B. Taljaard and G.J. Burger, *S. Afr. J. Chem.*, 2002, **55**, 56-66,
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RESEARCH ARTICLE

Palladium-Catalysed Dimerisation of Furfural

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Received 22 November 2001; Revised 14 February 2002; Accepted 28 February 2002

Abstract

5,5’-Diformyl-2,2’-difuran has been synthesized in 60% yield by the palladium acetate-catalysed aryl coupling of furfural in acetonitrile in the presence of dioxygen under pressure. Various reaction conditions have been exploited, and mechanistic aspects of the reaction are discussed.

Keywords: Furfural; heteroaromatic coupling; difurans; palladium catalysis; reoxidation.

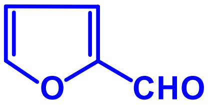
1. Introduction

Furfural (IUPAC name 2-furaldehyde) (**1**) is produced locally by Illovo Sugar from bagasse, which is the spent woody fibre obtained after extraction of sucrose from sugar cane. The bulk of the aldehyde is converted into furfuryl alcohol, which is used extensively in the resin field and as a solvent.[1] Furfural itself is used mainly in the refining of lubricating oils and butadiene extraction, and its derivatives are used in pharmaceutical, herbicide, fragrance and flavouring applications.[2]

In an attempt to add value to this product, we considered synthesizing furan-2,5-dicarbaldehyde or dimers of **1** having two aldehyde groupings in the respective furan rings. These compounds are considered to be more stable than **1**, easier to handle in reactions in an industrial environment, should be useful for the synthesis of novel polymers, and also be able to compete with benzene analogues already used in various industrial processes. These transformations of **1** should also be executed with the minimum contamination of the environment, and the products should then promote the use of **1** in the fine chemical niche.

2. Results and Discussion

We decided to direct our efforts to the synthesis of 5,5'-diformyl-2,2'-difuran (**2**) (IUPAC name [2,2'-bifuryl]-5,5'-dicarbaldehyde). Although various reports on the synthesis of **2** have appeared in the literature thus far, we were interested in developing a high-yielding industrial synthesis for this compound, which seemed to be an interesting substrate for the synthesis of novel polymeric materials. In addition, the chemistry of this compound has not been extensively studied, and syntheses of only a few of its derivatives have been reported.[3–9]



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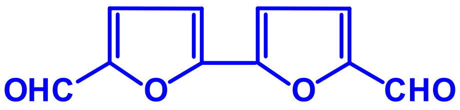


(2)

Coupling between two heteroaromatic rings usually involves the use of palladium and boronic acid derivatives and other expensive reagents, and produces variable yields of coupling products, though these reagents are usually quite effective in promoting aryl C–C bond formation.[9–12] We applied the classical Ullmann condensation reaction, utilizing copper powder in dimethylformamide, to effect coupling of 5-bromo-2-furaldehyde, but obtained **2** in low yield (<4%). From this reaction, 80% of the unreacted starting material could be recovered.[3,7] Repeating the reaction with the 5-iodo derivative led to a slightly improved yield of **2** (14%). Unfortunately, 5-iodo-2-furaldehyde cannot be synthesized directly from **1**, and is usually obtained from the corresponding bromo derivative, which in turn, is prepared by direct bromination of **1**.[13] As the latter transformations would be too problematic and expensive to perform effectively on an industrial scale, and in view of the mediocre yields of **2** obtained, it was decided to investigate a palladium acetate/cupric acetate catalytic system to effect the coupling reaction (Table 1).[10,14,15]

