HETEROCYCLES, Vol. 102, No. 6, 2021, pp. 1185 - 1193. © 2021 The Japan Institute of Heterocyclic Chemistry
Received, 6th March, 2021, Accepted, 26th March, 2021, Published online, 5th April, 2021
DOI: 10.3987/COM-21-14450

FACILE ACCESS TO HIGHLY-SUBSTITUTED DIHYDROFURANS USING RESONATED VINYLPENTANEDIONE RADICALS GENERATED BY Mn(III)-BASED OXIDATION

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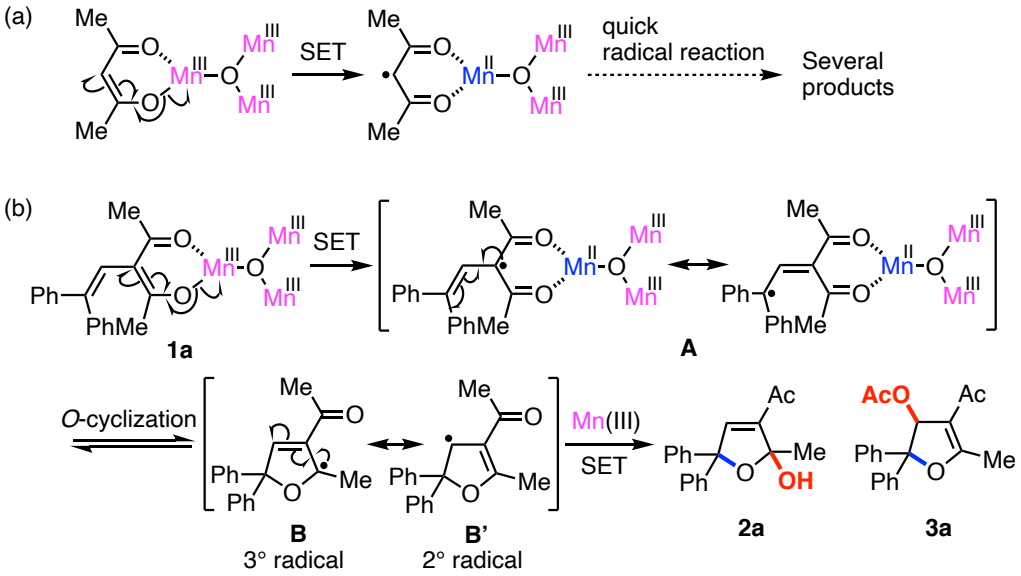
Abstract – Useful and easy access to highly-substituted dihydrofurans, which convert into various acetals, was established using the common Mn(III) oxidation. The key point is to use resonated vinylpentanedione radicals that cyclize to produce the desired acetoxydihydrofurans which are transformed into the hemiacetals and acetals in good yields under very mild conditions.

Highly-substituted simple heterocyclic compounds are needed for natural product synthesis as a starting material.[1] Therefore, it is important to establish an efficient and easy access to the heterocyclic compounds. During the course of these studies, a synthetic technique using the Mn(III) oxidation has been one of the most familiar methods for several decades. Although the Mn(III)-enolates producing 1,3-dicarbonyl radicals were used in a variety of carbon–carbon bond formation, those were limited in the preparation of heterocyclic compounds because the α-carbonyl radicals were somewhat active (Scheme 1(a)).[2] Especially, the reaction of pentane-2,4-dione was carried out under the Mn(III)-catalyzed aerobic oxidation conditions easily producing hydroxyfuranone via the predominant head-to-head radical coupling.[3] We then envisioned if the Mn(III)-enolate complex included a conjugate-available vinyl substituent, the produced radicals **A** during the single-electron transfer (SET) oxidation should resonate and might be stabilized, so that we could control the radical reaction (Scheme 1(b)). In order to prove the hypothesis, 3-(2,2-diphenylvinyl)pentane-2,4-dione (**1a**) was prepared[4] and underwent the Mn(III)-based oxidation that afforded the unexpected dihydrofuranyl acetate **3a** from the 2° radical **B'** instead of the dihydrofuran hemiacetal **2a** from the 3° radical **B** (Scheme 1(b)). In this paper, we describe the Mn(III)-based reaction of various 3-vinylpentane-2,4-diones to establish the new facile access to highly-substituted dihydrofurans.[5]

