 30 $^\circ\text{C}$, and a 35 wt % formaldehyde solution (16.0 g) was added. After 15 min, the reaction mixture was quenched with 6 M sodium hydroxide (229 mL) and hydroxylamine hydrochloride (32.2 g). The mixture was then extracted with chloroform (3 \times 150 mL). Crude 5-(hydroxymethyl)furfurylamine was recovered from the third extract. Vacuum microdistillation of the crude compound yielded 1.02 g (4.3%) of pure 5-(hydroxymethyl)furfurylamine. IR [film, NaCl]: 3360 (s), 3290 (s), 3200 (m), 3160 (w), 3120 (w), 2850 (w), 1010 (s), 980 (m), 960 (s), 930 (w), 790 cm^{-1} (s). $^1\text{H-NMR}$ [CDCl_3]: δ 6.16 and 6.06 (dd, 2H, $J = 3.1$ Hz, H^6 , H^6), 4.51 (s, 2H, CH_2 adjacent to OH), 3.76 (s, 2H, CH_2 adjacent to NH_2), 2.45 (b, 3H, OH and NH_2). $^{13}\text{C-NMR}$ [CDCl_3]: δ 156.1 (C^2), 153.8 (C^5), 108.1 (C^4), 106.0 (C^3), 57.0 (C^6), 39.2 (C^7); EIGC m/e (relative intensity): 127 (M^+ , 20), 96 (100), 78 (10), 68 (18), 55 (11), and 53 (13). HRMS: m/e 127.0632 (M^+); $\text{C}_6\text{H}_9\text{NO}_2$ requires m/e 127.0633.

5-(1'-Hydroxyethyl)furfurylamine (2b; Figure 1). Furfurylamine (9 g) and 3 M hydrochloric acid (60.5 mL) were combined in a round-bottom flask. This solution was brought to 30 $^\circ\text{C}$, and acetaldehyde (4.1 g) was introduced below the liquid surface via syringe. After 30 min, the reaction mixture was cooled in an ice bath and neutralized with a solution of sodium hydroxide (6 M, 70.3 mL) which contained hydroxylamine hydrochloride (16.06 g). The product was recovered by extraction with chloroform (4 \times 100 mL). The combined extract was washed with a dilute solution of sodium hydroxide and evaporated. Removal of unreacted furfurylamine by vacuum distillation yielded 1.2 g of crude product. A pure sample of 5-(1'-hydroxyethyl)furfurylamine (0.2 g, 2%) was prepared via vacuum distillation of the crude product in a microstill. IR [film, NaCl]: 3345 (s), 3290 (s), 3160 (s), 3110 (s), 2960 (s), 2920 (s), 2850 (s), 1590 (m), 1560 (m), 1440 (m), 1360 (s), 1310 (m), 1295 (m), 1225 (w), 1190 (w), 1090 (s), 1075 (w), 1005 (s), 970 (s), 950 (s), 925 (m), 875 (s), 795 (s), 780 cm^{-1} (s). $^1\text{H-NMR}$ [CDCl_3]: δ 6.09 and 6.03 (dd, 2H, $J = 3.1$ Hz, H^6 , H^6), 4.78 (q, 1H, $J = 6.6$ Hz, CH), 3.73 (s, 2H, CH_2), 2.72 (b, 3H, OH and NH_2), 1.48 (d, 3H, CH_3); $^{13}\text{C-NMR}$ [CDCl_3]: δ 157.4 (C^2), 155.3 (C^5), 105.8 (C^3), 105.5 (C^4), 63.0 (CH), 39.0 (CH_2), 21.4 (CH_3); EIGC, m/e (relative intensity): 141 (M^+ , 32), 109 (18), 97 (7), 96 (100), 78 (4), 68 (13). HRMS: m/e 141.0780 (M^+); $\text{C}_7\text{H}_{11}\text{NO}_2$ requires m/e 141.0790.

1,3,5-Trifurfurylhexahydro-1,3,5-triazine (3; Figure 1). Furfurylamine (40 g) and 10 wt % phosphoric acid (200 mL) were combined in a 500 mL flask in an ice bath. With dropwise addition of a 35 wt % formaldehyde solution (16 mL), the initially clear reaction mixture became cloudy, and a thick amber-colored solid deposited on the sides of the flask. The reaction mixture was extracted with chloroform (2 \times 100 mL), and the chloroform layer was washed with water (100 mL), dried over molecular sieves, and evaporated to yield 18.61 g of 1,3,5-trifurfurylhexahydro-1,3,5-triazine (41%). $^1\text{H-NMR}$ [CDCl_3]: δ 7.34 (dd, 3H, $J_{4,5} = 1.8$ Hz, $J_{3,5} = 0.6$ Hz, H^5), 6.28 (dd, 3H, $J_{3,4} = 3.2$ Hz, H^4), 6.14 (dd, 3H, H^3), 3.70 (s, 6H, H^6), 3.47 (b, 6H, H^7); $^{13}\text{C-NMR}$ [CDCl_3]: δ 151.8 (C^2), 142.0 (C^3), 110.0 (C^4), 108.3 (C^5), 72.8 (C^7), 49.4 (C^6).

