Organic & Biomolecular Chemistry

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Cite this: *Org. Biomol. Chem.*, 2012, **10**, 506

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COMMUNICATION

Oxidative cross-esterification of dithiolanes with alcohols through a cross-dehydrogenative coupling (CDC)/deprotection sequence†

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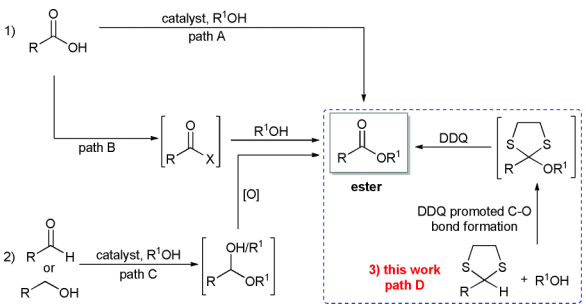
Received 8th October 2011, Accepted 9th November 2011
DOI: 10.1039/c1ob06890c

An unprecedented oxidative cross-esterification in an equimolar mixture of dithiolanes, alcohols and water through a CDC/deprotection sequence has been developed. The reaction itself features simple experimental procedures under very mild conditions and offers a new strategic protocol for the direct and efficient synthesis of structurally diverse esters.

Ester moieties occur widely in a myriad of natural isolates, synthetic compounds, and materials.[1] They also represent versatile intermediates for further synthetic transformations in both industrial and academic settings.[1,2] Ester synthesis has therefore intrigued and inspired chemists for over a century, and a variety of well-established methods are documented in the literature.[2,3] Traditionally, the most common approach to esters is the direct condensation of carboxylic acids with alcohols catalyzed by strong acids *in the presence of a large excess of either substrate* (Scheme 1, path A).[4] Alternative strategies have relied mainly upon the stoichiometric activation of the corresponding acid as an acyl halide, anhydride, or activated ester amenable to subsequent nucleophilic reactions with alcohols (path B).[3] In the last few years, transition metal-catalyzed oxidative esterifications of alcohols or aldehydes have become important tools for ester synthesis (path C).[5,6] Despite advances, some of these processes require harsh reaction conditions, excess substrates, noble metals, large amounts of condensing reagents or activators to attain satisfactory conversion. Particularly, stoichiometric amounts of organic by-products are generated in most cases. Therefore, more efficient alternatives are still in strong demand.

In recent years, cross-dehydrogenative coupling (CDC) reactions have significantly advanced state-of-the-art synthetic methodologies.[7] Cascade sequences that involve CDC reactions became a powerful platform for the construction of new C–C or C–heteroatom bonds. Critical to the success of these processes is that the C–H bonds to be oxidized are usually adjacent to the heteroatom, with nitrogen and oxygen being the most prevalent.[7] In contrast, CDC reactions of dithiolanes with the sp^3 C–H bond adjacent to sulfur are very rare.[8] As part of our ongoing research



Scheme 1 Common strategies for the synthesis of esters.

program developing cascade transformations,[9] we have found that the combination of DDQ and copper salts can efficiently promote *the CDC reaction of thioacetals with equimolar amounts of alcohols* to give 2-alkoxy-2-aryl-1,3-dithiolanes[10] which are further converted into synthetically useful esters under the reaction conditions (path D). Herein, we communicate this general catalytic oxidative cross-esterification of dithiolanes and alcohols under mild conditions. To the best of our knowledge, no similar reactions are documented to date.

Initially, we examined the reaction of 2-(4-methoxyphenyl)-1,3-dithiolane (**1a**) with methanol in $CHCl_3$, in the presence of 2,3-dichloro-5,6-dicyanoquinone (DDQ) (2.0 equiv.) and H_2O (1.0 equiv.) at room temperature for 12 h. To our delight, the oxidative cross-esterification did indeed work and gave methyl 4-methoxybenzoate (**2**) in 50% yield upon isolation (Table 1, entry 1). Thus, the influence of several metal salts was then investigated to improve the reaction efficiency (Table 1, entries 2–9). Notably, CuI (10 mol%) was identified to be the most efficient catalyst toward the formation of **2** in $CHCl_3$ (Table 1, entry 3). We also examined other metal complexes known to be effective for CDC reactions. For example, iron[11] and palladium chlorides,[12] which were reported as efficient catalysts for oxidative cross-coupling reactions, exhibited lower catalytic activities in this transformation (Table 1, entries 8 and 9). As revealed in entries 3 and 10–14, this oxidative esterification is readily accomplished in a variety of solvents. The superior levels of reaction efficiency observed with CuI in $CHCl_3$ at room temperature (Table 1, entry 3, 92% yield) prompted us to select these reaction conditions for further exploration.