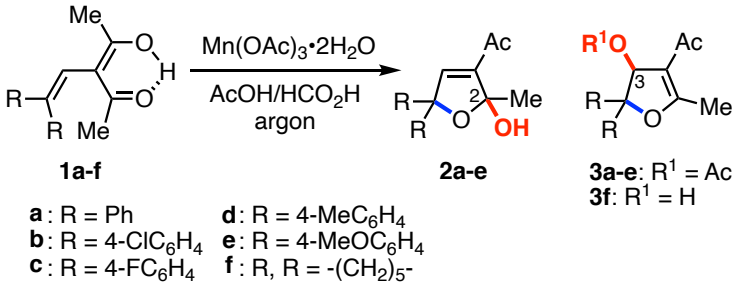


Scheme 1. (a) Single-Electron Transfer (SET) Oxidation of Mn(III)-Enolate Complex, and (b) the Oxidation of **1a**

In order to investigate this promising reaction, we prepared the 3-vinylpentane-2,4-diones by the acid-catalyzed ring-opening of the corresponding dihydrofurans[4] for **1a–e** and Knoevenagel condensation of the cyclohexanecarbaldehyde with pentane-2,4-dione for **1f**. With the 3-vinylpentane-2,4-diones **1a–f** as the enol form in hand, we chose the typical vinylpentanedione **1a** which was allowed to react **1a** (0.3 mmol) with $Mn(OAc)_3•2H_2O$ (0.6 mmol) in AcOH (10 mL) at reflux temperature. After work-up, the dihydrofuranyl acetate **3a** was obtained in moderate yield together with a trace amount of the desired dihydrofuran hemiacetal **2a** (Table 1, Entry 1). This showed that the 1,3-dicarbonyl radical **A** surely resonated via the vinyl group, finally producing **3a** (Scheme 1 (b)). Incidentally, **1a** did not cyclize in the absence of $Mn(OAc)_3$ under the stated conditions, and the corresponding dihydrofuran, such as **2a** and **3a**, was not produce.[4] Alternatively, although the 3-acetyl-2-methyl-5,5-diphenyl-4,5-dihydrofuran was directly oxidized with $Mn(OAc)_3$, the reaction did not proceed.

We then sought to optimize the reaction of **1a**, however, the reaction only became complicated. Since we reported that the addition of HCO_2H to the Mn(III) oxidation in AcOH increased the oxidation ability of $Mn(OAc)_3•2H_2O$ itself, accelerating the reaction time, allowing the reaction to occur at room temperature, and improving the product yield,[5a–d] the reaction was scrutinized in the presence of HCO_2H. Gratifyingly, the reaction dramatically changed and the product yield was improved (compared Entry 4 to Entries 1–3). The reactions of other vinylpentanediones **1b–e** were also investigated in the presence of HCO_2H at room temperature, mainly giving the corresponding dihydrofuranyl acetates **3b–e** along with the dihydrofuran hemiacetals **2b–e** as by-products (Table 1, Entries 7–21). In the case of bis(4-fluorophenyl)vinylpentane-

Table 1. Oxidation of Vinylpentanedione enols **1** with $Mn(OAc)_3•2H_2O$[a]



1a-f **2a-e** **3a-e**: R^1 = Ac; **3f**: R^1 = H

a: R = Ph **d**: R = 4-MeC_6H_4
b: R = 4-ClC_6H_4 **e**: R = 4-$MeOC_6H_4$
c: R = 4-FC_6H_4 **f**: R, R = -$(CH_2)_5$-

