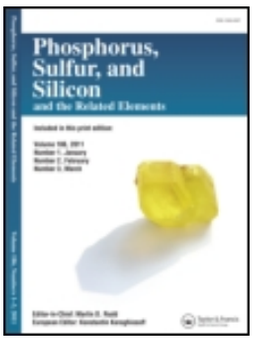

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ISSN: 1042-6507 (Print) 1563-5325 (Online) Journal homepage: http://www.tandfonline.com/loi/gpss20

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To cite this article: Jie-Ping Wan, Yanfeng Jing & Yunyun Liu (2016) Ethyl lactate mediated thioacetalization of aldehydes at ambient temperature, Phosphorus, Sulfur, and Silicon and the Related Elements, 191:10, 1302-1305, DOI: 10.1080/10426507.2016.1209504

To link to this article: http://dx.doi.org/10.1080/10426507.2016.1209504

PHOSPHORUS, SULFUR, AND SILICON
2016, VOL. 191, NO. 10, 1302–1305
http://dx.doi.org/10.1080/10426507.2016.1209504

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SHORT COMMUNICATION

Ethyl lactate mediated thioacetalization of aldehydes at ambient temperature

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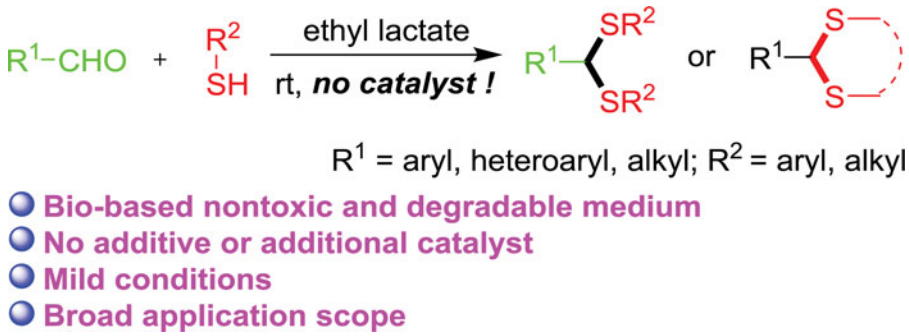
ABSTRACT

Dithioacetalization reactions of aldehydes with thiols/thiophenols have been successfully achieved at room temperature by employing the green, bio-based ethyl lactate as the reaction medium. By means of this sustainable approach, a class of dithioacetals has been acquired with high diversity and efficiency.

ARTICLE HISTORY
Received 12 June 2016
Accepted 24 June 2016

KEYWORDS
Ambient temperature; bio-based solvent; dithioacetalization; ethyl lactate; green

GRAPHICAL ABSTRACT



Introduction

Upon the daily increasing concern to sustainable development all around the world, discovering and making use of renewable and environmentally benign resources have attracted unprecedentedly high attention in the area of chemical industry.[1,2] Among the numerous renewable resources, the bio-mass derived chemicals are inarguably one of the most important classes of candidates because of their inherent advantages of low cost, high environment tolerance and broad application.[3] Ethyl lactate (EL) is a biomass available chemical that can be used as platform compound in the generation of many organic products. In addition, EL has also exhibited application in food additive, perfume flavor, and solvent in coating industry, etc.[4] In recent years, EL has attracted renewed interests by acting as reaction medium in organic synthesis because of its intrinsic advantages of non-toxicity, full degradability, good stability and solubility to both water and organic compounds. Although not a research topic of long history, the research work in recent several years discloses the high potential of EL as green solvent in mediating important organic reactions,[5,6] and these results indicate the broad space of EL in the designation of much more sustainable green syntheses.

The formation of dithioacetals is one of the most classical strategies in the group protection chemistry.[7] In addition, dithioacetals themselves are known as highly versatile building blocks in organic synthesis.[8–12] Owing to the significance of dithioacetal synthesis, extensive efforts have been made to the dithioacetalization reactions of carbonyl substrates which have led to the occurrence of numerous catalytic methods enabling efficient dithioacetal synthesis.[13–22] While these known methods contribute significantly to the advances of dithioacetalization chemistry, the reliance of toxic catalyst(s) and/or volatile organic solvent as reaction medium demonstrate the requirement of developing complementary catalytic approaches with further improved sustainability and cleanness.

In continuation of our longstanding endeavor in exploring alternative green organic synthesis employing bio-based solvents as reaction medium and the synthesis of sulfur-containing products,[23,24] we report herein an alternative method allowing ambient dithioacetalization reaction of aldehydes by employing EL as the green medium.

Results and discussion

To start the work, the reaction of *p*-chlorobenzaldehyde **1a** with ethanethiol **2a** was selected as model reaction, and a series of optimization experiments were first conducted. According to the results, EL was an ideal medium for the reaction which

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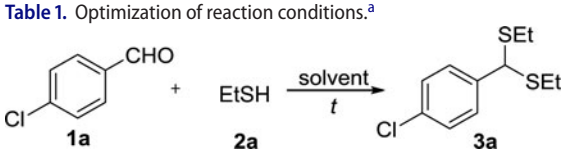
Supplemental data for this article can be accessed on the publisher's website at http://dx.doi.org/10.1080/10426507.2015.1209504.