We next examined the scope of the reaction with a variety of 2-aryl-1,3-dithiolanes (**1**). As highlighted in Table 2, significant

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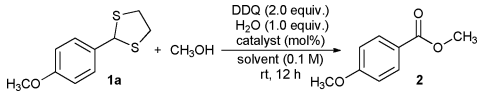
† Electronic supplementary information (ESI) available: Experimental procedures and compound characterization data. See DOI: 10.1039/c1ob06890c

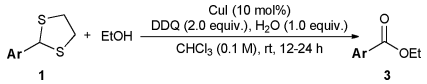
Table 1 Optimization of reaction conditions[a]

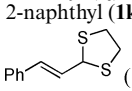
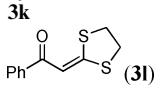


Entry	Catalyst (mol %)	Solvent	Yield (%)[b]
1	—	$CHCl_3$	50
2	CuI (5)	$CHCl_3$	88
3	**CuI (10)**	**$CHCl_3$**	**92**
4[c]	CuI (10)	Neat	43
5	CuBr (10)	$CHCl_3$	69
6	CuCl (10)	$CHCl_3$	60
7	$CuBr_2$ (10)	$CHCl_3$	30
8	$FeCl_2$ (10)	$CHCl_3$	64
9	$PdCl_2$ (10)	$CHCl_3$	39
10	CuI (10)	THF	35
11	CuI (10)	toluene	29
12	CuI (10)	CH_3NO_2	77
13	CuI (10)	CH_2Cl_2	73
14	CuI (10)	$(CH_2Cl)_2$	89

[a] Reaction conditions: **1a** (0.5 mmol), methanol (20.5 μL, 0.5 mmol), catalyst (10 or 5 mol%) and DDQ (1.0 mmol) in dried solvent (5 mL) with stirring for an hour. Then water (9 μL, 0.5 mmol) was added and the reaction mixture was stirred for 12 h at room temperature. [b] Yield of isolated products. [c] **1a** (10.0 mmol), methanol (405 μL, 10.0 mmol), CuI (10 mol%), water (180 μL, 10.0 mmol) and DDQ (20.0 mmol). DDQ = 2,3-dichloro-5,6-dicyanoquinone.

Table 2 Oxidative cross-esterification of various 2-aryl-1,3-dithiolanes (**1**) with ethanol[a]

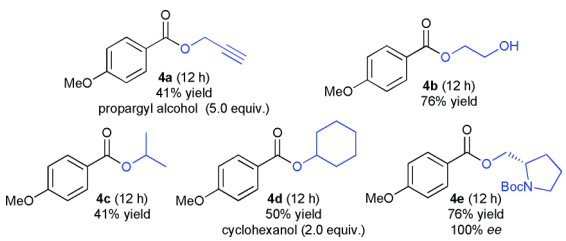


Entry	Ar	Product **3**	*t* (h)	Yield (%)[b]
1	4-MeO-Ph (**1a**)	**3a**	12	90
2	3-MeO-Ph (**1b**)	**3b**	12	74
3	3,4-$(MeO)_2$-Ph (**1c**)	**3c**	12	89
4	4-Me-Ph (**1d**)	**3d**	15	71
5	4-Br-Ph (**1e**)	**3e**	17	81
6	4-Cl-Ph (**1f**)	**3f**	19	80
7	4-NO_2-Ph (**1g**)	**3g**	21	92
8	3-NO_2-Ph (**1h**)	**3h**	20	84
9	4-CN-Ph (**1i**)	**3i**	21	87
10[c]	2-thienyl (**1j**)	**3j**	12	62
11[c]	2-naphthyl (**1k**)	**3k**	12	78
12[d]	 (**1l**)	 (**3l**)	12	65
13[e]	4-MeO-Ph (**1a**)	**3a**	12	87

[a] Reaction conditions: **1** (0.5 mmol), ethanol (30 μL, 0.5 mmol), CuI (0.05 mmol) and DDQ (1.0 mmol) in dried $CHCl_3$ (0.1 M) with stirring for an hour. Then water (9 μL, 0.5 mmol) was added and the reaction mixture was stirred for 12–24 h at room temperature. [b] Yield of isolated products. [c] $CHCl_3$ (0.05 M) was used. [d] DDQ (1.1 mmol) and ethanol (145 μL, 2.5 mmol) were used. [e] Reaction was carried out with **1a** (10.0 mmol), ethanol (585 μL, 10.0 mmol), DDQ (20.0 mmol), water (180 μL, 10.0 mmol) and CuI (5 mol%).