Entry	Substrate	$AcOH:HCO_2H$/mL[b]	Temperature	Time/min	Product/Yield/%[c]	
					2	**3**
1	**1a**	10:0	reflux	1.5	trace	54
2	**1a**	10:0	rt	12 h	9	47
3	**1a**	9:1	reflux	2		30
4	**1a**	9:1	rt	10	19	66
5	**1a**	8:2	rt	10	7	41
6	**1a**	7:3	rt	10	6	39
7	**1b**	10:0	reflux	3		57
8	**1b**	9:1	rt	10	6	44
9	**1b**	6:4	rt	10	20	76
10	**1b**	4:6	rt	8	18	66
11	**1c**	10:0	reflux	0.5		quant
12	**1c**	9:1	rt	7	9	67
13	**1c**	8:2	rt	3.5	9	74
14	**1c**	7:3	rt	3	13	73
15	**1c**	6:4	rt	3	10	66
16	**1d**	10:0	reflux	1		32
17	**1d**	9:1	rt	8	14	77
18	**1d**	8:2	rt	5.5	3	60
19	**1e**	10:0	reflux	0.5		53
20	**1e**	9:1	rt	12	4	95
21	**1e**	8:2	rt	8.5		20
22[d]	**1f**	150:0	reflux	40		44
23	**1f**	15:0	rt	120	dimeric product/29[e]	
24	**1f**	10:5	rt	3	dimeric product/20[e]	

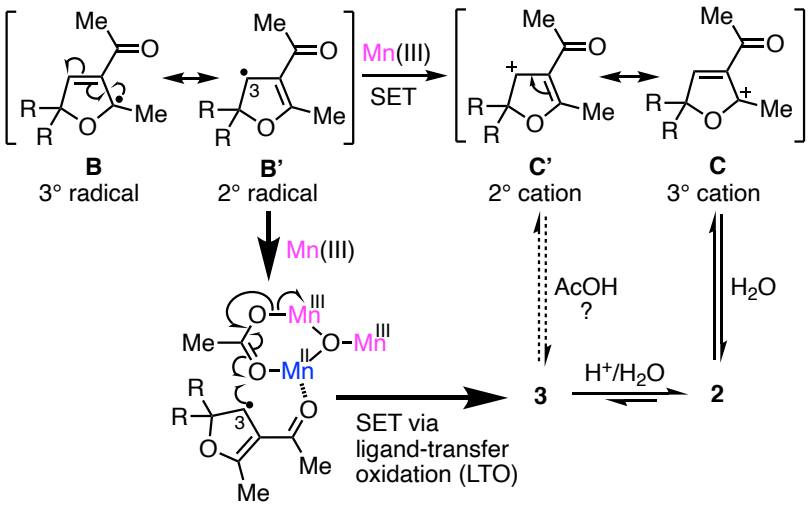
a) The reaction was carried out under argon at the molar ratio of **1** (0.3 mmol):oxidant = 1:2. b) $AcOH:HCO_2H$. c) The yield based on **1** used. d) The cyclohexylidenemethylpentanedione enol **1f** (0.5 mmol) was dropwise added to a mixture of $Mn(OAc)_3•2H_2O$ (2 mmol) and AcOH (150 mL) at reflux temperature. e) The desired **3f** was not obtaied, but instead the dimeric product, 3,4-diacetyl-3,4-bis(cyclohexylidenemethyl)hexane-2,5-dione.

dione **1c**, the dihydrofuranyl acetate **3c** was quantitatively produced in boiling acetic acid rather than in $AcOH/HCO_2H$ (Entry 11). The reaction of (cyclohexylidenemethyl)pentanedione enol **1f** was complicated under various conditions and a dimeric product, 3,4-diacetyl-3,4-bis(cyclohexylidenemethyl)hexane-2,5-dione, was somehow isolated (Entries 23, 24). In order to quit the

dimerization reaction, dilution conditions were applied and the desired 1-oxaspiro[4.5]dec-2-ene **3f** having a hydroxy group at the C-4 position was obtained in 44% yield (Entry 22).

The structures of the dihydrofuran hemiacetals **2** and dihydrofuranyl acetates **3** were easily distinguishable by 1D and 2D NMR spectroscopies. For example, a characteristic H-4 sp^2 methine proton (δ 7.34) and C-4 sp^2 carbon (δ 145.4), a hydroxyl proton (δ 2.95) and C-2 hemiacetal carbon (δ 109.0) appeared in the ^{1}H and ^{13}C NMR spectra of the hemiacetal **2a** containing two methyl groups, while a characteristic H-3 sp^3 methine proton (δ 6.81) and C-3 sp^3 methine carbon (δ 80.6), C-5 enol carbon (δ 172.7) showed in the ^{1}H and ^{13}C NMR spectra of the acetate **3a** including three methyl groups. The HMQC and HMBC spectra of **2b** and **3b** also supported their structures as well as the 1D NMR spectra.