Results and Discussion

We have discovered that a difurfuryl diamine (**1**, Figure 1) is the major product when furfurylamine reacts with either formaldehyde or acetaldehyde in hydrochloric acid.²⁰ In 5.1 M hydrochloric acid at 30 $^\circ\text{C}$, for example, 5,5'-methylenedifurfurylamine (**1a**, Figure 1; 29% yield by GC) and 5,5'-ethylidenedifurfurylamine (**1b**; Figure

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Table 1. Initial Reactant Concentrations and Final Product Distributions for Experiments Involving the Reaction of Furfurylamine and Formaldehyde

| experiment | reaction temp (°C) | reaction time (min) | initial reactant concentrations (mol/liter) | | | final product concentrations ^b (mol/liter) | | | yield of 1a ^c (%) |
|------------|--------------------|---------------------|---|------------------|-------|---|--------------------|--------------------|------------------------------|
| | | | [FA] ^a | [F] ^a | [HCl] | [FA] | [1a ^c] | [2a ^c] | |
| F1 | 30 | 120 | 1.17 | 0.59 | 5.05 | 0.27 | 0.17 | 0.0 | 29 |
| F2 | 50 | 60 | 1.17 | 0.58 | 5.05 | 0.25 | 0.16 | 0.0 | 27 |
| F3 | 50 | 120 | 1.17 | 0.59 | 3.77 | 0.26 | 0.16 | 0.0 | 27 |
| F4 | 50 | 480 | 1.17 | 0.59 | 2.53 | 0.28 | 0.12 | 0.0 | 21 |
| F5 | 40 | 90 | 1.17 | 0.59 | 5.05 | 0.25 | 0.17 | 0.0 | 29 |
| F6 | 30 | 90 | 1.13 | 1.12 | 4.85 | 0.06 | 0.08 | 0.12 | 14 |

^a FA = furfurylamine. F = formaldehyde. ^b Determined by gas chromatography. ^c See Figure 1.

Table 2. Initial Reactant Concentrations and Final Product Distributions for Experiments Involving the Reaction of Furfurylamine and Acetaldehyde

| experiment | reaction temp (°C) | reaction time (min) | initial reactant concentrations (mol/liter) | | | final product concentrations ^b (mol/liter) | | | yield of 1b ^c (%) |
|------------|--------------------|---------------------|---|-------------------|-------|---|--------------------|--------------------|------------------------------|
| | | | [FA] ^a | [AC] ^a | [HCl] | [FA] | [1b ^c] | [2b ^c] | |
| A1 | 30 | 90 | 1.20 | 0.60 | 5.16 | 0.20 | 0.40 | 0.0 | 67 |
| A2 | 30 | 1800 | 1.19 | 0.60 | 2.57 | 0.22 | 0.37 | 0.0 | 62 |
| A3 | 40 | 60 | 1.20 | 0.60 | 5.18 | 0.19 | 0.40 | 0.0 | 67 |
| A4 | 30 | 480 | 1.19 | 0.59 | 3.87 | 0.20 | 0.41 | 0.0 | 69 |
| A5 | 30 | 90 | 1.17 | 1.17 | 5.05 | 0.01 | 0.28 | 0.0 | 48 |
| A6 | 30 | 90 | 1.21 | 0.30 | 5.23 | 0.63 | 0.26 | 0.0 | 43 |
| A7 | 20 | 180 | 1.19 | 0.60 | 5.18 | 0.21 | 0.40 | 0.0 | 67 |
| A8 | 40 | 900 | 1.20 | 0.60 | 2.59 | 0.20 | 0.36 | 0.0 | 60 |
| A9 | 50 | 480 | 1.20 | 0.60 | 2.59 | 0.18 | 0.36 | 0.0 | 60 |
| A10 | 40 | 240 | 1.19 | 0.60 | 3.87 | 0.18 | 0.38 | 0.0 | 64 |
| A11 | 50 | 120 | 1.19 | 0.60 | 3.86 | 0.18 | 0.37 | 0.0 | 62 |
| A12 | 50 | 120 | 1.19 | 0.60 | 5.14 | 0.16 | 0.37 | 0.0 | 62 |
| A13 | 40 | 180 | 2.14 | 1.07 | 4.60 | 0.31 | 0.75 | 0.0 | 70 |

^a FA = furfurylamine, AC = acetaldehyde. ^b Determined by gas chromatography. ^c See Figure 1.

