RSC Advances

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2014, **4**, 54039

Received 13th August 2014
Accepted 24th September 2014

DOI: 10.1039/c4ra08627a

www.rsc.org/advances

Metal-free DDQ-mediated oxidative C–O coupling of acetalic sp^3 C–H bonds with carboxylic acids†

Jiang-Sheng Li,*[a] Yuan Xue,[a] Dong-Mei Fu,[a] Dao-Lin Li,[a] Zhi-Wei Li,*[a] Wei-Dong Liu,[b] Huai-Lin Pang,[b] Yue-Fei Zhang,[a] Zhong Cao[a] and Ling Zhang[a]

A simple and efficient DDQ-mediated oxidative C–O coupling reaction between acetalic sp^3 C–H and carboxylic acid O–H bonds has been developed. This novel transformation smoothly proceeds without any metal catalyst and allows for the highly efficient synthesis of (un)symmetric glycol diesters in a single step.

Carboxylic acid esters are ubiquitous in nature and serve as an important building block in organic synthesis and chemical industry.[1] Their traditional preparative methods[2] usually require strongly acidic catalysts, expensive dehydrating agents, and even produce undesired byproducts. With the booming of C–H functionalization,[3] novel oxidative esterification of carboxylic acids with hydrocarbons *via* C–H activation has been developed.[4] However, to the best of our knowledge, it focuses on the synthesis of monoesters. In fact, glycol diesters also widely occur in pharmaceuticals,[5] such as binifibrate, diniprofylline, and etofibrate (Fig. 1).

They are commonly formed by esterification of alcohols with carboxylic acids/activated carboxylic acid derivatives, or alkylation of carboxylate anions. However, the synthesis of unsymmetric diesters is a challenging issue. Therefore, methods for the direct and efficient synthesis of glycol diesters, especially unsymmetric ones, are still in high demand. Recently, our group has reported the DDQ-mediated domino cross-dehydrogenative coupling (CDC)[6] reaction of cyclic acetals with simple ketones,[7] which suggested that cyclic acetals could be an excellent acyloxyethyl synthon under oxidative conditions. On the basis of the continued interest in acetalic C–H functionalization, we herein present the efficient oxidative C–O coupling between acetalic sp^3 C–H bonds and carboxylic acids using DDQ without the presence of any metal catalyst (Scheme 1).

We set about our evaluation of the reaction parameters with 2-phenyl-1,3-dioxolane (**1a**) and benzoic acid (**2a**) as standard substrates using DDQ as dehydrogenative reagent and the results are compiled in Table 1. First, the reaction was performed in a series of solvents at 80 °C. When the reaction was conducted in CH_3NO_2, and CH_3CN, it afforded the desired product **3aa** in low yield (Table 1, entries 1 and 2). However, **3aa** was obtained in high yield in EtOAc, $CHCl_3$, 1,2-dichloroethane (DCE), benzene, and CH_2Cl_2 (Table 1, entries 3–7). Among these solvents, CH_2Cl_2 was the best choice, giving the highest yield of 90% (Table 1, entry 7). When the coupling reaction was performed at lower temperatures such as 60 °C, and 40 °C, the yield decreased dramatically (Table 1, entry 8 and 9). Additionally, the equivalents of **1a** and DDQ were examined. Increasing either of them led to no obvious improvement (Table 1, entry 10 and 11), whereas decreasing the amount of **1a** resulted in the incomplete consumption of **2a** obtaining only a 68% yield (Table 1, entry 12). Thus, the optimized reaction conditions for the oxidative

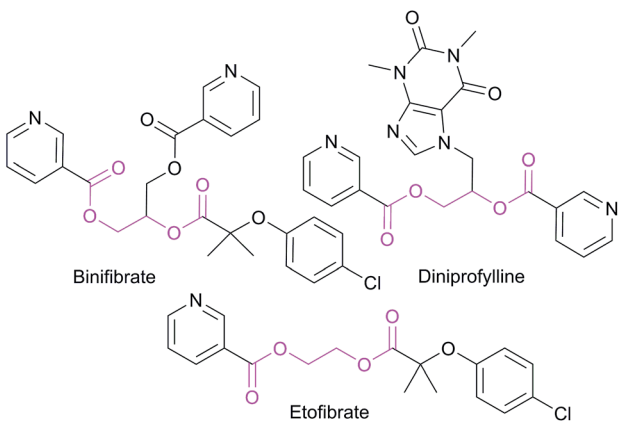


Fig. 1 Selected examples of glycol diesters.