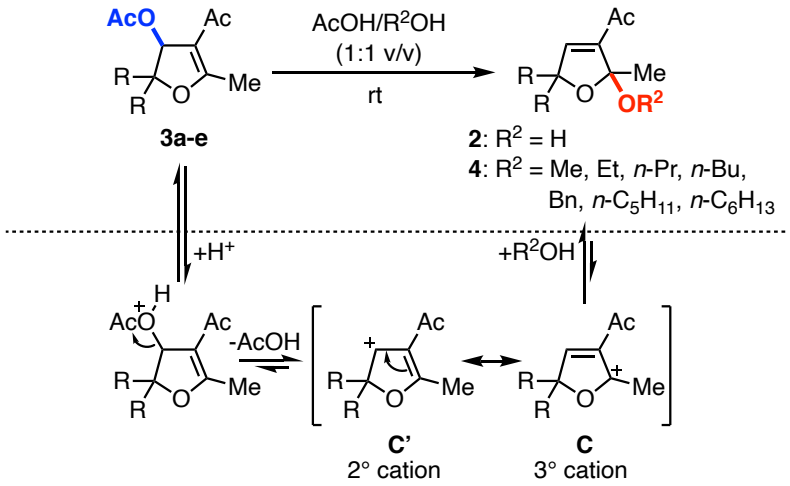
Superior production of the acetates **3** rather than the hemiacetals **2** deserves comment. Apparently, the formed 3-vinylpentanedione radicals **A** in Scheme 1 (b) were stabilized by resonance followed by *O*-cyclization to give the dihydrofuranyl tertiary radicals **B**. The radicals **B** would also be stabilized in a similar manner as shown in Scheme 2, and further oxidized to produce the hemiacetals **2** via the thermodynamically more stable tertiary carbocations **C**. However, since the acetate substituent was predominantly introduced at the C-3 position, the reaction via 2° radical **B'** must be kinetically controlled, such as via ligand-transfer oxidation (LTO), to produce **3** (Scheme 2).[7] The preferential LTO is considered to proceed under kinetic control at room temperature, exclusively producing the dihydrofuranyl acetates **3** (Table 1, Entries 4–6, 8–10, 12–15, 17, 18, 20, 21). In the case of **1f**,[4c] it is not clear at this moment why the hydroxy-oxaspirodecene **3f** instead of the corresponding acetate was obtained (Entry 22). Probably, the reason might be that high dilution conditions were adopted in the reaction.



Scheme 2. Mechanism for the Formation of **2** and **3**

From the point of thermodynamic stability of the dihydrofuranyl carbocation, such as **C** (Table 2), we thought that the dihydrofuranyl acetates **3** might be converted by the treatment of water into the hemiacetals **2**. In fact, stirring of **3a** in AcOH/H_2O at room temperature resulted in the expected hemiacetal **2a** (Table 2, Entry 1). Other dihydrofuranyl acetates **3b–e** also gave the hemiacetals **2b-e** according to the same procedure described above (Entries 2–5). Use of various alcohols instead of water caused similar transformations to produce the envisaged dihydrofuran acetals **4** (Entries 6–20).

Table 2. Treatment of Dihydrofuranyl Acetates **3** with R^2OH[a)]



Entry	Sub.	R^2OH	Time/h	Yield/%[b,c)]
1	**3a**	H_2O	3	92
2	**3b**	H_2O	24	90
3	**3c**	H_2O	3	74
4	**3d**	H_2O	3	94
5	**3e**	H_2O	3	68
6	**3a**	MeOH	6	92
7	**3b**	MeOH	24	72
8	**3c**	MeOH	24	97
9	**3d**	MeOH	6	95
10	**3e**	MeOH	6	41
11	**3a**	EtOH	6	58
12	**3b**	EtOH	24	62
13	**3c**	EtOH	24	47
14	**3d**	EtOH	6	87
15	**3e**	EtOH	6	60
16	**3a**	*n*-PrOH	24	42
17	**3a**	*n*-BuOH	24	57
18	**3a**	*n*-BnOH	72	54
19	**3a**	*n*-Pentanol	26	54
20	**3a**	*n*-Hexanol	26	30