1; 67% yield by GC, 47% after isolation and purification) were obtained from the reactions of furfurylamine with formaldehyde and acetaldehyde, respectively. Under these conditions, each reaction proceeded to completion in approximately 1 h. The ¹H-NMR, ¹³C-NMR, and IR spectra of the products from these reactions matched those of the same products prepared by an earlier synthesis described in the literature.⁷

The reaction of furfurylamine with acetone in 5.0 M hydrochloric acid at 35 °C was extremely slow (several days), and a number of products in addition to 5,5'-isopropylidenedifurfurylamine (**1c**, Figure 1) were formed (unpublished results). Although reactions with other ketones were not attempted, the unsatisfactory results from this reaction suggest that this procedure is less suitable for the preparation of difurfuryl diamines when neither R nor R' is a hydrogen. Yields of difurfuryl diamines from the reactions of furfurylamine with formaldehyde and acetaldehyde are comparable to those from an earlier three-step procedure which involved protection and deprotection of the amino group.⁷ The elimination of these unnecessary steps in the present synthesis leads to a procedure with greater potential for commercial utility.

Hydrochloric acid functions as both a catalyst and a blocking group during the formation of difurfuryl diamines from furfurylamine and aldehydes. Acid is believed to facilitate attack of the 5-position of furfurylamine on the aldehyde carbon by protonating the carbonyl group and enhancing its electrophilicity. This mechanism is the proposed explanation for the catalytic effect of acids on the coupling reactions of other furan compounds with carbonyl groups.^{9,11,21} Protonation of the amino group of furfurylamine by hydrochloric acid also significantly reduces its reactivity toward the activated

carbonyl species. Side reactions between carbonyl and amino groups are therefore limited by the relatively low equilibrium concentration of unprotonated furfurylamine under the reaction conditions. The proposed dual role of hydrochloric acid as both catalyst and blocking group distinguishes the carbonyl coupling reaction of furfurylamine from those of other furan compounds.

The reaction times, initial reactant concentrations, final product distributions, and yields of diamines for experiments performed under a variety of conditions are summarized in Tables 1 and 2. Examination of these data indicates that, for a given aldehyde, the yield of the difurfuryl diamine is relatively insensitive to either acid concentration (2.5 to 5.2 M) or reaction temperature (20 to 50 °C) over the ranges investigated. The single exception to this constant yield was observed for the reaction of furfurylamine and formaldehyde in 2.5 M hydrochloric acid (experiment F4). This experiment gave approximately equal amounts of 5,5'-methylene-difurfurylamine and a compound with M⁺ m/e = 206. The latter compound was not isolated and identified, but is believed to be 5-[5'-(aminomethyl)furfuryl]furfurylamine (**4**, Figure 1), which is formed by the reaction of furfurylamine and formaldehyde under mildly acidic conditions.¹

When a stoichiometric ratio (2:1) of furfurylamine to aldehyde was employed, the final product contained unreacted furfurylamine along with some viscous species, presumably oligomeric in nature. At lower furfurylamine:aldehyde ratios (e.g., 1:1, experiments F6 and A5), furfurylamine was nearly completely consumed, but increased formation of side-products decreased the yield of the desired diamino product. In the case of acetaldehyde, the optimal furfurylamine:aldehyde ratio under the conditions investigated was between 1.8 and 2.0.

Experiments in which significantly less than 2 equiv of hydrochloric acid (relative to furfurylamine) were utilized gave low reaction rates and poor selectivity for difurfuryl diamines. In the presence of 1 equiv of

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hydrochloric acid, for example, the product from the reaction of furfurylamine and formaldehyde at 24 °C was primarily unreacted furfurylamine along with some unidentified resinous species. Although minor amounts of 5,5'-methylenedifurfurylamine were obtained when the reaction was conducted at 95 °C, these conditions promoted extensive formation of a tarry substance, presumed to be the product of ring-cleavage reactions. When furfurylamine and formaldehyde were reacted in 10% phosphoric acid, the trimeric Schiff base 1,3,5-trifurfurylhexahydro-1,3,5-triazine (**3**, figure 1) was isolated in 41% yield along with unreacted furfurylamine.