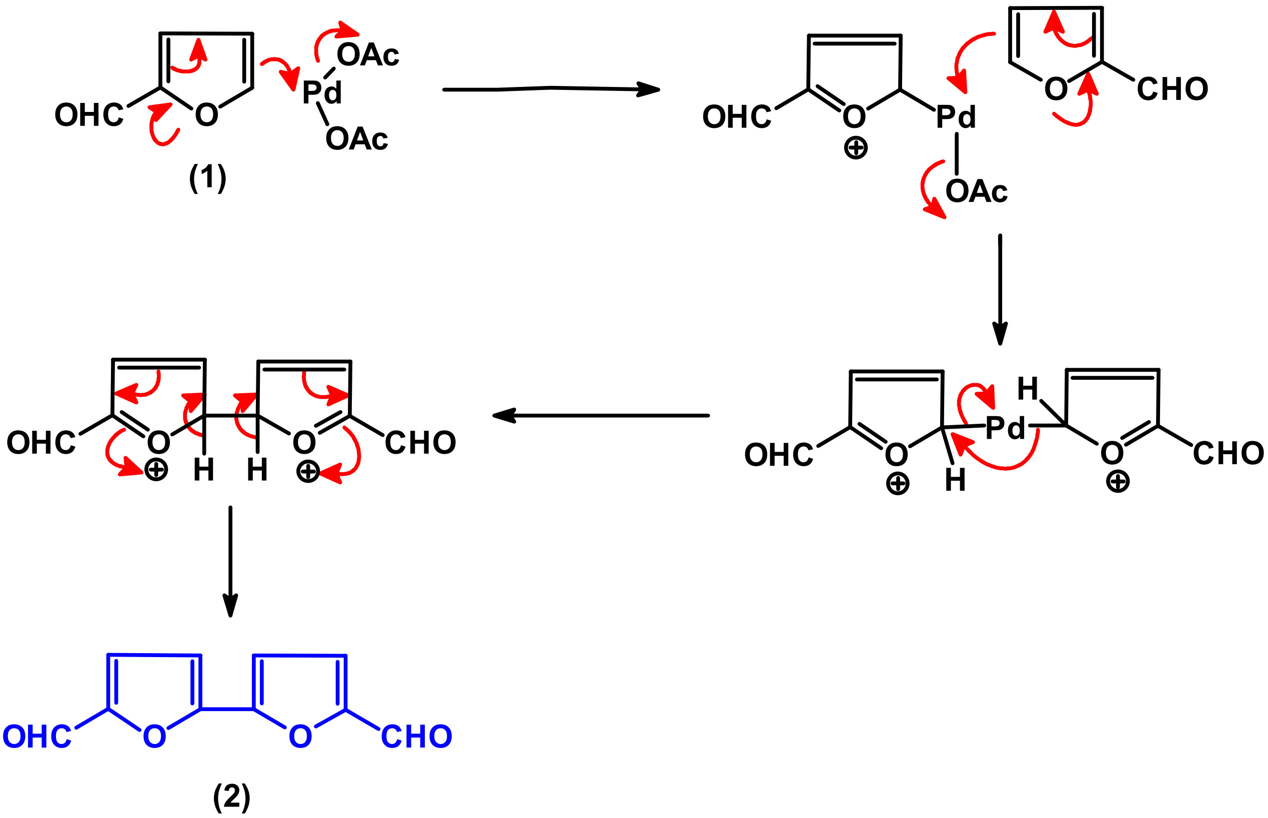
Table 1 Oxidative coupling reactions of furfural (**1**).

Furfural (**1**) (mol)	Catalyst (mmol)	Co-catalysts (mmol)	Dimer **2** (%)
12	$Pd(OAc)_2$ (450)	none	4.6
12	$Pd(OAc)_2$ (0.45)	$Cu(OAc)_2$ (100) $CaCl_2$ (40)	0.2
12	$Pd(OAc)_2$ (0.45)	$Cu(OAc)_2$ (250) $CuCl_2$ (220)[a]	1.0

[a] charcoal (50 g) was also added

Kozhevnikov reported the synthesis of **2** by oxidative coupling of **1** using palladium acetate.[14] Repeating this reaction in glass ampoules at 100 °C with furfural as solvent gave low yields of **2** (Table 1). The presence of co-catalysts led to higher yields of **2** relative to palladium, making the reaction catalytic in nature, while the presence of an inert adsorbent (charcoal) resulted in the isolation of a purer product. The catalyst half-life, however, proved to be relatively short, and yields based on **1** were still unacceptably low. It is surmised that the limited amounts of dioxygen present in the excess furfural in the sealed glass tubes also had a deleterious effect on the yields.

Itahara has noted that acetic acid had a more favourable effect on the reaction, although when we repeated the reaction, the yield of **2** was only 10%.[15] The low yields were attributed to the inefficient re-oxidation of Pd^0 to Pd^{2+} by the co-catalyst Cu^{2+}, as envisaged in our proposed catalytic cycle (Scheme 1). From this scheme, it is evident that limiting factors in the sequence would be the availability of dioxygen and the re-oxidation of the co-catalyst. The latter will be determined by the amount of dissolved dioxygen in the acetic acid, which would be expected to be relatively low at 120 °C.

