3-Formylpyrroles from 3-Furfurylamines by Bromine Oxidation Reaction

Piin-Jye Harn[a,b] (韓品杰), Chu-Chung Lin[a,c] (林助強) and Hsien-Jen Wu[a,d,*] (吳獻仁)
[a]*Department of Applied Chemistry, National Chiao Tung University, Hsinchu, Taiwan, R.O.C.*
[b]*SinoPharm Taiwan Ltd., Tainan County, Taiwan, R.O.C.*
[c]*Department of Medicinal Chemistry, TaiGen Biotechnology Co., Ltd., Taipei, Taiwan, R.O.C.*
[d]*Department of Environmental Engineering and Health, Yuanpei University, Hsinchu, Taiwan, R.O.C.*

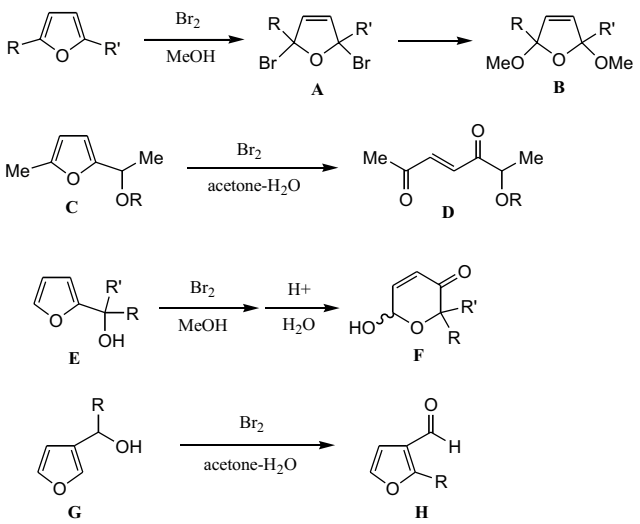
Oxidation of 3-furfurylamines **3a-e** with bromine in acetone-water solution gave N-substituted 3-formylpyrroles **4a-e** in good yields. A reaction mechanism *via* the Clauson-Kaas reaction followed by the *cis-trans* isomerization of the 2-ene-1,4-diones **13** and **14** was proposed to account for the formation of the pyrroles **4a-e**.

Keywords: 3-Furfurylamines; 3-Formylpyrroles; Oxidation with bromine.

INTRODUCTION

Furan derivatives and their oxidation products are important intermediates in organic synthesis.[1,2] The oxidation of a furan ring has oftentimes been used to express the latent functionality present within this heterocyclic framework.[3] Oxidation of 2-trimethylsilylfurans with peracetic acid gave Δ^3-butenolides.[4] This transformation was applied for the synthesis of natural products.[5] Oxidation of 2,5-dialkylfurans with peroxy acids afforded the *Z*-isomers of 2-ene-1,4-diones,[6] whereas the *E*-isomers were obtained with pyridinium chlorochromate (PCC) as the oxidation reagent.[7] Treatment of 2-alkylthiofurans with PCC initially gave the *Z*-isomers of *S*-alkyl 4-oxo-2-alkenoates, which were converted to the *E*-isomers when longer reaction times proceeded.[8] The oxidation reaction of furan derivatives with bromine in absolute methanol is known as Clauson-Kaas reaction to give the 2,5-dimethoxy-2,5-dihydrofuran derivatives **B**,[9] presumably *via* the dibromo intermediates **A** (Scheme I). About two decades ago, a direct transformation of **C** to **D** by modified reaction conditions of the bromine oxidation with furan **C** was reported.[10] Reaction of 2-furfuryl alcohols **E** with bromine in methanol followed by mild acid hydrolysis gave 6-hydroxyl-2*H*-pyran-3(6*H*)-ones **F**,[3,11] a route to monosaccharides from furan compounds. This transformation from **E** to **F** was also accomplished with peroxy acids[12] and PCC.[13] 6-Hydroxy-2*H*-pyran-3(6*H*)-ones are useful intermediates for the synthesis of natural products.[3,11] Recently, we reported the oxidation reaction of 3-furfuryl alcohols **G** with bromine in aqueous acetone solution to give 2-substituted-3-furfurals **H**.[14] In this paper, we report the oxidation reaction of 3-furfuryl amines with bromine to give 3-formyl pyrroles in an one-step conversion,[15] a new route to pyrroles from furans *via* oxidative rearrangement.

