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Received March 14, 1995

The oxidation of 5-hydroxymethylfurfural (1) or 5-hydroxymethylfurfurylideneacetophenone (4) with various 4-substituted 2,2,6,6-tetramethylpiperidine radicals (TEMPO) 3a-d and supporting co-oxidants gave corresponding aldehydes 2 or 5 in fair yields.

J. Heterocyclic Chem., **32**, 927 (1995).

Interesting synthetic applications of furan-2,5-dicarbaldehyde (2), which is a starting material in the preparation of annulene oxides [1], polyenylsubstituted furans [2] or macrocyclic ligands [3,4] encourage us to search for new and more efficient methods of its synthesis. This compound 2 has already been synthesized from 2-diethoxymethylfuran [5], 2,5-bis(hydroxymethyl)furan [6], furan-2,5-dicarbonitrile [7] and from furan itself [8].

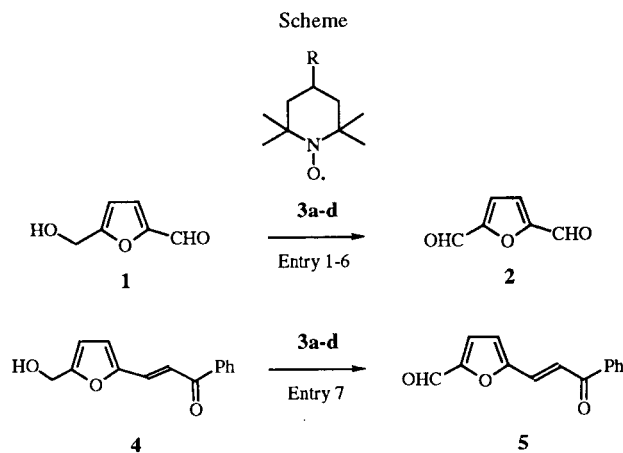
The furan-2,5-dicarbaldehyde (2) was also prepared by the regioselective oxidation of 5-hydroxymethyl-2-furfural (HMF) 1, raw material easily accessible from biomass [9]: Morikawa used chromium trioxide in pyridine [10] or nitrogen oxide in dimethylsulfoxide [11], El-Hajj *et al* [12] oxidized HMF (1) with barium manganate to obtain the dialdehyde 2 in 90% yield.

We previously reported the synthesis of the dialdehyde 2 by the oxidation of HMF (1) with pyridinium chlorochromate-aluminium oxide system under sonochemical conditions [13] and from 5-(trialkylsilyloxy)methyl-2-furfural using *N*-bromosuccinimide-azobisisobutyronitrile [14] pair.

Now we would like to report the oxidation of 5-hydroxymethyl-2-furfural (1) with 2,2,6,6-tetramethylpiperidine oxide free radicals (TEMPO). Nitroxides, well known as stable radicals for spin labelling and radical trapping, have a great value as organic oxidants due to their participation in reversible redox reactions [15]. The oxidation of a variety of substrates including alcohols, vic-diols, amines, thiols, phosphines, phenols and ketones were reported [16-18]. While nitroxides can be used as oxidants, the corresponding oxammonium salts are more powerful oxidizers. These relatively unstable salts, easily prepared by in situ oxidation of the nitroxide convert back to the nitroxide after performing the oxidation. With this sequence, tetramethylpiperidine oxide (TEMPO) reagents can be used as recyclable oxidation catalysts in the pres-

ence of a secondary oxidant. Following compounds were reported to play this role: bleach [19,20], sodium bromite and calcium hypochlorite [21], copper(I) chloride-oxygen [22], *p*-toluenesulfonic acid [23], electrochemically generated bromine radical [24] or electrons generated at the electrode surface [25].

To our knowledge, such studies have never been performed for furfuryl alcohol derivatives. Here we report the selective oxidation of HMF (1) with TEMPO 3a-d in the presence of various secondary oxidants and an application to 5-hydroxymethylfurfurylideneacetophenone (4). The detailed results of all experiments are presented in the Table.