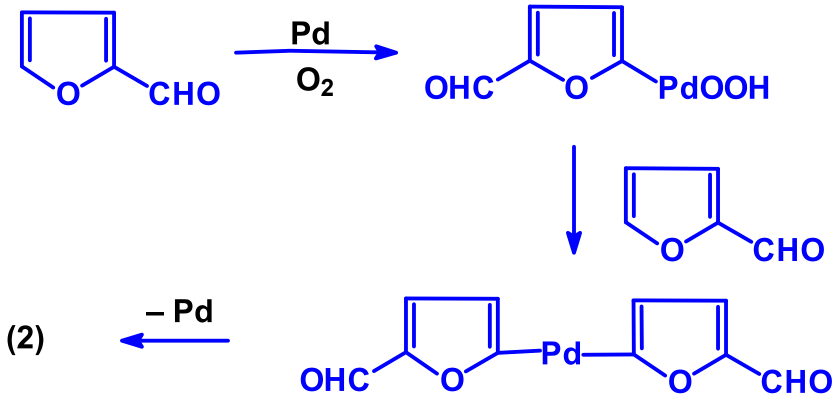


Re-oxidation of palladium

(a) In the presence of Cu (II) as catalyst

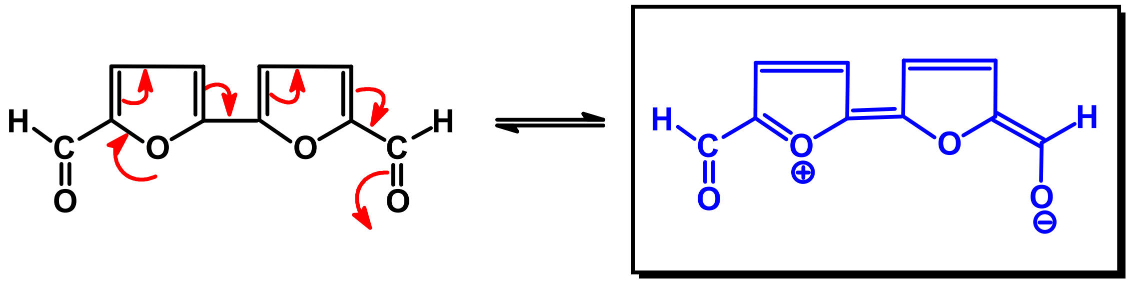
$$\begin{tikzcd} \mathrm{Pd}\ (0) + \mathrm{Cu}\ (\mathrm{II}) \arrow[r] & \mathrm{Pd}\ (\mathrm{II}) + \mathrm{Cu}\ (0) \arrow[l, bend left, "O_2"] \end{tikzcd}$$

(b) In the absence of copper catalysts



Scheme 1 Proposed mechanism for the palladium acetate-catalysed aryl coupling of furfural (**1**) to give 5,5’-diformyl-2,2’-difuran (**2**).

Attempts to increase the concentration of dioxygen by bubbling the gas through the reaction mixtures at reflux temperatures did not improve the yields of difurfural. The reaction was subsequently repeated in a sealed glass tube under a positive dioxygen pressure of two atmospheres with palladium acetate instead of the corresponding palladium chloride. The latter could possibly effect chlorinations in the oxidative milieu, or produce hydrogen chloride, which would favour polymerisation reactions of **1**. This reaction, however, gave 0.8% of dimer **2** and 34.5% of unreacted starting material. Increasing the dioxygen pressure to 50 atm at 120 °C resulted in a remarkable improvement in the yield of **2**. All the starting material reacted, and **2** (34.7%) precipitated out of the solution. Saturating the latter solution with sodium chloride, followed by continuous extraction with chloroform for 48 h, gave a further 21.1% of **2** (total yield: 55.8%). Although complete conversion of furfural to the dimer occurred (TLC and HPLC), isolation of the product from the acetic acid proved to be tedious. Compound **2** is more soluble in water than in most common organic solvents, possibly as a result of the compound existing in a zwitterionic form (equation 1), which makes extractive work-up of the reaction mixture and isolation of (**2**) difficult.



Equation 1 Zwitterionic nature of 5,5'-diformyl-2,2'-difuran (**2**).

Compound **2** is also sparingly soluble in most organic solvents, but could be purified effectively by sublimation under reduced pressure. In a duplicate experiment, freeze-drying of the acetic acid layer gave **2** in 60% yield, but the product polymerised rapidly as a result of the presence of trace amounts of residual acid. Distillation of the acetic acid under reduced pressure is surmised to promote the polymerisation of the dimer as a result of the higher temperature promoting acidcatalysed condensation. To alleviate these problems, various other solvents (chloroform and methanol) were tested, but all of these retarded the oxidative coupling reaction, emphasizing the important role of the solvent in the coupling reaction. In the absence of acetic acid, minimal coupling of furfural occurred as this solvent promotes the re-oxidation of Pd^0, whereas in neutral solvents rapid precipitation of palladium black occurred, thereby interrupting the catalytic cycle.