Scheme I

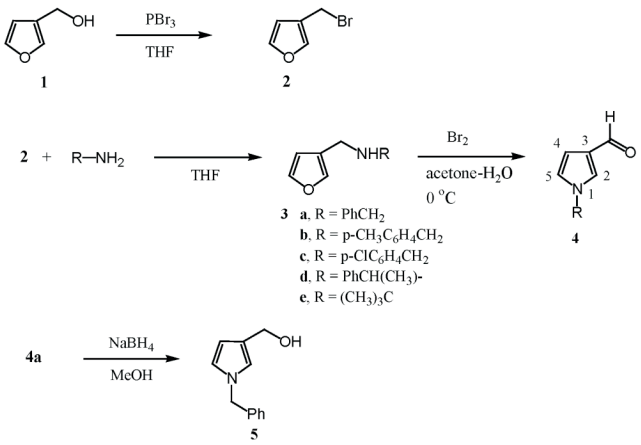


RESULTS AND DISCUSSION

Reaction of 3-furfuryl alcohol **1** with phosphorus tribromide in dry tetrahydrofuran (THF) at 0 °C for one hour gave 3-furfuryl bromide **2** in 75% yield. Treatment of 3-furfuryl bromide **2** with benzylamine, *p*-methylbenzylamine, *p*-chlorobenzylamine, 1-phenylethylamine, and *t*-butylamine in dry THF at room temperature for 20 h gave the corresponding 3-furfurylamines **3a-e** in 60-75% yields. Oxidation of the 3-furfurylamines **3a-e** with 1.2 equivalents of bromine in acetone-water (volume ratio 85:15) at 0

°C for 2 h gave N-alkyl-3-formylpyrroles **4a-e** in 50-65% yields, respectively (Scheme II). Reaction of **4a** with sodium borohydride in methanol gave compound **5** in 80% yield.

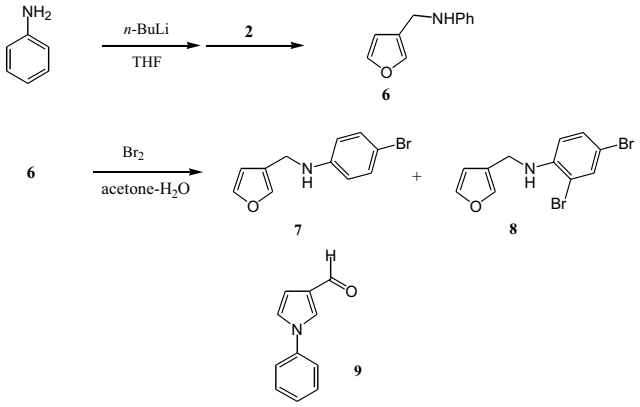
Scheme II



The structure of compounds **4a-e** was identified by their spectral data. The infrared (IR) spectra of **4a-e** revealed strong absorptions at 1670 cm^{-1} for the formyl carbonyl group. The ^1H NMR spectrum of **4b** showed a singlet at δ 9.72 for the aldehyde proton, a triplet (J = 1.8 Hz) at δ 7.29 for the C_2 proton on the pyrrole ring, two doublets (J = 7.6 Hz) at δ 7.16 and δ 7.06 for the benzene ring protons, two doublets of doublet (J = 2.4, 1.8 Hz) at δ 6.69 and δ 6.64 for the C_4 and C_5 protons on the pyrrole ring, a singlet at δ 5.04 for the methylene protons and a singlet at δ 2.35 for the methyl protons. The ^{13}C NMR spectrum of **4b** displayed one peak (CH) at δ 185.4 for the aldehyde carbonyl carbon, four peaks at δ 138.2 (C), 132.9 (CH), 129.6 (2CH), and 127.4 (2CH) for the benzene ring carbons, four peaks at δ 129.1 (CH), 126.7 (C), 123.6 (CH), and 108.5 (CH) for the pyrrole ring carbons, one peak (CH_2) at δ 53.7 for the methylene carbon, and one peak (CH_3) at δ 21.1 for the methyl carbon. The mass spectrum of **4b** showed its molecular parent peak at δ 199. In the case of the oxidation of **3e**, the 3-formylpyrrole **4e** was obtained in a good yield (65%) even in the presence of a *tert*-butyl group on the nitrogen atom. In other words, the formation of the pyrrole ring was not affected by the steric effect of the *tert*-butyl group on the nitrogen atom.