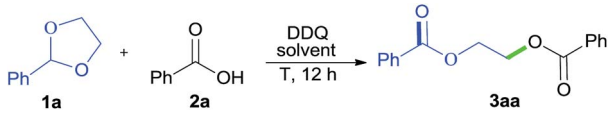
[a]*School of Chemistry and Biological Engineering, Changsha University of Science & Technology, Changsha 410114, People's Republic of China. E-mail: jslichem@gmail.com; lizwhn@126.com; Fax: +86-731-85258733*

[b]*National Engineering Research Center for Agrochemicals, Hunan Research Institute of Chemical Industry, Changsha 410007, People's Republic of China*

† Electronic supplementary information (ESI) available. CCDC 1009912. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ra08627a

Scheme 1 Oxidative C–O coupling reaction of the acetalic sp^3 C–H bond with a carboxylic acid.

Table 1 Optimization of the reaction conditions for **3aa**



Entry[a]	1a[b]	Solvent[c]	T (°C)	Yield[d] (%)
1	2	CH_3NO_2	80	10
2	2	CH_3CN	80	12
3	2	EtOAc	80	65
4	2	$CHCl_3$	80	88
5	2	DCE	80	76
6	2	Benzene	80	72
7	2	CH_2Cl_2	80	90
8	2	CH_2Cl_2	60	78
9	2	CH_2Cl_2	40	57
10	3	CH_2Cl_2	80	90
11[e]	2	CH_2Cl_2	80	91
12	1	CH_2Cl_2	80	68

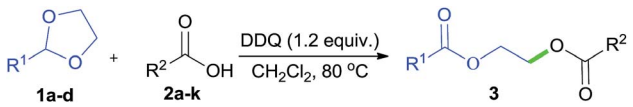
[a] Reaction conditions: **1a**, **2a** (1 mmol) and DDQ (1.2 mmol) in solvent (4 mL) for 12 h. [b] **1a** (mmol). [c] Dried using standard methods. [d] Isolated yield based on **2a**. [e] DDQ (1.5 mmol) used.

transformation were acetal (2.0 equiv.), DDQ (1.2 equiv.) in CH_2Cl_2 in a sealed tube at 80 °C for 12 h.

Under the optimized reaction conditions, various carboxylic acids **2** combined with 2-phenyl-1,3-dioxolane were tested, providing the corresponding (un)symmetric glycol diesters **3** (Table 2, entries 1–10). The data in Table 2 show that the yields were good to excellent. This oxidative C–O coupling was compatible with different Me, OMe, Cl, and NO_2 groups on the benzene ring. Notably, steric effects of the substituents had little influence on the yields (Table 2, **3ab** and **3af**). However, slight electronic effects of the substituents were observed. The presence of electron-withdrawing groups favored the oxidative coupling reaction (Table 2, **3ae**, **3af** and **3ag**). Fortunately, cinnamic acid and 2-furoic acid could also be readily introduced in the transformation (Table 2, **3ah** and **3ai**). However, no reactions occurred for the tested aliphatic carboxylic acids such as acetic acid, propionic acid, hexanoic acid, and cyclohexanecarboxylic acid except for formic acid that delivered the coupled diester **3aj** in a 86% yield. Probably, the pK_a values of the carboxylic acids **2** could well account for these experimental results.

Next, several cyclic acetals **1b–d** were also tested in this oxidative transformation (Table 2, entries 11–18). 2-Aryl-1,3-dioxolanes could react satisfactorily with aromatic carboxylic acids **2** to afford unsymmetric diesters in good to excellent

Table 2 DDQ-mediated oxidative C–O coupling of cyclic acetals **1** with carboxylic acids **2**

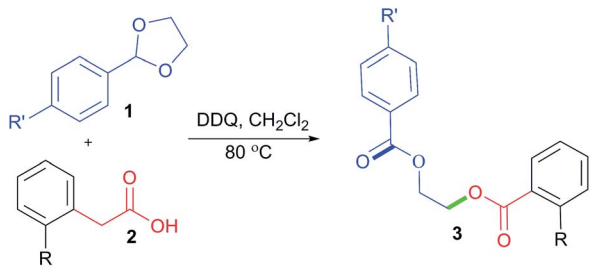


Entry[a]	R^1	R^2	3	Yield[b] (%)
1	Ph	Ph	**3aa**	90
2	Ph	2-MeC_6H_4	**3ab**	74
3	Ph	3-$MeOC_6H_4$	**3ac**	87
4	Ph	4-$MeOC_6H_4$	**3ad**	83
5	Ph	4-ClC_6H_4	**3ae**	92
6	Ph	2-ClC_6H_4	**3af**	93
7	Ph	3,4-Di-$NO_2C_6H_3$	**3ag**	91
8	Ph	*E*-PhCH=CH	**3ah**	72
9	Ph	2-furyl	**3ai**	94
10	Ph	H	**3aj**	86
11	4-MeC_6H_4	2-MeC_6H_4	**3bb**	72
12	4-MeC_6H_4	2-$MeOC_6H_4$	**3bk**	73
13	4-MeC_6H_4	4-ClC_6H_4	**3be**	87
14	4-ClC_6H_4	2-MeC_6H_4	**3cb**	81
15	4-ClC_6H_4	2-$MeOC_6H_4$	**3ck**	74
16	4-ClC_6H_4	2-ClC_6H_4	**3cf**	93
17	4-ClC_6H_4	4-ClC_6H_4	**3ce**	86
18	H	Ph	**3da**	0

