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Furan oxidation by Mn(III)/Co(II) catalysts – application to benzofuran synthesis†

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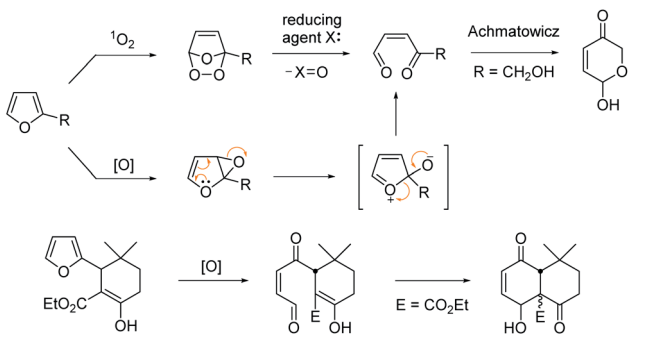
Furans containing a β-ketoester group at 2-position undergo oxidative ring-opening by Mn(III)/Co(II) catalysts under an O_2 atmosphere to produce 1,4-dicarbonyl moieties through an endoperoxide intermediate, which consecutively cyclized with the β-ketoester unit to afford 4-hydroxy-2-cyclohexen-1-ones. This oxidation/cyclization products were efficiently transformed into versatile benzofuran derivatives after consecutive aromatization and Paal–Knorr reaction.

Furan is a hetero-aromatic compound, ready to react with various oxidants or reactive electrophiles to serve as versatile C_4 building blocks in organic synthesis.[1] Furan can produce a conjugated 1,4-dicarbonyl unit by singlet oxygen through an endoperoxide intermediate,[2] which may be trapped by a nearby internal hydroxy group to generate a pyranose structure as was reported by Achmatowicz.[3] This oxidative conversion may also be attained through the epoxide intermediate by other oxidants including dioxiranes, metal oxides, *N*-bromosuccinimide, H_2O_2, peroxy acids *etc.*[4] Lallemand *et al.* demonstrated that the furan oxidation product by MCPBA would be trapped by a nearby enolic carbon of β-ketoester leading to a polyoxygenated decalin system (Scheme 1).[5]

We recently reported that the Mn^{III}-mediated peroxy radical in β-ketoester **A** induced oxidation of the acetyl group to α-ketoester **C** through the dioxetane intermediate **B**, which was eventually transformed into bichalcophen **D** by hetero-aromatization (Paal–Knorr reaction).[6a] In the present work, we want to report that β-ketoester **2a** containing a proximal furan moiety undergoes the furan oxidation to the conjugated 1,4-dicarbonyl intermediate **E** under the same reaction conditions, and is trapped by the active α-methinyl carbon radical of β-ketoester to produce 4-hydroxy-2-cyclohexen-1-ones **3a-1** and **3a-2** (Scheme 2). Whereas the distal electron-deficient furan ring in **A** was not affected, the proximal furan ring in **2a** was smoothly oxidized by Mn^{III}/Co^{II} catalysts under aerobic condition. Cyclohexenones **3a-1** and **3a-2**, stereoisomers at the α-carbon of β-ketoester with both hydroxy and benzoyl substituents in equatorial positions (*vide infra*), were produced in equal amounts, which would be perfect substates for the conversion into versatile benzofuran derivative **4a** after decarbonylative aromatization and Paal–Knorr reaction.

We herein delineated the optimal condition for the furan oxidation of β-ketoester **2a** to produce 4-hydroxy-2-cyclohexen-1-ones **3a-(1/2)**. Generality of the furan oxidation was demonstrated for β-ketoesters **2** with various aroyl substituents. Finally, the transformation of the above oxidative cyclization products **3** into versatile benzofuran derivatives **4** was described.

The substrate **2a** for furan oxidation was prepared by conjugate addition of ethyl acetoacetate to chalcone derivative **1a** containing a furan-2-yl group at β-position. Ethyl acetoacetate was utilized as reagent and solvent at 60 °C under $CeCl_3$ and NaI catalysts (10 mol% each).[7] The Michael adduct **2a** was



Scheme 1 Furan as versatile C_4 building blocks for pyranose and cyclohexenone by oxidation.