In order to understand the feasibility of the formation of N-phenyl-3-formylpyrroles from the oxidation of 3-furfuryl anilines, the following experiments were performed. The S_N2 substitution reaction of 3-furfuryl bromide with aniline proceeded very slowly at room temperature. Treatment of aniline with *n*-BuLi in dry THF at room temperature followed by addition of furfuryl bromide **2** gave the S_N2 substitution product **6** in 75% yield. Reaction of compound **6** with 1.5 equivalents of bromine in acetone-water (85:15) at 0 °C gave compound **7** as the major product and compound **8** as the minor product (Scheme III). No detectable amount of N-phenyl-3-formylpyrrole **9** was obtained. Thus, electrophilic substitution reaction of bromine on the benzene ring of aniline moiety of **6** is much faster than the

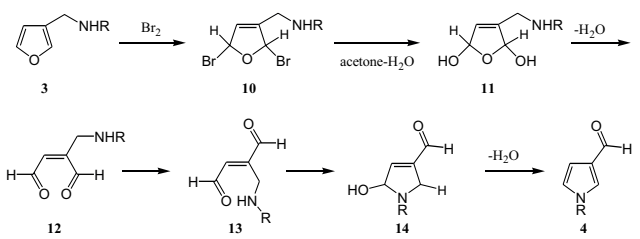
Scheme III



oxidation of bromine on the furan ring.

A reaction mechanism was proposed for the transformation from the 3-furfurylamines **3a-e** to the 3-formylpyrroles **4a-e** (Scheme IV). The initial step of this oxidation is similar to the Clauson-Kaas reaction as shown in the first line of Scheme I. The oxidation reaction of **3** with bromine in acetone-water solution gives the 2,5-dihydroxy-2,5-dihydrofuran **11**, presumably *via* the dibromo intermediate **10**. Dehydration of **11** followed by ring opening gives the *Z*-iosmer of 2-ene-1,4-dione **12**. *Cis-trans* isomerization of **12** gives the *E*-isomer **13**. Intramolecular nucleophilic ad-

Scheme IV



dition of the amino group of **13** on the aldehyde group gives the intermediate **14** which was followed by dehydration to yield the pyrroles **4**.

CONCLUSION

In summary, we have demonstrated the reaction of the 3-furfurylamines **3a-e** with bromine in acetone-water solution gave the N-sustituted-3-formylpyrroles **4a-e**, a new entry from furans to pyrroles by oxidative rearrangement. In the case of the oxidation of 3-furfurylaniline **6** with bromine under the same reaction conditions, electrophilic substitution reaction of bromine on the benzene ring of aniline moiety was found to proceed much faster than the oxidation of bromine on the furan ring. A reaction mechanism *via* the Clause-Kaas reaction followed by the *cis-trans* isomerization from the *Z*-iosmer **12** of the 2-ene-1,4-dione to the *E*-isomer **13** was proposed to account for the formation of the pyrroles **4**.

EXPERIMENTAL SECTION

Infrared spectra were recorded in $CHCl_3$ solutions or on neat thin firms between NaCl disks. ^{1}H NMR spectra were determined at 300 MHz, and ^{13}C NMR spectra were determined at 75 MHz on Fourier transform spectrometers. Chemical shifts are reported in ppm relative to TMS in the solvents specified. The multiplicities of ^{13}C signals were determined by DEPT techniques. High-resolution mass values were obtained with a high-resolution mass spectrometer at the Department of Chemistry, National Tsing Hua University. For thin-layer chromatography (TLC) analysis, precoated TLC plates (Kieselgel 60 F_{254}) were used, and column chromatography was done by using Kieselgel 60 (70-230 mesh) as the stationary phase. THF was distilled immediately prior to use from sodium benzophenone ketyl under nitrogen.

General Procedure for the Preparation of Compounds 3a-e

To a solution of benzylamine (1.98 g, 18.5 mmol) in THF (50 mL) was slowly added 3-furfuryl bromide (1.19 g, 7.39 mmol) at 25 °C. The reaction mixture was stirred at room temperature for 20 h. To this reaction mixture was added saturated $NaHCO_3$ (20 mL) at 0 °C, and the mixture was stirred at room temperature for 20 min. After extraction with ether (5 × 30 mL), the organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by flash column chromatography to give **3a** (0.95 g, 70%).