[a] Standard reaction conditions for diesters: **1** (2 mmol), **2** (1 mmol) and DDQ (1.2 mmol) in CH_2Cl_2 (4 mL) for 12 h. [b] Isolated yield.

yields. All the functional groups involved were also considered. As mentioned earlier, the acids with lower pK_a values resulted in higher yields. Unfortunately, 1,3-dioxolane could not yield the desired coupled product (Table 2, **3da**).

After the investigation of aromatic and aliphatic carboxylic acids, we further attempted the reaction of acetals with 2-aryl acetic acids, as coupling partners, under standard conditions (Scheme 2). The products were obtained in moderate yields. To our surprise, however, it was found that their NMR spectra indicated the presence of benzoate and ethylene moieties, but a lack of signals for CH_2 protons and C atom of 2-aryl acetic acids,[8] which were essentially identical for those of **3aa**, **3ae**, **3af**, and **3cf** produced from the corresponding benzoic acids. Furthermore, the structure of the coupled product of **1c** with 2-



Scheme 2 DDQ-mediated oxidative C–O coupling of **1** with 2-aryl acetic acids.

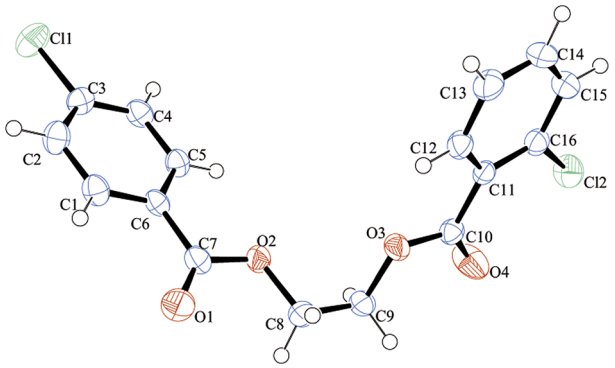
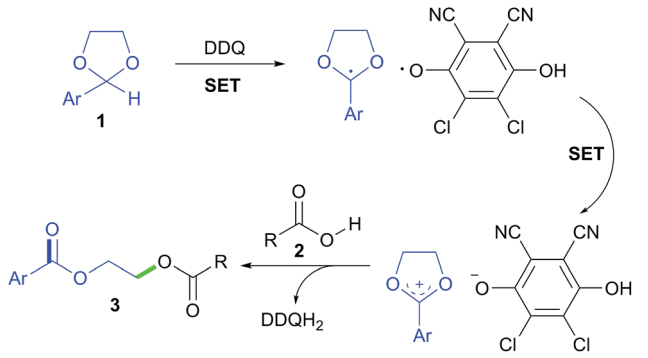


Fig. 2 X-ray crystal structure of the diester **3cm**.



Scheme 5 Plausible mechanism.

(2-chlorophenyl) acetic acid was confirmed by single-crystal X-ray experiments (Fig. 2).[9]

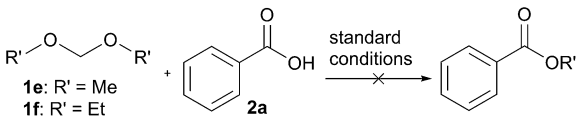
Alkylation is an important transformation in organic synthesis.[10] The direct *O*-alkylation of carboxylic acid is an alternative strategy toward the construction of carboxylic esters.[2] On the basis of the results mentioned above, we reasoned that acyclic acetals, such as dimethoxymethane or diethoxymethane, would be likely to be alkylating agents in the oxidative coupling reactions.

Based on this hypothesis, we examined the reaction of **1e**, **1f** with **2a**, respectively, under standard conditions (Scheme 3). To our disappointment, **2a** was recovered quantitatively, and no desired benzoates were detected by TLC analysis, even though the equivalents of **1e** or **1f** amounted up to 10.