First, we tested calcium hypochlorite as a co-oxidant (entry 1). Reactions carried out in a biphasic system (water-dichloromethane) permitted to afford the compound 2 in an excellent yield in each case; the most powerful oxidant turned out to be the 4-benzoyloxy-2,2,6,6-tetramethylpiperidine oxide 3d, as it permitted to obtain 2 in 81% yield after 10 minutes of the reaction. We per-

Table

Entry No.	Co-oxidant with 1	Yields % without TEMPO	Yields % of 2 or 5 in the presence of				Molar ratios		Reaction time (hour)
			3a	3b	3c	3d	TEMPO/HMF	Coxid/HMF	
1	Ca(ClO) ₂	0.002	75	65	68	81	1:100	1.1:1	1/6
2	NaClO/KBr	2	45	26	38	32	2:100	4:1	1
3	CuCl/O ₂	0	65	60	57	63	2:10	1:5	18
4	<i>p</i> -TsOH	—	—	53	81	—	2.1:1	2.1:1	3
5	I ₂ ⁻ /OH	0	16	58	58	19	2:100	1:2	2
6	Electrochem. generated Br [•] with 4	—	31	53	34	20	2:100	—	5
7	Ca(ClO) ₂	—	—	—	59	—	1:100	1.1:1	1/6

formed also the oxidation of **1** with potassium bromide-sodium hypochlorite pair as a co-oxidant (entry 2). Unfortunately, this system is less suitable because the yields of product **2** were less than 48% after 1 hour of the reaction.

When **1** was oxidized with radicals **3a-d** in the presence of copper(I) chloride under oxygen in acetonitrile (entry 3), the dialdehyde **2** was obtained in about 60% yield in all four cases. However, non-substituted TEMPO **3a** seems to be the best oxidant as it provides the compound **2** in 65% yield. Such a compound as *p*-toluenesulfonic acid (entry 4), when applied to this reaction as a secondary oxidant gave the desired dialdehyde **2** in 81% yield. But the necessity of using more than two-fold excess of the radical in respect to HMF (**1**) is highly disadvantageous.

It is well known that iodine is able to oxidize certain chemical species in an alkaline solution through formation of iodate anion [26]. Therefore, we used iodine as a co-oxidant (entry 5) and we performed the reaction in a biphasic (water-methylene chloride) system. Experiments showed that only the presence of a hydrophilic substituent in a position '4' of the TEMPO molecule **3b** and **3c** makes results satisfactory giving **2** in fair yields.

We also tested electrochemically generated bromine radical as a secondary oxidant for TEMPO **3a-d** (entry 6). The electrochemical reaction performed in a biphasic (water-methylene chloride) system gave the compound in rather moderate yields (less than 60%), which limits the preparative value of this method.

We also made comparative studies with some of these secondary oxidants in the absence of TEMPO radicals but exactly in the same conditions. We tested sodium and calcium hypochlorites, iodine as well as copper(I) chloride under oxygen. In all cases, the conversion rate of **1** was lower than 2%. We recovered the substrate **1** and a little amount of **2** contaminated by degradation products. This above allows us to state that the absence of TEMPO radicals in this type of reaction makes it ineffective and non-selective, while the presence of a catalytic amount of a

radical increases the regioselectivity of the oxidation to a very high degree.

We were also interested very much in the synthesis of 5-formylfurfurylideneacetophenone (**5**) for a subsequent conversion into unsaturated acrylic ester. The oxidation of corresponding alcohol **4** with barium manganate or with pyridinium chlorochromate gave the aldehyde **5** in about 55% yield [13]. We slightly improve the yield up to 59% using TEMPO **3c** with calcium hypochlorite as co-oxidant (entry 7). Although the yields are similar, this last method is more convenient because the reaction proceeds in a shorter time (10 minutes) with an easier experimental work.