3-Furfuryl benzylamine (3a)

Pale yellow liquid; IR ($CHCl_3$) 3320, 1600, 1500, 750, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.20 (m, 7H), 6.37 (s, 1H), 3.78 (s, 2H), 3.63 (s, 2H), 1.54 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 142.94 (CH), 140.02 (C), 139.70 (CH), 128.25 (2CH), 128.02 (2CH), 126.82 (CH), 123.85 (C), 110.30 (CH), 52.99 (CH_2), 43.41 (CH_2); LRMS *m/z* (rel int) 187 (M^+, 10), 106 (100); HRMS (EI) calcd for $C_{12}H_{13}ON$ 187.0997, found 187.0988.

3-Furfuryl *p*-methylbenzylamine (3b)

Pale yellow liquid; IR ($CHCl_3$) 3320, 1600, 1500, 830 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, *J* = 1.5 Hz, 1H), 7.34 (s, 1H), 7.21 (d, *J* = 9.0 Hz, 2H), 7.12 (d, *J* = 9.0 Hz, 2H), 6.39 (d, *J* = 1.5 Hz, 1H), 3.75 (s, 2H), 3.63 (s, 2H), 2.33 (s, 3H), 1.63 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 142.97 (CH), 139.73 (CH), 136.96 (C), 136.44 (C), 128.98 (2CH), 128.02 (2CH), 123.88 (C), 110.36 (CH), 52.76 (CH_2), 43.38 (CH_2), 20.97 (CH_3); LRMS *m/z* (rel int) 201 (M^+, 40), 105 (100); HRMS (EI) calcd for $C_{13}H_{15}ON$ 201.1154, found 201.1146.

3-Furfuryl *p*-chlorobenzylamine (3c)

Pale yellow liquid; IR ($CHCl_3$) 3320, 1600, 1500, 835 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.35 (d, *J* = 1.5 Hz, 1H), 7.32-7.24 (m, 4H), 6.39 (d, *J* = 1.5 Hz, 1H), 3.76 (s, 2H), 3.64 (s, 2H), 1.57 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 143.14 (CH), 139.82 (CH), 138.60 (C), 132.59 (C), 129.45 (2CH), 128.46 (2CH), 123.76 (C), 110.33 (CH), 52.29 (CH_2), 43.44 (CH_2); LRMS *m/z* (rel int) 223 (M^+, 22), 221 (M^+, 65), 125 (100).

3-Furfuryl-1-phenylethylamine (3d)

Pale yellow liquid; IR ($CHCl_3$) 3320, 1600, 1500, 760, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.20 (m, 7H), 6.34 (s, 1H), 3.80 (q, *J* = 6.6 Hz, 1H), 3.47 (s, 2H), 1.58 (brs, 1H), 1.26 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 145.33 (C), 142.97 (CH), 139.64 (CH), 128.43 (2CH), 126.91 (2CH), 126.59 (CH), 124.06 (C), 110.36 (CH), 57.39 (CH), 41.98 (CH_2), 24.29 (CH_3); LRMS *m/z* (rel int) 201 (M^+, 45), 105 (100); HRMS (EI) calcd for $C_{12}H_{15}ON$ 201.1154, found 201.1163.

3-Furfuryl *tert*-butylamine (3e)

Pale yellow liquid; IR ($CHCl_3$), 3320, 1500 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (s, 2H), 6.39 (s, 1H), 3.60 (s, 2H), 1.21 (brs, 1H), 1.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 142.91 (CH), 139.41 (CH), 124.81 (C), 110.42 (CH), 50.49 (C), 37.55 (CH_2), 28.90 ($3CH_3$); LRMS *m/z* (rel int) 153 (M^+, 100), 138 (77); HRMS (EI) calcd for $C_9H_{15}ON$ 153.1154, found 153.1166.