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† Electronic supplementary information (ESI) available: Experimental section, $^1H/^{13}C$-NMR spectra, ORTEP diagrams for **3j-1**, **3a-2**, and **5-2**, UV/FL spectra for **4a**. CCDC 2076252–2076254. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1ra05305a

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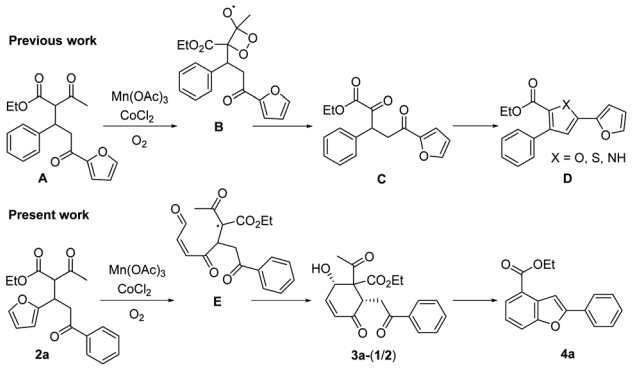


Scheme 2 Disparate reactivity of β-ketoesters **A** and **2a** under the Mn^{III}/Co^{II} catalyzed oxidation.

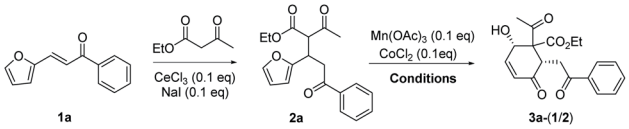
obtained in 58% yield as a 1 : 1 diastereomeric mixture, which was utilized for the oxidation reaction without separation. The typical condition for the previous oxidative deacetylation of chalcone derivative **A** under $Mn(OAc)_3$ and $CoCl_2$ catalysts (10 mol% each) in AcOH was utilized as a standard condition for the optimization study of the furan oxidation of **2a** (Table 1).[6a]

The furan oxidation/cyclization product, 4-hydroxy-2-cyclohexen-1-ones **3a-(1/2)**, was obtained in 44% yield at 25 °C under the above standard condition in 48 h (entry 1). UV irradiation at 365 nm wavelength not only speed up the rate (13 h), but also increase the yield of the reaction (57%, entry 2). Similar improvement on the yield (55%) and the reaction time (18 h) was observed under O_2 atmosphere, supplied by a balloon filled with O_2 (entry 3). These two effects can be combined to further speed up the oxidation reaction (5 h), but the yield remained almost the same (63%) within experimental errors (entry 4). The positive O_2 effect was obvious in the Mn^{III} catalyst regeneration as well as in the peroxy radical formation.[8] UV irradiation would generate singlet oxygen for the furan oxidation in the presence of metal catalysts just as in organic dye sensitizer.[9] In the absence of Mn^{III} catalyst (only in the presence of Co^{II} catalyst), normal illumination was not enough to generate singlet oxygen (entry 5), and UV irradiation was necessary to produce the oxidation products **3a-(1/2)** in 44% yield (entry 6). The reactions under argon[8b] atmosphere as well as in the presence of TEMPO[10] (1 equiv.) were unable to generate the peroxy radical or singlet oxygen as was expected (entries 7 and 8).

Temperature and solvent effects on the furan oxidation by peroxy radical were then studied (entries 9–12). Low temperature would be beneficial to the reaction utilizing a gaseous reagent because of the increased solubility of gas in solution. When the reaction was proceeded at 0 °C (15% volume of CF_3CO_2H was added to lower the m.p. of AcOH solution),[11] however, only 20% yield of products **3a-(1/2)** was obtained presumably due to insufficient activation energy for the reaction. Higher temperature reaction (at 40 °C) produced even lower 16% product yield, presumably because of lower solubility of O_2 in solution. AcOH was superior to Ac_2O as solvent, but only a trace amount of the product was obtained in EtOH even for a prolonged reaction time. Therefore, we determined the optimal condition for the furan oxidation utilizing $Mn(OAc)_3$ and $CoCl_2$ (10 mol% each) as that of entry 4 in Table 1 (in AcOH at 25 °C under O_2 with 365 nm UV irradiation).