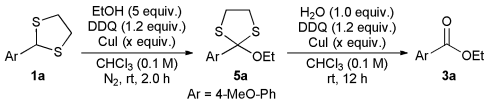
structural variation in the 2-aryl-1,3-dithiolane component can be realized. The reaction appears quite general with respect to the electronic nature of the substituent on the aromatic ring (Table 2, entries 1–9, 71–92% yields). For example, Me, MeO, Cl, Br, CN, and nitro groups can be introduced on the aromatic ring at both the C3 and C4 positions without significant loss in reaction efficiency (Table 2, entries 1–9). Furthermore, the aryl framework can be successfully extended to heteroaromatic (Table 2, entry 10) and naphthalene-derived systems (Table 2, entry 11). In the case of 1,3-dithiolane **1l**, derived from the cinnamaldehyde, we got the tandem oxidation/isomerization/oxidation product **3l** in 65% yield instead of the desired ester (Table 2, entry 12). To demonstrate the preparative utility, the oxidative esterification reaction of **1a** (2.13 g) with EtOH (585 μL) was performed on a 10-mmol scale in the presence DDQ and 5 mol% CuI to afford the corresponding ester in 87% yield. Thus, our methodology is feasible on a preparative scale.

More importantly, a wide array of structurally diverse alcohols was also suitable for this oxidative cross-esterification reaction. As revealed in Scheme 2, not only primary alcohols but also sterically hindered secondary alcohols can react smoothly with **1a** under our optimal conditions. Importantly, the reaction appears quite tolerant with respect to other functional groups in the alcohol component (Scheme 2), such as triple bonds (product **4a**). Note that the synthesis of glycol monoester, an important building block in the synthesis of natural isolates (*e.g.* sex pheromones of Lepidoptera)[13] and fine chemicals,[14] is a difficult task.[15] Gratifyingly, the glycol monoester was obtained in 76% yield without the formation of diesters under our standard conditions (Scheme 2, product **4b**). Moreover, we were delighted to find that an enantiopure *N*-Boc-L-prolinol was also suitable for the reaction and afforded the corresponding ester in 76% yield without loss of the stereochemistry (Scheme 2, product **4e**).



Scheme 2 Oxidative cross-esterification of **1a** with various alcohols.

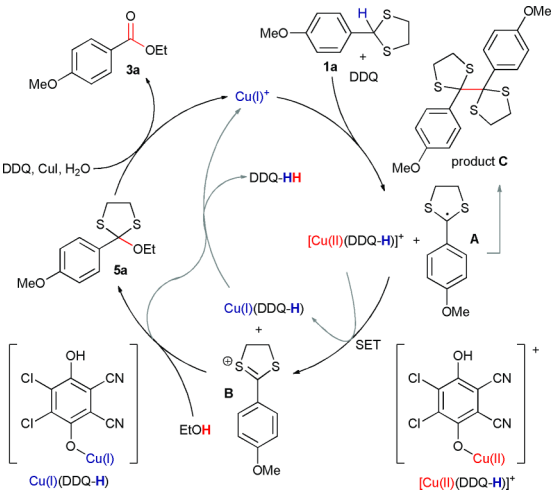
To gain insight into the possible reaction mechanism, a few experiments were performed using **1a** and ethanol as the substrates under various reaction conditions (eqn (1)). It was found that the oxidative esterification reaction passed through an intermediate **5a**, which could be isolated in 56% yield in the early stage of the reaction and could be readily converted into the product **3a**.



(1)

CuI (X)	yield of **5a**	CuI (X)	yield of **3a**
0	56%	0	64%
0.1	77%	0.1	92%

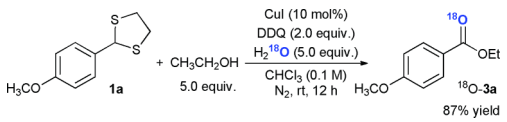
While a precise reaction mechanism awaits further study, a plausible catalytic cycle is depicted in Scheme 3. The oxidative cross-esterification was initiated by copper(I)-catalyzed direct hydrogen atom transfer to generate the benzylic radical **A**.[7,11] Subsequent oxidation of **A** through single electron transfer (SET) would afford thiocarbenium **B**. We assumed that the nucleophilic attack of ethanol to **B** gave the key intermediate **5a**, which then



Scheme 3 Possible mechanism for the oxidative cross-esterification reaction.

yielded the corresponding ester **3a** by a copper(I)-assisted oxidative deprotection.[16]

To support this proposed mechanism, we have carried out an ^{18}O-labeling experiment.[17] When the model substrate **1a** was subjected to our standard conditions with $H_2{}^{18}O$ instead of H_2O, the ^{18}O-labeling ethyl 4-methoxybenzoate was obtained in 87% yield (eqn (2)).