General Procedure for the Oxidation of 3-Furfuryl-amines 3a-e with Bromine in Acetone-Water

To a solution of 3-furfurylamine **3a** (0.79 g, 4.2 mmol) in acetone (34 mL) and water (6 mL) was dropwise added bromine (0.80 g, 5.0 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. This solution was neutralized with saturated $NaHCO_3$ (20 mL) at 0 °C, and the mixture was stirred at room temperature for 30 min. After extraction with ether (5 × 30 mL), the organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by flash column chromatography to give **4a** (0.50 g, 64%).

N-Benzyl-3-formylpyrrole (4a)

Pale yellow liquid; IR ($CHCl_3$), 1665, 1150, 750, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.69 (s, 1H), 7.35-7.24 (m, 4H), 7.15-7.10 (m, 2H), 6.67 (dd, *J* = 2.4, 1.8 Hz, 1H), 6.61 (dd, *J* = 2.4, 1.8 Hz, 1H), 5.03 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 184.98 (CH), 135.94 (C), 129.16 (CH), 138.66 (2CH), 127.96 (CH), 127.09 (2CH), 126.47 (C), 123.53 (CH), 108.09 (CH), 53.52 (CH_2); LRMS *m/z* (rel int) 185 (M^+, 5), 91 (100); HRMS (EI) calcd for $C_{12}H_{11}NO$ 185.0841, found 185.0831.

N-(*p*-Methylbenzyl)-3-formylpyrrole (4b)

Pale yellow liquid; IR ($CHCl_3$), 1670, 1155, 820 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.72 (s, 1H), 7.29 (t, *J* = 1.8 Hz, 1H), 7.17 (d, *J* = 7.8 Hz, 2H), 7.06 (d, *J* = 7.8 Hz, 2H), 6.69 (dd, *J* = 2.4, 1.8 Hz, 1H), 6.64 (dd, *J* = 2.4, 1.8 Hz, 1H), 5.04 (s, 2H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 185.36 (CH), 138.22 (C), 132.97 (C), 129.65 (2CH), 129.10 (CH), 127.44 (2CH), 126.71 (C), 123.62 (CH), 108.53 (CH), 53.72 (CH_2), 21.09 (CH_3); LRMS *m/z* (rel int) 199 (M^+, 100); 105 (60); HRMS (EI) calcd for $C_{13}H_{13}NO$ 199.0997, found 199.0989.

N-(*p*-Chlorobenzyl)-3-formylpyrrole (4c)

Pale yellow liquid; IR ($CHCl_3$), 1670, 820 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.74 (s, 1H), 7.34 (d, *J* = 8.7 H_z, 2H), 7.29 (t, *J* = 1.8 Hz, 1H), 7.09 (d, *J* = 8.7 Hz, 2H), 6.69-6.65 (m, 2H), 5.07 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 185.21 (CH), 134.57 (C), 134.17 (C), 129.10 (2CH), 128.95 (CH), 128.60 (2CH), 126.85 (C), 123.56 (CH), 108.73 (CH), 53.14 (CH_2); LRMS *m/z* (rel int) 221 (M^+, 31), 219 (M^+, 100).

N-(1-Phenylethyl)-3-formylpyrrole (4d)

Pale yellow liquid; IR ($CHCl_3$), 1670, 755, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.28 (m, 4H), 7.14-7.12 (m, 2H), 6.73 (dd, *J* = 2.4, 1.8 Hz, 1H), 6.64 (dd, *J* = 2.4, 1.8 Hz, 1H), 5.29 (q, *J* = 6.6 Hz, 1H), 1.83 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 185.21 (CH), 141.33 (C), 128.72 (2CH), 127.90 (CH), 127.49 (CH), 126.18 (C), 125.80 (2CH), 122.31 (CH), 108.03 (CH), 58.70 (CH), 21.58 (CH_3); LRMS *m/z* (rel int) 199 (M^+, 100); HRMS (EI) calcd for $C_{13}H_{13}NO$ 199.0997, found 199.0988.

N-(*tert*-Butyl)-3-formylpyrrole (4e)

Pale yellow liquid; IR ($CHCl_3$), 1670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.73 (s, 1H), 7.47 (dd, *J* = 1.8, 1.5 Hz, 1H), 6.87 (dd, *J* = 2.4, 1.5 Hz, 1H), 6.63 (dd, *J* = 2.4, 1.8 Hz, 1H), 1.56 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 185.45 (CH), 126.15 (CH), 125.75 (C), 120.41 (CH), 107.91 (CH), 55.96 (C), 30.32 ($3CH_3$); LRMS *m/z* (rel int) 151 (M^+, 100), 136 (30); HRMS (EI) calcd for $C_9H_{13}NO$ 151.0997, found 151.0985.