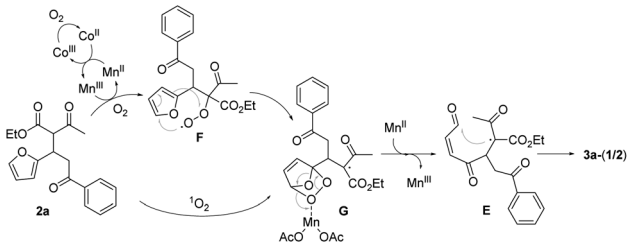
Singlet oxygen mechanism would partly explain the oxidation of **2a** to **3a-(1/2)**.[2] We were also inclined to suggest the peroxy radical mechanism based on the optimization study as well as our previous work (Scheme 3).[8a] The initially formed α-

Table 1 Optimization study for the oxidation of **2a** to **3a-(1/2)** under Mn^{III}/Co^{II} catalysts[a]



Entry	Solvent	Temp. (°C)	Time (h)	Atmosphere	Light	Yield (%) **3a-(1/2)**
1	AcOH	25	48	Air	Normal	44
2	AcOH	25	13	Air	UV[b]	57
3	AcOH	25	18	O_2	Normal	55
4	AcOH	25	5	O_2	UV[b]	63
5[c]	AcOH	25	24	O_2	Normal	0
6[c]	AcOH	25	24	O_2	UV[b]	44
7	AcOH	25	24	Argon	Normal	0
8[d]	AcOH	25	48	O_2	UV[b]	0
9[e]	AcOH	0	24	Air	Normal	20
10	AcOH	40	24	Air	Normal	16
11	Ac_2O	25	43	Air	Normal	30
12	EtOH	25	120	Air	Normal	Trace

[a] The catalytic oxidation reactions were carried out in 0.5–1.0 g scale (1.5–3.0 mmol) of the Michael adduct **2a**. [b] UV at 365 nm was irradiated to the reaction flask in a darkroom lamp. [c] The reaction was carried out only with Co^{II} (without Mn^{III}). [d] The reaction was carried out in the presence of TEMPO (1 equiv.). [e] CF_3CO_2H (15% of total volume) was added to lower the melting point of the solution.

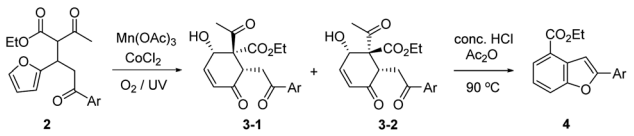


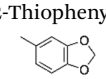
Scheme 3 Mechanism of the oxidation of **2a** to **3a-(1/2)** by Mn^{III}/Co^{II} catalysts.

carbon radical of β-ketoester unit in **2a** by $Mn(OAc)_3$ captured O_2 to afford the peroxy radical **F**, which would oxidize the proximal furan moiety by peroxy radical transfer. The endoperoxide **G** would be a common intermediate in both mechanisms, which would be reductively ring-opened by the assistance of $Mn(OAc)_2$. $Mn(OAc)_3$ can be regenerated in this way together with the general oxidation by $CoCl_2$ catalyst and O_2. Cyclization between methinyl carbon radical and the formyl group in **E** produced 4-hydroxy-2-cyclohexen-1-ones **3a-(1/2)**.

Generality of the furan oxidation under Mn^{III}/Co^{II} catalysts was demonstrated for various β-ketoesters **2**, prepared in 58–94% yields by conjugate addition of ethyl acetoacetate to β-furyl-α,β-unsaturated aryl ketones **1** of diverse aromatic moieties (Table 2). Two diastereomeric 4-hydroxy-2-cyclohexen-1-ones **3-1** and **3-2** were obtained in most cases at the quaternary carbon center, while the substituents at the other two chiral centers were fixed as *syn* in equatorial positions. The structures of both racemates were identified by X-ray diffraction experiments on **3j-1** (Ar = 2-naphthalene) and **3a-2** (Ar = Ph).[12] The ORTEP diagrams of both structures were included in the ESI.† The ^{1}H-NMR spectra of diastereomers were very similar in each group, and the stereochemistry of the other products was decided unambiguously by comparison of the ^{1}H-NMR with that of the above authentic.