In summary, the oxidation of furfuryl alcohols such as HMF (**1**) or furfurylidene derivative **4** with TEMPO **3a-d** in presence of co-oxidant leads to the corresponding furfural in a fair or excellent yield. The best co-oxidant is the calcium hypochlorite, cheaper than barium manganate or pyridinium chlorochromate. Other advantages of this method are the use of a catalytic amount of TEMPO, the possibility of working in biphasic system, the high purity of the formed product and a short time of reaction.

EXPERIMENTAL

All solvents were distilled and dried prior to use. TEMPO radicals (FLUKA) were used as received; as bleach, commercial bleaching hypochlorite solution (48 deg chlorimetric, 12.5% of active chlorine) was used. The constant current electrolysis was performed on EG&G Princeton Applied Scanning apparatus Model 362, in divided, H-shaped cell, at a platinum net anode (20 cm² of a real surface) and a platinum-iridium cathode. Mercury(I) sulfate electrode was used as a reference electrode. All spectra were recorded on a Perkin Elmer (ir) and a Bruker 200 MHz (¹H nmr) spectrometers.

General Procedure for the Oxidation of HMF **1** with TEMPO **3a-d**-Calcium Hypochlorite Pair.

HMF **1** (2.52 g, 20 mmoles) and a TEMPO radical **3a-d** (0.2 mmole) were dissolved in methylene chloride (100 ml) and 5% aqueous sodium hydrogen carbonate (200 ml) was added. On

cooling to 0-3°, calcium hypochlorite (2.65 g, 22 mmoles) was added portionwise with a vigorous stirring. The mixture was then stirred for 10 minutes at 10-15° and then, filtrated through fritted glass funnel packed with celite. An organic layer was separated and washed with 5% aqueous potassium hydrogen sulfate (80 ml) which was joined with the aqueous layer and both were extracted with methylene chloride (3 x 50 ml). All organic fractions were dried (magnesium sulfate) and evaporated; the solid residue was recrystallized from carbon tetrachloride to afford the product **2** as white crystals, mp 108-109° (lit [5] 109-110°); ir (potassium bromide): ν 2920 (-CHO), 1690 (C=O), 1580, 1520, 1410 (C_{furan}) cm⁻¹; ¹H nmr (deuteriochloroform): δ 7.35 (s, 2H, =CH-CH=), 9.85 (s, 2H, CHO).

General Procedure for the Oxidation of HMF **1** with TEMPO **3a-d-p**-Toluenesulfonic Acid Pair.

To a stirred and cooled (-2°) solution of HMF **1** (0.252 g, 2 mmoles) and *p*-toluenesulfonic acid (0.8 g, 4.2 mmoles) in methylene chloride (6 ml), a solution of TEMPO radical **3a-d** (4.2 mmoles) in 6 ml of methylene chloride, cooled to -2°, was added dropwise within 30 minutes. The mixture was stirred for 1 hour at 0°, and then at a room temperature for 1.5 hour until complete decoloration. After cooling to -5°, the mixture was filtered. The filtrate was washed first with water then with brine and the aqueous solutions were extracted with methylene chloride (3 x 10 ml). Collected organic layers were dried (sodium sulfate) and evaporated. The solid residue was recrystallized from carbon tetrachloride to give the dialdehyde **2** identical to the sample described above.

General Procedure for the Oxidation of HMF **1** with TEMPO **3a-d**-Potassium Bromide-Sodium Hypochlorite System.

HMF **1** (1.26 g, 10 mmoles) and TEMPO radical **3a-d** (0.2 mmole) were dissolved in methylene chloride (20 ml) and 2*M* aqueous potassium hydroxide (2 ml). The bleaching solution (37 ml) in water (11 ml) was added to this biphasic mixture cooled to 0° and vigorously stirred. Afterwards, the mixture was stirred at 0-5° for 1 hour. Then, the aqueous layer was separated, extracted with methylene chloride (3 x 10 ml), extracts were combined with the organic layer and washed with water. Aqueous solutions were extracted with methylene chloride; all organic phases were dried (magnesium sulfate) and evaporated. The residue was recrystallized from carbon tetrachloride to give the compound **2** identical to the sample described above.