Reduction of Compound 4a with $NaBH_4$

To a solution of compound **4a** (0.15 g, 0.81 mmol) in methanol (25 mL) was added sodium borohydride (0.080 g, 2.1 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. To this reaction mixture was added saturated NH_4Cl (10 mL). The solvents were evaporated. After extraction with ether (5 × 30 mL), the organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by flash column chromatography to give **5** (0.12 g, 80%).

N-Benzyl-3-hydroxymethylpyrrole (5)

Pale yellow oil; IR ($CHCl_3$) 3500-3200, 750, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34-7.24 (m, 3H), 7.14-7.10 (m, 2H), 6.66 (dd, *J* = 2.4, 1.5 Hz, 1H), 6.63 (t, *J* = 1.5 Hz, 1H), 6.19 (dd, *J* = 2.4, 1.5 Hz, 1H), 5.00 (s, 2H), 4.52 (s, 2H), 1.70 (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 137.75 (C), 128.66 (2CH), 127.67 (CH), 127.06 (2CH), 124.26 (C), 121.64 (CH), 119.66 (CH), 108.15 (CH), 58.67 (CH_2), 53.31 (CH_2); LRMS *m/z* (rel int) 187 (M^+, 60), 91 (100).

Preparation of Compound 6

To a solution of aniline (0.60 g, 6.6 mmol) in dry THF (40 mL) was dropwise added *n*-BuLi (2.78 mL, 6.96 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. To this solution was added compound **2** (0.80 g, 4.97 mmol) at 0 °C. The reaction mixture was then stirred at room temperature for 3 h. To this solution was added saturated NH_4Cl (10 mL) at room temperature. After extraction with ether (5 × 30 mL), the organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by flash column chromatography to give **6** (0.65 g, 75%); pale yellow liquid; IR ($CHCl_3$) 3420, 1600,

1500, 750, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, J = 1.5 Hz, 2H), 7.18-7.14 (m, 2H), 6.74-6.61 (m, 3H), 6.38 (d, J = 1.5 Hz, 1H), 4.31 (s, 2H), 3.79 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 147.95 (C), 143.20 (CH), 139.88 (CH), 129.18 (2CH), 123.30 (C), 117.68 (CH), 112.87 (2CH), 110.10 (CH), 39.24 (CH_2); LRMS *m/z* (rel int) 173 (M^+, 100), 81 (75).

Reaction of Compound 6 with Bromine in Acetone-Water

The same reaction conditions for the oxidation of compounds **3a-e** were applied for the reaction of compound **6** with bromine to give compound **7** as the major product (45%) and compound **8** as the minor product (30%). No detectable amount of N-phenyl-3-formylpyrrole **9** was obtained.

3-Furfuryl *p*-bromoaniline (7)

Pale yellow oil; IR ($CHCl_3$), 3400, 1600, 1500, 820 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.37 (m, 2H), 7.24 (d, J = 10 Hz, 2H), 6.50 (d, J = 10 Hz, 2H), 6.38 (s, 1H), 4.11 (s, 2H), 3.86 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 146.90 (C), 143.37 (CH), 139.94 (CH), 131.86 (2CH), 122.89 (C), 114.47 (2CH), 109.98 (CH), 109.25 (C), 39.27 (CH_2); LRMS *m/z* (rel int) 253 (M^+, 100), 251 (M^+, 95).

3-Furfuryl 2,4-dibromoaniline (8)

Pale yellow oil; IR ($CHCl_3$) 3400, 1600, 1500, 880, 800 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.40-7.38 (m, 2H), 7.26-7.22 (m, 1H), 6.52 (d, J = 9.0 H_z, 1H), 6.39 (s, 1H), 4.53 (brs, 1H), 4.17 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 143.78 (C), 143.55 (CH), 139.96 (CH), 134.22 (CH), 131.14 (CH), 122.34 (C), 112.46 (CH), 109.90 (C), 109.84 (CH), 108.38 (C), 39.24 (CH_2); LRMS *m/z* (rel int) 333 (M^+, 58), 331 (M^+, 100), 329 (M^+, 60).

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