(2)

In conclusion, we have developed an unprecedented one-pot oxidative cross-esterification of dithiolanes with alcohols and water through a CDC/deprotection sequence. Notably, merging DDQ with cuprous iodide was quite effective for the reaction of an equimolar mixture of 2-aryl dithiolanes, alcohol, and water under very mild conditions. The combination of two mechanistically distinct transformations relying on the same catalytic system makes this tandem reaction particularly useful. Future work will be focus on the investigation of the precise reaction mechanism and the extension of the current strategy to the esterification of 2-alkyl dithiolanes.

We are grateful to the National Science Foundation of China (NO.21072069 and 21002036) for support of this research.

Notes and references

1 J. Otera, *Esterification: Methods, Reactions, and Applications*, Wiley-VCH, Weinheim, 2003.

2 (*a*) R. C. Larock, *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, 2nd ed., Wiley-VCH, New York, 1999; (*b*) P. G. M. Wuts and T. W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New Jersey, 2007.

3 For representative reviews, see: (*a*) J. M. Humphrey and A. R. Chamberlin, *Chem. Rev.*, 1997, **97**, 2243; (*b*) J. Otera, *Acc. Chem. Res.*, 2004, **37**, 288; (*c*) K. Ekoue-Kovi and C. Wolf, *Chem.–Eur. J.*, 2008, **14**, 6302.

4 For selected examples, see: (*a*) K. Ishihara, S. Ohara and H. Yamamoto, *Science*, 2000, **290**, 1140; (*b*) J. Otera, *Angew. Chem., Int. Ed.*, 2001, **40**, 2044; (*c*) T. Funatomi, K. Misaki and Y. Tanabe, *Green Chem.*, 2006, **8**, 1022; (*d*) K. Manabe, X.-M. Sun and S. Kobatashi, *J. Am. Chem. Soc.*, 2001, **123**, 10101; (*e*) J. Xiang, S. Toyoshima, A. Orita and J. Otera, *Angew. Chem., Int. Ed.*, 2001, **40**, 3670.

5 For examples, see: (*a*) S. Gowrisankar, H. Neumann and M. Beller, *Angew. Chem., Int. Ed.*, 2011, **50**, 5139; (*b*) C. Liu, J. Wang, L.-K. Meng, Y. Deng, Y. Li and A.-W. Lei, *Angew. Chem., Int. Ed.*, 2011, **50**, 5144; (*c*) B.-J. Xu, L. Zhou, R. J. Madix and C. M. Friend, *Angew. Chem., Int. Ed.*, 2010, **49**, 394; (*d*) M.-L. Zhang, S.-H. Zhang, G.-Y. Zhang, F. Chen and J. Cheng, *Tetrahedron Lett.*, 2011, **52**, 2480; (*e*) X.-F. Wu and C. Darcel, *Eur. J. Org. Chem.*, 2009, 1144; (*f*) A. S. K. Hashimi, C. Lothschutz, M. Ackermann, R. Doepp, S. Anantharaman, B. Marchetti, H. Bertagnolli and F. Rominger, *Chem.–Eur. J.*, 2010, **16**, 8012; (*g*) T. Zweifel, J.-V. Naubron and H. Grützmacher, *Angew. Chem., Int. Ed.*, 2009, **48**, 559.

6 For other examples of oxidative esterifications, see: (*a*) A. Sakakura, K. Kawajiri, T. Ohkubo, Y. Kosugi and K. Ishihara, *J. Am. Chem. Soc.*, 2007, **129**, 14775; (*b*) B. Maji, S. Vedachalan, X. Ge, S.-T. Cai and X.-W. Liu, *J. Org. Chem.*, 2011, **76**, 3016; (*c*) R. S. Reddy, J. N. Rosa, L. F. Veiros, S. Caddick and P. M. P. Gois, *Org. Biomol. Chem.*, 2011, **9**, 3126; (*d*) R. Lerebours and C. Wolf, *J. Am. Chem. Soc.*, 2006, **128**, 13052; (*e*) Y. Leng, J. Wang, D. Zhu, X.-Q. Ren, H.-Q. Ge and L. Shen, *Angew. Chem., Int. Ed.*, 2009, **48**, 168; (*f*) B. E. Maki and K. A. Scheidt, *Org. Lett.*, 2008, **10**, 4331.