Table 2 Metal-catalysed oxidative coupling of furfural (**1**).[a]

Entry No	Catalyst	Solvent	Temp (°C)	Pressure of O_2 (atm)	(2) (%) [a]
1	$Pd(OAc)_2$	AcOH	25	1	1
2	$Pd(OAc)_2$	AcOH	120	50	60
3	$Pd(OAc)_2$	AcOH	150	70	35
4	$Pd(OAc)_2$	Ac_2O	100	50	5
5	$Pd(OAc)_2$ / HCl (cat.)	AcOH	100	50	17.5
6	$Pd(OAc)_2$ / $Cu(OAc)_2$	AcOH	100	50	5
7	$Pd(OAc)_2$ / *p*-TsOH	MeOH	80	70	1
8	$Pd(OAc)_2$	$(CH_3CO)_2CH_2$	100	50	[b]
9	$Pd(OAc)_2$	—	100	50	[b]
10	$Pd(OAc)_2$	AcOH	100	50 (N_2)	5
11	$Pd(OAc)_2$	AcOH	120	1	5[c]
12	$Pd(OAc)_2$ / $Cu(OAc)_2$ / Reillex (1:4:5)	AcOH	120	1	10[c]
13	$Pd(OAc)_2$ / $Cu(OAc)_2$ / Reillex (1:1:2)	AcOH	120	1	10(23)[d]
14	$Pd(OAc)_2$ / $Cu(OAc)_2$ / Reillex (1:1:1)	AcOH	120	1	10(50)[d]
15	$Pd(OAc)_2$ / $Cu(OAc)_2$ / Reillex (1:5:1)	AcOH	120	1	12(65)[d]

[a] Reaction conditions: Furfural (**1**) (2 g, 20.8 mmol), $Pd(OAc)_2$ (0.2 g, 1 mmol) and solvent (40 cm^3) reacted for 24 h in the absence or the presence of $Cu(OAc)_2$ (8 g, 4.6 mmol);
[b] **EXPLOSION!;**
[c] dioxygen bubbled through the solution;
[d] yields in parentheses were determined by HPLC.

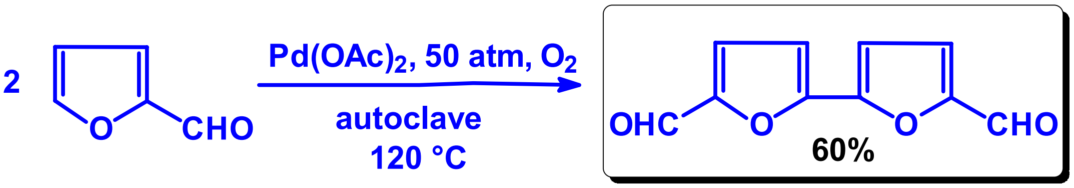
As electrophilic palladation can be achieved through the addition of acids to palladium acetate, hydrochloric acid and *p*-toluenesulphonic acid, respectively, were added to reaction mixtures using ethanol, 1,4-dioxane and acetonitrile, respectively, as solvents.[16] In the presence of acid, the furfural, however, rapidly polymerised, and no dimer **2** could be detected. With acetic acid as solvent and a catalytic amount of hydrochloric acid, **2** was isolated in 17.5% yield (Table 2, entry 5). In the presence of *p*-toluenesulphonic acid with methanol (or chloroform) as solvent, the reaction failed to produce dimer (Table 2, entry 7).

As it has been reported that acetylacetone promoted the $Pd(OAc)_2$-catalysed aryl coupling of tolyl derivatives to form dimers by a mechanism whereby the inactive palladium is retained in solution, thereby facilitating the re-oxidation of the latter to an active form, a stoichiometric quantity of this diketone was added to furfural under dioxygen at a pressure of 50 atm.[17] This reaction, however, resulted in a **VIOLENT EXPLOSION** after 20 min, demolishing a stainless steel autoclave designed to withstand cap pressures in excess of 180 atm. Similarly, the use of excess furfural in the absence of solvent also resulted in an **EXPLOSION** (Table 2, entries 8 and 9). This is attributed to an accumulation of peroxidic species, which have been proposed to form during the re-oxidation of Pd^0 to Pd^{2+}.[17] In order to determine the optimum ratio of air to dinitrogen necessary to achieve the optimum yield achieved, the reaction mixture was pressurized under dinitrogen at 50 atm, yielding a mere 5% of dimer **2**, suggesting the necessity for a relatively high concentration of dioxygen to effect efficient conversion of **1** into the dimer (Table 2, entry 10). Addition of copper(II) acetate did not promote coupling in the absence of palladium acetate, but in the presence of the latter a low yield of **2** was obtained (5%) (entry 6).