Table 2 Generality of furan oxidation by Mn^{III}/Co^{II} catalysts and application to benzofuran synthesis[a]

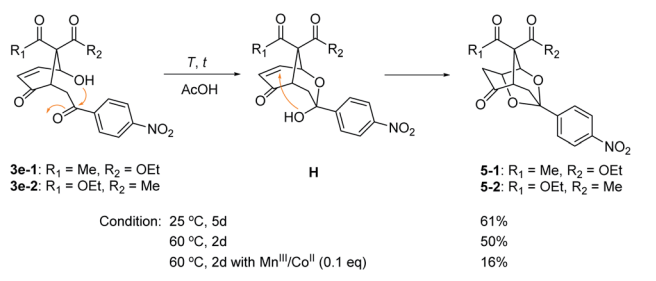


Entry	Compd.	Ar–	Yield (%) **3-1**[b]	Yield (%) **3-2**[c]	Yield (%) **4**
1	**a**	C_6H_5–	30	33	41
2	**b**	*p*-F–C_6H_4–	25	23	38
3	**c**	*p*-Cl–C_6H_4–	22	24	56
4	**d**	*p*-Br–C_6H_4–	19	18	46
5[d]	**e**	*p*-NO_2–C_6H_4–	31	31	11
6	**f**	*p*-MeO–C_6H_4–	27	36	52
7	**g**	*m*-MeO–C_6H_4-	35	9	43
8	**h**	*o*-MeO–C_6H_4-	21	21	42
9	**i**	*p*-Me–C_6H_4–	31	23	45
10	**j**	2-Naphthyl–	24	21	56
11	**k**	2-Furyl–	20	16	33
12	**l**	2-Thiophenyl–	19	20	47
13	**m**		44	—	44

[a] The catalytic oxidation reactions were carried out in 0.5–1.0 g scale (1.5–3.0 mmol) of the Michael adducts **2a–m**. [b] The stereochemistry of **3-1** was assigned by X-ray diffraction analysis of compound **j**. [c] The stereochemistry of **3-2** was assigned by X-ray diffraction analysis of compound **a**. [d] Compounds **5-1** and **5-2** (1 : 1) were also obtained in 20% yield. See Scheme 4 for the structure and the mechanism of formation.

Furan oxidation and subsequent cyclization under the above optimized condition were progressed smoothly for β-ketoesters **2** with various aroyl substituents to produce 4-hydroxy-2-cyclohexen-1-ones **3-1** and **3-2** in total 36–63% yields. The furan oxidation/cyclization seems to be insensitive to the identity of distal aromatic moiety. Highest yields (total 62–63%) of **3** were obtained for 4-nitrophenyl (**2e**) and 4-methoxyphenyl (**2f**) as well as the parent phenyl (**2a**) cases. It is interesting to note that further cyclization to 1,3-dioxolanes **5-1** and **5-2** (20% yield, 1 : 1 diastereomers, see Scheme 4) was observed for the electron-withdrawing 4-nitrophenyl case (*vide infra*). The structure of **5-2** was also identified by X-ray analysis (see ORTEP diagram in ESI†).[12] Halogen substituents survived during this radical reaction even though somewhat lower yields of **3** (total 37–48%) were obtained (entries 2–4). Furan oxidation also progressed smoothly for the phenyl group with *ortho*- and *meta*-alkoxy substitutions with a little diminished yield, in which diastereomer **3-1** was obtained as the major isomer in *meta* cases (entries 7 and 13). Diversity of the aromatic substituents included 2-naphthalene, 2-furan, 2- thiophene, and 2-benzodioxolane (entries 10–13). It was noteworthy that the proximal furan in **2k** was readily oxidized, while the remote electron-deficient (less reactive) furan survived under this condition (entry 11).