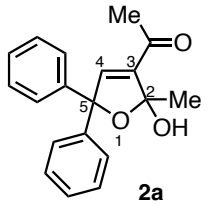
a) The reaction of **3** (0.15 mmol) was carried out in AcOH (5 mL)/R^2OH (5 mL) at room temperature. b) The unchanged starting acetates **3** were recovered in all the reactions. c) The yield based on **3** was used.

In conclusion, the facile access to highly-substituted dihydrofurans **3** was established by the Mn(III)-based oxidation of the vinylpentanedione enols **1**. Especially, it was effective to add HCO_2H to the reaction which was conducted at room temperature. The activation of the reaction by adding HCO_2H was derived from the newly formed HCO_2-Mn(III)-1,3-dicarbonyl enolate complex during the reaction.[5a–d] In addition, the resonance stability of the vinylpentanedione radicals **A** (Scheme 1 (b)) and the dihydrofuranyl radicals **B** (Scheme 2) was proved based on the product distribution. Furthermore, we demonstrated the easy transformation of the dihydrofuranyl acetates **3** into the corresponding hemiacetals **2** and acetals **4**.

EXPERIMENTAL

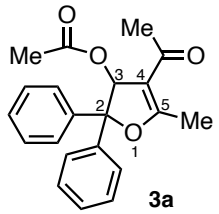
Preparation of Vinylpentanedione Enols 1a–f. The vinylpentanediones **1a–e** were synthesized by the acid-catalyzed ring-opening of the 3-acetyl-5,5-diaryl-2-methyl-4,5-dihydrofurans which were prepared by the Mn(III)-based oxidation of the corresponding diarylethenes with pentane-2,4-dione (see SI).[4] The vinylpentanedione enol **1f** was prepared by the Knoevenagel condensation of cyclohexanecarbaldehyde with pentane-2,4-dione.

Oxidation of Vinylpentanedione Enol 1a. To a vinylpentanedione enol **1a** (0.3 mmol, 84.7 mg) in AcOH (10 mL), $Mn(OAc)_3$•$2H_2O$ (0.6 mmol, 162.2 mg) was added and the mixture was heated under reflux for 1.5 min. After cooling, the solvent was removed in vacuo, and the residue was triturated with water (10 mL). The aqueous mixture was extracted with $CHCl_3$ (10 mL x 3), and the combined extracts were washed with a saturated aqueous solution of $NaHCO_3$, water, dried over anhydrous $MgSO_4$, then concentrated to dryness. The residue was separated by column chromatography on silica gel eluting with hexane/EtOAc (7:3 v/v), giving **2a** (trace) and **3a** (55.3 mg, 54%) (see Table 1). A similar reaction of **1a** (0.3 mmol, 75.4 mg) was stirred in AcOH (9 mL)/HCO_2H (1 mL) at room temperature for 10 min. After the same work-up described above, **2a** (15.1 mg, 19%) and **3a** (59.8 mg, 66%) were obtained.



2a

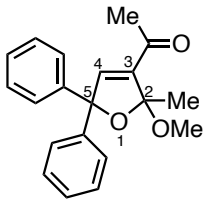
3-Acetyl-2-hydroxy-2-methyl-5,5-diphenyl-2,5-dihydrofuran (2a): Yellowish oil; R_f = 0.33 (EtOAc/hexane 3:7 v/v); IR ($CHCl_3$) ν 3414 (OH), 1674 (C=O); ^{1}H NMR ($CDCl_3$) δ 7.44–7.26 (10H, m, arom H), 7.34 (1H, s, H-4), 2.95 (1H, brs, OH), 2.43 (3H, s, Me), 1.79 (3H, s, Me); ^{13}C NMR ($CDCl_3$) δ 194.6 (2C) (=C–O), 145.4 (C-4), 143.5 (C-3), 142.8, 141.4 (arom C), 128.7 (2C), 128.6 (2C), 128.03, 128.0, 126.7 (2C), 126.6 (2C) (arom CH), 109.0 (C-2), 91.7 (C-5), 28.1 (CO<u>Me</u>), 27.0 (Me); FAB HRMS (acetone/NBA) *m/z*: $[M+Na]^+$ Calcd for $C_{19}H_{18}O_3Na$ 317.1147; found 317.1154.