7 For selected reviews, see: (*a*) C.-J. Li, *Acc. Chem. Res.*, 2009, **42**, 335; (*b*) C. J. Scheuermann, *Chem.–Asian J.*, 2010, **5**, 436For examples, see: (*c*) Y.-H. Zhang and C.-J. Li, *J. Am. Chem. Soc.*, 2006, **128**, 4242; (*d*) Y. Li and W.-L. Bao, *Adv. Synth. Catal.*, 2009, **351**, 865; (*e*) W.-Y. Tu, L. Liu and P. E. Floreancig, *Angew. Chem., Int. Ed.*, 2008, **47**, 4184; (*f*) H.-J. Mo and W.-L. Bao, *Tetrahedron*, 2011, **67**, 4793; (*g*) J. Jin, Y. Li, Z.-J. Wang, W.-X. Qian and W.-L. Bao, *Eur. J. Org. Chem.*, 2010, 1235.

8 (*a*) Z.-P. Li, R. Yu and H.-J. Li, *Angew. Chem., Int. Ed.*, 2008, **47**, 7497; (*b*) Z.-P. Li, H.-J. Li, X.-G. Guo, L. Cao, R. Yu, H.-R. Li and S.-G. Pan, *Org. Lett.*, 2008, **10**, 803.

9 (*a*) L.-Q. Lu, Y.-J. Cao, X.-P. Liu, J. An, C.-J. Yao, Z.-H. Ming and W.-J. Xiao,, *J. Am. Chem. Soc.*, 2008, **130**, 6946; (*b*) J.-R. Chen, C.-F. Li, X.-L. An, J.-J. Zhang, X.-Y. Zhu and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2008, **47**, 2489; (*c*) Y.-Q. Zou, L.-Q. Lu, L. Fu, N.-J. Chang, J. Rong, J.-R. Chen and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2011, **50**, 7171.

10 For representative transformations of dithiolanes, see: (*a*) T. Okuyama, N. Haga and T. Fueno, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 3056; (*b*) T. Okuyama, W. Fujiwara and T. Fueno, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 453; (*c*) R. Breslow and P. S. Pandey, *J. Org. Chem.*, 1980, **45**, 740.

11 For examples, see: (*a*) Y.-Z. Li, B.-J. Li, X.-Y. Lu, S. Lin and Z.-J. Shi, *Angew. Chem., Int. Ed.*, 2009, **48**, 3817; (*b*) C. Qin and N. Jiao, *J. Am. Chem. Soc.*, 2010, **132**, 15893.

12 (*a*) H.-J. Chen, H.-F. Jiang, C.-B. Cai, J. Dong and W. Fu, *Org. Lett.*, 2011, **13**, 992; (*b*) H.-J. Mo and W.-L. Bao, *Adv. Synth. Catal.*, 2009, **351**, 2845.

13 (*a*) C. C. Leznoff, *Acc. Chem. Res.*, 1978, **11**, 327; (*b*) R. Rossi, *Synthesis*, 1977, **12**, 817; (*c*) C. A. Henrick, *Tetrahedron*, 1977, **33**, 1845.

14 (*a*) T. Hosokawa, Y. Imada and S. Murahashi, *J. Chem. Soc., Chem. Commun.*, 1983, 1245; (*b*) R. I. Stutz, A. J. Del Vecchio and R. J. Tenney, *Food Prod. Dev.*, 1973, **7**, 52.

15 Basically, the synthesis of glycol monoester requires harsh reaction conditions and accompanies with the formation of diesters. (*a*) S. Sayama and T. Onami, *Synlett*, 2004, 2739; (*b*) T. Yasukawa, H. Miyamura and S. Kobayashi, *Chem.–Asian J.*, 2011, **6**, 621; (*c*) R. Gopinath, B. Barkakaty, B. Talukdar and B. K. Patel, *J. Org. Chem.*, 2003, **68**, 2944; (*d*) H. Sharghi and M. H. Sarvari, *J. Org. Chem.*, 2003, **68**, 4096.

16 (*a*) L. Mathew and S. Sankararaman, *J. Org. Chem.*, 1993, **58**, 7576; (*b*) K. Tanemura, H. Dohya, M. Imamura, T. Suzuki and T. Horaguchi, *J. Chem. Soc., Perkin Trans. 1*, 1996, 453; (*c*) K. Tanemura, H. Dohya, M. Imamura, T. Suzuki and T. Horaguchi, *Chem. Lett.*, 1994, 965.

17 See the ESI for details†.