General Procedure for the Oxidation of HMF **1** with TEMPO **3a-d**-Iodine System.

HMF **1** (1.26 g, 10 mmoles) was dissolved in methylene chloride (25 ml) and TEMPO **3a-d** (0.2 mmole) was added. To this solution was added 1*M* aqueous potassium hydroxide (50 ml) and then, on stirring, iodine (1.27 g, 5 mmoles) was added portionwise. The biphasic mixture was stirred vigorously for 2 hours. Then, sodium thiosulfate (0.5 g) was added to destroy the excess of iodine, the organic layer was separated, and the aqueous one was extracted with methylene chloride (3 x 10 ml). All the organic fractions were collected, washed with brine, dried (magnesium sulfate) and evaporated. The solid residue was recrystallized from carbon tetrachloride to give the dialdehyde **2** identical to the sample described above.

General Procedure for the Oxidation of HMF **1** with TEMPO **3a-d**-Copper(I) Chloride-Oxygen System.

To a solution of HMF **1** (1.26 g, 10 mmoles) and TEMPO radical **3a-d** (2 mmoles) in acetonitrile (25 ml), cuprous chloride (0.194 g, 2 mmoles) was added. The suspension was stirred under oxygen for 16 hours. After being filtered, the filtrate was evaporated. The residue was recrystallized from carbon tetrachloride to give the dialdehyde **2** as yellowish crystals identical to the sample describe above.

General Procedure for the Electrochemical Oxidation of HMF **1** with TEMPO **3a-d**-Potassium Bromide System.

A solution of HMF **1** (0.63 g, 5 mmoles) and TEMPO radical **3a-d** (0.1 mmoles) in methylene chloride (10 ml) was placed in an anodic compartment. Then, 25% aqueous potassium bromide saturated with sodium hydrogen carbonate (50 ml) was added to this compartment, and a similar aqueous solution (60 ml) was placed in a cathodic compartment. The whole mixture was submitted to the constant current electrolysis at 5 mA/cm² of a current density, for 5 hours with moderate stirring. After separation of the organic layer, an aqueous layer of anolyte and the catholyte were extracted with methylene chloride (3 x 10 ml). All organic fractions were dried (magnesium sulfate) and evaporated. The residue was recrystallized from carbon tetrachloride to give the dialdehyde **2** as almost white crystals identical to the sample described above; ir (potassium bromide): ν 2920 (-CHO), 1690 (C=O), 1580, 1520, 1410 (C_{furan}) cm⁻¹; ¹H nmr (deuteriochloroform): δ 7.35 (s, 2H, =CH-CH=), 9.85 (s, 2H, CHO).

5-Formylfurfurylideneacetophenone (**5**).

Compound **5** was obtained following the procedure for the oxidation of **1** with **3c** and calcium hypochlorite as co-oxidant. Compound **4** (0.228 g, 1 mmole) gave after reaction and purification on a silica gel column (2.5 x 30 cm) eluted with ethyl acetate:hexane (1:1, v/v) 0.133 g (59%) of **5** as yellow crystals, mp 98-99°, lit [13] 98.1-98.9°; ¹H nmr (deuteriochloroform): δ 9.72 (s, 1H, CHO), 8.08 (m, 2H, CH arom), 7.77 and 7.59 (2d, 2H, J = 15.5 Hz, -CH=CH-), 7.57 (m, 3H, arom), 7.30 and 6.85 (2d, 2H, J = 3.7 Hz, =CH-CH=).

Acknowledgement.

The authors are thankful to Professor B. Beden and to Dr. E. M. Belghsir from the University of Poitiers for the help with the electrochemical measurements. The participation of Südzucker GmbH in providing HMF is kindly acknowledged.

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