In order to develop a safer coupling method, the reaction was conducted at room temperature with dioxygen at atmospheric pressure, yielding **2** in 5% yield (entry 11). In an effort to retain the palladium in solution, a Reillex–$Pd(OAc)_2$–$Cu(OAc)_2$ catalytic system was introduced.[18] The rationale was to complex the palladium to the pyridine-based polymer, thereby keeping the palladium catalyst in solution, and also to provide a basic environment whereby polymerisation of the starting material is minimised. Using equivalent amounts of $Pd(OAc)_2$ and $Cu(OAc)_2$ (entry 13) gave **2** (10%), but when dioxygen was bubbled through the solution, more than double the yield of **2** was obtained (23%). Under the same reaction conditions as for the reactions reported in Table 2, and various ratios of substrates and catalysts, HPLC analysis indicated only moderate conversions of **1**, affording low yields of **2** on isolation (Table 2, entries 13–15).

3. Conclusions

The target compound **2** has been successfully synthesized in 60% yield under the conditions contained in Scheme 2 and Table 2 (entry 2).



(1) (2)

Scheme 2 Optimum conditions for the conversion of furfural (**1**) into 5,5'-diformyl-2,2'-difuran (**2**).

The catalytic nature of the reaction constitutes an attractive industrial route to this valuable product, the only problem at this stage being the relatively high toxicity of the solvent acetonitrile, which unfortunately is the solvent of choice.

4. Experimental

Melting points were determined on a Reichert melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Fourier Transform infrared spectrophotometer, model 1600 FTIR. ^{1}H-NMR (200 MHz) and ^{13}C-NMR (50 MHz) spectra were recorded on a Varian Gemini NMR spectrometer in $CDCl_3$ with TMS as internal standard. Low resolution mass spectra were determined at the University of Port Elizabeth on a Hewlett-Packard Mass Spectrometer, model HP 1000 E with a 70 eV electron impact source. Micro-analyses were determined in the analytical laboratories of the University of Port Elizabeth. Analytical HPLC was performed on a Waters instrument with a model 441 UV absorbance detector (254 nm) linked to a Hewlett-Packard data module using an internal standard quantification programme. Separation was achieved on a C_{18} reverse phase radial pack column using acetonitrile–water (40:60 v/v) as mobile phase and a flow rate of 2.5 cm^3 min^{-1}. Under these conditions furfural (**1**) had an elution time of 2.66 min, 5-bromo-2-furaldehyde (6.08 min), 5,5'-diformyl-2,2'-difuran (**2**) (8.16 min) and nitrobenzene (internal standard; 11.68 min).

*Ullmann Synthesis of 5,5'-Diformyl-2,2'-difuran (**2**) from 5-Bromo- or 5-Iodo-2-furaldehyde*

5-Bromo-2-furaldehyde (2 g, 11.4 mmol), copper powder (0.76 g, 11.4 mmol) in dry redistilled DMF (50 cm^3) was stirred, while heating under reflux for 24 h. The hot solution was filtered, the filtrate cooled to 5 °C and allowed to stand at this temperature for 24 h. The resultant precipitate of 5,5'-diformyl-2,2'-difuran (**2**) was filtered (40 mg, 3.7%). Concentration of the organic layer gave unreacted starting material (1.6 g, 80%).

The above reaction was repeated with 5-iodofurfural to give **2** (120 mg, 14%) and unreacted starting material **1** (1.46 g, 73%).