3a

4-Acetyl-5-methyl-2,2-diphenyl-2,3-dihydrofuran-3-yl acetate (3a): Colorless liquid; R_f = 0.51 (EtOAc/hexane 3:7 v/v); IR ($CHCl_3$) ν 1735, 1670 (C=O); ^{1}H NMR ($CDCl_3$) δ 7.77–7.67 (2H, m, arom H), 7.44–7.37 (3H, m, arom H), 7.29–7.23 (5H, m, arom H), 6.81 (1H, s, H-3), 2.49 (3H, s, Me), 2.14 (3H, s, COMe), 1.54 (3H, s, OAc); ^{13}C NMR ($CDCl_3$) δ 193.8 (C=O), 172.7 (C-5), 170.5 (OCOMe), 141.0, 137.9 (arom C), 128.72, 128.70 (2C), 128.1, 127.8 (2C), 127.5 (2C), 126.8 (2C) (arom CH), 111.6 (C-4), 95.5 (C-2), 80.6 (C-3), 29.0 (COMe), 20.4 (OCOMe), 15.7 (Me); FAB HRMS (acetone/NBA) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{20}O_4Na$ 359.1259; found 359.1275.

Treatment of Dihydrofuranyl Acetates 3 with R^2OH. Dihydrofuranyl acetate **3a** (12.9 mg) was dissolved in AcOH/H_2O (5/5 mL) at room temperature and stirred under argon for 3 h. Additional water (10 mL) was added to the mixture and the aqueous solution was extracted with $CHCl_3$ (10 mL x 3). The combined extracts were washed with a saturated aqueous solution of $NaHCO_3$ followed by water, dried over anhydrous $MgSO_4$, and concentrated to dryness. The residue was separated by column chromatography on silica gel eluting with hexane/EtOAc (3:7 v/v), giving **2a** (10.4 mg, 92%). A similar reaction of **3a** (34.0 mg) was carried out in AcOH/MeOH (5/5 mL) instead of water for 6 h, producing the acetal **4a** (28.6 mg, 92%).



4a: R^2 = Me

3-Acetyl-1-(2-methoxy-2-methyl-5,5-diphenyl-2,5-dihydrofuran (4a: R^2 = Me): Yellow oil; R_f = 0.33 (EtOAc/hexane 3:7 v/v); IR ($CHCl_3$) ν 1678 (C=O); ^{1}H NMR ($CDCl_3$) δ 7.46 (1H, s, H-4), 7.40–7.37 (4H, m, arom H), 7.35–7.32 (4H, m, arom H), 7.29–7.25 (2H, m, arom H), 3.00 (3H, s, OMe), 2.44 (3H, s, COMe), 1.75 (3H, s, Me); ^{13}C NMR ($CDCl_3$) δ 193.7 (C=O), 146.2 (C-4), 143.7, 143.6 (arom C), 139.7 (C-3), 128.7 (2C), 128.6 (2C), 127.8, 127.7, 126.5 (2C), 126.1 (2C) (arom CH), 112.9 (C-2), 90.7 (C-5), 50.9 (OMe), 28.1 (COMe), 25.5 (Me); FAB HRMS (acetone/NBA) *m/z*: $[M+Na]^+$ Calcd for $C_{20}H_{20}O_3Na$ 331.1310; found 331.1329.

ACKNOWLEDGEMENTS

This research was supported by a Grant-in-Aid for Scientific Research (C), No. 18K05109, from the Japan Society for the Promotion of Science.

SUPPORTING INFORMATION

Measurements, materials, preparation of starting dihydrofurans, vinylpentanediones **1a–f**, and the physical properties of **1a–f**, the new compounds **2b–e**, **3b–e**, **4b–e**, and the dimeric product.

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