The benzofuran structure is widely distributed in biologically active nature products and regarded as a core skeleton for the drug discovery.[13] Fluorescent 2-arylbenzofurans might be important as labelling and optoelectrical materials (see ESI† for UV/FL spectra of **4a**), for which efficient synthetic methods have been studies.[14] The above furan oxidation/cyclization product, 4-hydroxy-2-cyclohexen-1-ones **3** with 6-aroyl substituent, provided versatile 2-arylbenzofuran derivatives **4** after decarbonylative aromatization and Paal–Knorr reaction (Table 2). Various conditions for Paal–Knorr reaction of 4-hydroxy-2-



Scheme 4 1,3-Dioxolanes **5** by further cyclization of furan oxidation product **3e**.

cyclohexen-1-ones **3-1** and **3-2** were tried, among which the one using concentrated HCl in acetic anhydride at 90 °C produced highest yields of the desired 2-arylbenzofuran derivatives **4**. The conversion requires a strong acid at high temperature for decarbonylative aromatization as well as Paal–Knorr reaction. An appreciable amount of tar formation seemed to be indispensable under the condition using benzene solvent, which was significantly reduced in acetic anhydride solvent. The corresponding benzofuran derivatives **4** were obtained in 33–56% yield ranges except the electron-withdrawing 4-nitrophenyl case (entry 5), where the Paal–Knorr reaction might be slowed down to produce **4e** in only 11% yield presumably due to the competition to form 1,3-dioxolane **5**.

The caged 1,3-dioxolanes **5-1** and **5-2** (1 : 1 stereoisomers) were obtained in 20% yield as by-product from β-ketoester **2e** with *p*-nitrophenyl substituent (*vide supra*). It was presumed to be formed by intramolecular Michael addition of the hemiacetal **H**, which was derived from the nucleophilic addition of *syn* 4-hydroxyl group onto the electron-deficient carbonyl group in **3e** (Scheme 4). Further cyclization to 1,3-dioxolane **5** was observed only for **3e** with *p*-nitrophenyl group. This structure is similar to anticonvulsant paeonimetabolin I, a metabolite from paeoniflorin, which is an important ingredient of traditional Chinese medicine curing for abdominal pain.[15] An optimal condition for intramolecular cyclic acetalization of **3e** (a 1 : 1 mixture of stereoisomers) has been screened. 1,3-Dioxolane **5** (a 1 : 1 mixture of stereoisomers) was produced in 61% yield at 25 °C for 5 days and in 50% yield at 60 °C for 2 days in AcOH. The presence of Mn^{III}/Co^{II} catalysts at 60 °C deteriorated the acetalization reaction to give **5** in only 16% yield.

In conclusion, β-ketoesters **2**, easily prepared from chalcones **1** containing a β-furan-2-yl substituent by conjugate addition of ethyl acetoacetate, undergo facile furan oxidation by Mn^{III}/Co^{II} catalyst under O_2 atmosphere. The resulting 1,4-dicarbonyl moiety participates in consecutive intramolecular cyclization with the β-ketoester unit to produce 4-hydroxy-2-cyclohexen-1-ones **3**. The furan oxidation may proceed through the endoperoxide intermediate formed by the α-peroxy radical of the β-ketoesters and partly by singlet oxygen. Generality of the furan oxidation by Mn^{III}/Co^{II} catalyst was demonstrated for β-ketoesters **2** with various aroyl substituents. 4-Hydroxy-2-cyclohexen-1-one **3e** with 4-nitrophenyl substituent underwent further intramolecular acetalization to produce caged 1,5-dioxolane **5**. 4-Hydroxy-2-cyclohexen-1-ones **3** were smoothly converted into versatile 4′-carboethoxy-5-arylbenzofurans **4** after simultaneous decarbonylative aromatization and Paal–Knorr reaction under conc. HCl in acetic anhydride at 90 °C. The new inventions described in this paper undoubtedly contribute to the valuable addition to the repertoires of furan oxidation in organic synthesis.

Author contributions

T. Wang: synthesis (lead), analysis (supporting); M. Zhang: synthesis (equal), analysis (supporting); Y. Zheng: synthesis (supporting); J. Seong: data curation (supporting), M.-S. Lah: data curation (lead), S. Koo: project administration (lead), funding acquisition (lead), investigation (lead), formal analysis (lead), writing manuscript (lead).

Conflicts of interest

There are no conflicts to declare.

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