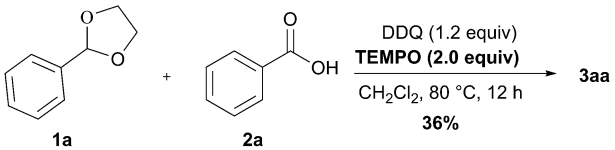
To gain insight into the mechanism of this novel oxidative C–O coupling protocol, the radical scavenger TEMPO was added to the standard reaction system to monitor whether radical species are formed (Scheme 4). The reaction was partially inhibited by 2 equivalents of TEMPO, and **3aa** was isolated in a 36% yield, indicating that this transformation may involve radical intermediates.

The proposed mechanism is depicted in Scheme 5. The reaction might be initiated by a single electron transfer (SET) oxidation to form an acetal radical, which can be further oxidized to a 1,3-dioxonium ion and to a $DDQH^-$ anion. H-atom abstraction of carboxylic acid **2** by $DDQH^-$ and subsequent nucleophilic attack at the C-4/5 rather than the C-2 position by carboxylic anion produces the C–O coupled product **3** together with the reduced hydroquinone $DDQH_2$.

In conclusion, we have demonstrated an efficient DDQ-mediated oxidative cross-coupling reaction between acetalic sp^3 C–H and carboxylic acid O–H bonds. This novel protocol makes cyclic acetals excellent acyloxyethyl synthons under oxidative conditions, and further achieves short reaction steps, good functional group tolerance, and good to excellent yields. Most importantly, it allows for the highly efficient synthesis of unsymmetric glycol diesters in one step. Further investigation of acetalic C–H functionalization is ongoing in our laboratory.



Scheme 3 Failure in the alkylation of benzoic acid **2a** with acyclic acetals **1** under standard oxidative conditions.



Scheme 4 Radical-trapping experiment.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (21202010, 21376031 & 21275022), the Hunan Provincial Natural Science Foundation of China (12JJ4021) and Hunan Provincial Science and Technology Project (2013NK3002).

Notes and references

1 (*a*) F. A. Carey and R. M. Giuliano, *Organic Chemistry*, McGraw-Hill, New York, 8th edn, 2011; (*b*) R. C. Larock, *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, Wiley-VCH, New York, 1999.

2 B. R. Buckley, in *Comprehensive Organic Functional Group Transformations II*, ed. A. R. Katritzky and R. J. K. Taylor, Elsevier, 2004, vol. 5.

3 (*a*) C. Liu, H. Zhang, W. Shi and A. Lei, *Chem. Rev.*, 2011, **111**, 1780–1824; (*b*) J. Q. Yu and Z. Shi, *C–H Activation*, Springer, New York, 2010; (*c*) G. Dyker, *Handbook of C–H transformations*, Wiley-VCH, Weinheim, 2005.

4 (*a*) J. Feng, S. Liang, S. Y. Chen, J. Zhang, S. S. Fu and X. Q. Yu, *Adv. Synth. Catal.*, 2012, **354**, 1287–1292; (*b*) E. Shi, Y. Shao, S. Chen, H. Hu, Z. Liu, J. Zhang and X. Wan, *Org. Lett.*, 2012, **14**, 3384–3387; (*c*) M. Uyanik, D. Suzuki, T. Yasui and K. Ishihara, *Angew. Chem.*, 2011, **123**, 5443–5446; (*d*) L. Chen, E. Shi, Z. Liu, S. Chen,

W. Wei, H. Li, K. Xu and X. Wan, *Chem.–Eur. J.*, 2011, **17**, 4085–4089; (*e*) D. J. Covell and M. C. White, *Angew. Chem., Int. Ed.*, 2008, **47**, 6448–6451; (*f*) M. S. Chen, N. Prabagaran, N. A. Labenz and M. C. White, *J. Am. Chem. Soc.*, 2005, **127**, 6970–6971; (*g*) A. R. Dick, K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2004, **126**, 2300–2301.

5 Q. Q. Chen, *Anticancer Drug Research Guide – New Drugs in Development for Cancers*, Sciencepublisher, Beijing, 2009 (in Chinese).

6 (*a*) S. A. Girard, T. Knauber and C. J. Li, *Angew. Chem., Int. Ed.*, 2014, **53**, 74–100; (*b*) W. J. Yoo and C. J. Li, *Top. Curr. Chem.*, 2010, **292**, 281–302; (*c*) C. J. Scheuermann, *Chem.–Asian J.*, 2010, **5**, 436–451.

7 J. S. Li, F. F. Cai, Z. W. Li, Y. Xue, C. Cheng, W. D. Liu and Z. Cao, *Chin. J. Chem.*, 2012, **30**, 1699–1701.

8 W. P. Mai, G. Song, J. W. Yuan, L. R. Yang, G. C. Sun, Y. M. Xiao, P. Mao and L. B. Qu, *RSC Adv.*, 2013, **3**, 3869–3872.

9 ESI.†

10 M. B. Smith, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, John Wiley & Sons, New Jersy, 7th edn, 2013.