*Oxidative Coupling of Furfural (**1**)*

(i) Under Reflux Conditions (Atmospheric Pressure). Furfural (**1**) (2 g, 20.8 mmol), $PdCl_2$ (0.4 g, 2.3 mmol) and $Cu(OAc)_2$ (0.8 g, 4.6 mmol) in AcOH (20 cm^3) were refluxed while stirring for 24 h. The reaction mixture was filtered, the filtrate was poured into water (100 cm^3), which was extracted with $CHCl_3$ (4 × 50 cm^3). The organic layer was washed with a concentrated Na_2CO_3 solution (3 × 50 cm^3), dried (Na_2SO_4) and concentrated under reduced pressure to afford light brown crystals of 5,5'-diformyl-2,2'-difuran (**2**) (0.28 g, 14.7%, based on furfural; 64% based on Pd); mp 264–266 °C (lit.[14], mp 262–265 °C); ν_{max} ($CHCl_3$) / cm^{-1} 1670 (C=O); δ_H ($CDCl_3$) 7.1 (2H, d, J 3.9 Hz, C-4 ArH), 7.3 (2H, d, J 3.9Hz, C-3 ArH) and 9.7 (2H, s, CHO); m/z 190 (M^+, 100%) and 133 ($M - C_2H_2O_2$); HRMS: M^+, 190.02792; Calc. for $C_{10}H_6O_4$: M, 190.02661 (Found: C, 63.55; H, 3.55. Calc. for $C_{10}H_6O_4$: C, 63.16; H, 3.18%).

(ii) In the Presence of Dioxygen (Under Pressure). Furfural (**1**) (2 g, 20.8 mmol) and $Pd(OAc)_2$ (0.2 g, 1 mmol) dissolved in AcOH (40 cm^3) were transferred to an autoclave, purged with O_2 and subsequently pressurized with the latter to 2 atm. The reaction mixture was stirred at ambient temperature for 3 days, the autoclave depressurized, and the mixture filtered. The filtrate was poured into cold water (40 cm^3), which was extracted with $CHCl_3$ (5 × 100 cm^3). The organic layer was washed with 20% aqueous Na_2CO_3 (2 × 100 cm^3), dried (Na_2SO_4), filtered and allowed to stand at 5 °C for 2 h. The precipitate was filtered, giving 5,5'-diformyl-2,2'-difuran (**2**) [32 mg, 0.8%; 80.9% based on $Pd(OAc)_2$]. Concentration of the filtrate gave unreacted furfural (710 mg, 35.5%)

The above reaction was repeated using a modified work-up procedure. The hot reaction mixture was filtered to afford palladium black (50 mg). The hot filtrate allowed to stand at 0 °C for 5 h, and the resulting precipitate was filtered and air-dried to give dimer **2** (589 mg, 29.8%). Freeze-drying of the mother liquor yielded **2** (574 mg, 29.1%), which polymerised on standing.

*Oxidative Coupling of Furfural (**1**) under Various Conditions*

The oxidative coupling of furfural was conducted under various reaction conditions. In all reactions furfural (2 g, 20.8 mmol) as substrate and $Pd(OAc)_2$ (0.2 g, 1 mmol) in solvent (40 cm^3) in the presence of O_2 were treated as summarized in Table 2. The reaction time in all cases was 24 h. The reported yields are for pure isolated 5,5'-diformyl-2,2'-difuran (**2**).

*Oxidative Coupling of Furfural (**1**) Utilizing a Reillex–palladium acetate–copper catalyst*

(i) Preparation of the Catalyst. Reillex (1 eq.), $Pd(OAc)_2$ (1 eq.) and powdered $Cu(OAc)_2$ (1 eq.) in acetonitrile (40 cm^3) were left to stand at room temperature for 24 h. The acetonitrile was distilled off under reduced pressure and the catalyst heated at 100 °C for 6 h before use.

*(ii) Reaction of (**1**) with the Reillex–palladium Catalyst and Dioxygen under Reflux Conditions.* Reillex–$Pd(OAc)_2$ catalyst (860 mg, 2.23 mmol) in AcOH (80 cm^3) was heated at 120 °C with O_2 bubbling through the solution for 10 min. Furfural (2.5 g, 26 mmol) was added, and the mixture was heated under reflux for 24 h with a continuous flow of O_2 through the solution. The cooled mixture was poured into water (50 cm^3) and extracted with CH_2Cl_2 (5 × 50 cm^3). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give starting material **1** (860 mg, 34.4%), as well as 5,5'-diformyl-2,2'-difuran (**2**) 560 mg, 22.7%), which precipitated from the reaction mixture. Other variations in catalyst composition had little effect on the yields of **2** (Table 2).

Acknowledgements

The authors thank Illovo Sugar for generous financial assistance and emeritus Prof. A. Goosen and Mr. Alan Wills for helpful suggestions. Mr H. Marchand is thanked for his invaluable technical assistance, and thanks are also extended to Dr P.R. Boshoff, Cape Technikon, for the recording of high resolution mass spectra.

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