The selectivity of the reaction of furfurylamine with acetaldehyde toward production of the difurfuryl diamine was greater (67% yield by GC) than that of the reaction with formaldehyde (29% yield by GC). This difference in selectivities is characteristic of the coupling reactions of other furan compounds with acetaldehyde and formaldehyde.^{1,6} Mixtures of 2-methylfuran, formaldehyde, and substituted ammonium chlorides undergo a Mannich reaction, yielding secondary and tertiary 5-methylfurfurylamines.²² By contrast, when acetaldehyde rather than formaldehyde is employed, the product of the reaction is 1,1-bis(5-methyl-2-furyl)ethane. Whereas acetaldehyde reacts preferentially at the 5-position of a furan compound, formaldehyde appears to react more readily with an amino group. This interpretation is consistent with the observed better selectivity for difurfuryl diamines when acetaldehyde is used.

GC-mass spectral analyses of aliquots from reaction mixtures of furfurylamine with formaldehyde and acetaldehyde indicated the formation and subsequent consumption of species with molecular weights of 127 and 141 g/mol, respectively. Resonances attributed to these transient species were also observed in ¹H-NMR spectra of reacting mixtures.²³ These compounds were isolated from the reaction mixtures and identified via ¹H-NMR, ¹³C-NMR, and IR spectroscopies and GC mass spectrometry as 5-(hydroxymethyl)furfurylamine (**2a**, Figure 1) and 5-(1'-hydroxyethyl)furfurylamine (**2b**, Figure 1), respectively.

A sample of 5-(hydroxymethyl)furfurylamine in 5.1 M hydrochloric acid at 30 °C was slowly converted in low yield (< 10%) to 5,5'-methylenedifurfurylamine in the absence of both furfurylamine and formaldehyde. Under these conditions, the methylene linkage in the diamino product is thought to form via the elimination of formaldehyde from a difurfuryl ether linkage between two furan rings (see Figure 2A). A similar mechanism has been proposed for the formation of methylene linkages between furan rings during the acid-catalyzed resinification of furfuryl alcohol.^{24,25} The observation of a compound giving $M^+ m/e = 236$ ($C_{12}H_{16}N_2O_3$ requires $M^+ m/e = 236$) in the GC-mass spectra of samples taken from a reacting mixture of furfurylamine and formaldehyde lends support to this proposed mechanism.

When a 3-fold excess of furfurylamine was present,

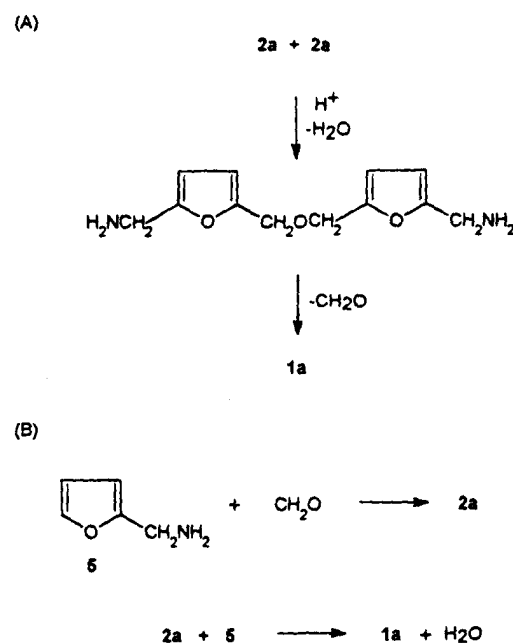


Figure 2. Postulated mechanistic pathways for the formation of a difurfuryl diamine from furfurylamine and formaldehyde.

5-(hydroxymethyl)furfurylamine was rapidly converted to 5,5'-methylenedifurfurylamine in 87% yield. These results are consistent with a mechanism involving the formation of a furyl-substituted carbinol intermediate which undergoes reaction with another molecule of furfurylamine to give product (see Figure 2B). The acid-catalyzed carbonyl coupling reactions of other furan compounds are generally considered to proceed by this type of mechanism.^{9,11,15,26} The faster rate and higher yield of reaction 2B relative to reaction 2A suggest that reaction 2B is the more significant mechanistic pathway.

Conclusions

Difurfuryl diamino compounds can be obtained from the reaction of furfurylamine with formaldehyde or other aldehydes in 2.5-5.2 M hydrochloric acid at 20-50 °C. The selectivity for production of difurfuryl diamines is highest when 2 or more equiv of acid (relative to furfurylamine) are employed. The reaction is believed to proceed through a [5-(aminomethyl)furyl]carbinol intermediate.

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Supplementary Material Available: ¹H-NMR and ¹³C-NMR spectra for compounds **1a,b**, **2a,b**, and **3** (10 pages). This material is contained in libraries on microfiche, immediately following this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.

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