Table 1. Optimization of reaction conditions.[a]



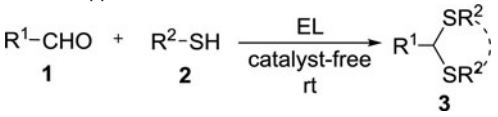
Entry	Solvent	t(°C)	Yield (%)[b]
1	EL	rt	84
2	EL	40	82
3	EL	50	84
4	EL	60	81
5	EL	70	83
6	EL	80	82
7	H_2O	rt	NR
8	CH_3CN	rt	trace
9	*p*-xylene	rt	trace

[a]General conditions: 1a (0.2 mmol), 2a (0.4 mmol) in 2 mL solvent, stirred for 12 h.
[b]Yield of isolated product.

allowed the formation of dithioacetal **3a** with excellent yield at different temperatures without using any catalyst or additive. In the range of room temperature to 80 °C, no evident difference in the product yield was observed (entries 1-6, Table 1). In corresponding comparing experiments, other solvents of different properties and polarity such as water, acetonitrile and *p*-xylene were all found inapplicable in enabling the production of **3a**, suggesting the unique advantage of EL for this dithioacetalization reaction (entries 7-9, Table 1).

After optimizing the reaction conditions, the scope of this EL-mediated synthetic protocol was subsequently investigated by employing different alkyl thiols, thiophenols, and aldehydes as starting materials. As shown in Table 2, broad application and good functional group tolerance were demonstrated by the experimental results acquired in this section. For the aldehyde component, besides conventional aromatic aldehydes

Table 2. Application of the dithioacetalization reaction in EL.[a]



R1	R2	Product	Yield(%)[b]
4-ClC_6H_4	Et	3a	84
Ph	Et	3b	75
4-MeC_6H_4	Et	3c	72
4-MeOC_6H_4	Et	3d	71
4-BrC_6H_4	Et	3e	76
4-CNC_6H_4	Et	3f	78
4-$NO_2C_6H_4$	Et	3g	76
2-ClC_6H_4	Et	3h	81
3-$NO_2C_6H_4$	Et	3i	79
furyl-2-yl	Ph	3j	59
4-ClC_6H_4	$HSCH_2CH_2$	3k	62
Ph	$HSCH_2CH_2$	3l	72
4-MeOC_6H_4	$HSCH_2CH_2$	3m	63
3,4-$(MeO)_2C_6H_3$	$HSCH_2CH_2$	3n	67
4-ClC_6H_4	*n*-Bu	3o	71
4-$NO_2C_6H_4$	*n*-Bu	3p	69
n-propyl	Ph	3q	67
Ph	Ph	3r	74
4-MeC_6H_4	Ph	3s	78

[a]General conditions: aldehyde **1** (0.2 mmol), thiol **2** (0.4 mmol) in 2 mL EL, stirred at rt for 12 h.
[b]Yield of isolated product.

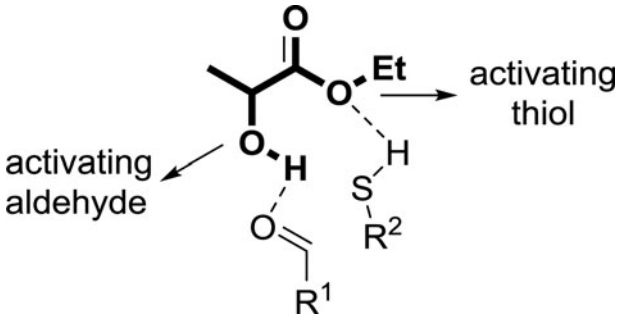


Figure 1. The proposed activation model of EL to both aldehydes and thiols.

containing different substituents, heteroaryl and alkyl aldehydes also displayed smooth applicability in the synthesis of the corresponding thioacetals (**3j** and **3q**, Table 2). On the other hand, general application of different alkyl thiols (**3a**–**3i**, **3o**–**3p**, Table 2), dithiols (**3k**–**3n**, Table 2), and thiophenols (**3j**, **3q**–**3s**, Table 2) were also well tolerated. The dithioacetals were generally obtained with good to excellent yields without being evidently effected by the functional group in either component. On the basis of the aldehyde-based dithioacetalization with the present protocol, corresponding reactions employing ketones, including aliphatic methyl ketone (acetone) and aromatic methyl ketone (acetophenone) were also subjected for potential reactions with ethyl thiol, respectively. However, no transformation was observed.

To illustrate the unique function of EL in mediating the dithioacetalization reaction, a possible model of substrate activation has been proposed. As outlined in Figure 1, upon the analysis to the structural features of EL and the reactants, it is plausible that both aldehyde and thiol are activated by EL. At first, the slightly acidic hydroxyl group in EL activates aldehyde via the O–H–O hydrogen bond; simultaneously, the oxygen atom of the ethoxy group in EL could activate the thiol substrate via the O–H–S interaction. Besides the activation effect, this activation model is also beneficial in keeping the aldehyde and thiol close to each other and facilitating the final reaction of the two reactants.

Conclusions

In conclusion, we have developed a new biomass-based EL-mediated method for the dithioacetalization reactions of aldehydes with thiols/thiophenols. Besides the inherent greenness of EL, the present method is also advantageous and practical because no additional catalyst is required and the reaction is run at room temperature operation. The sustainability, broad application scope and satisfactory yields of products reasonably make the method a useful complement to known methodologies of dithioacetalization.

Experimental

General information

All reactions were performed under air atmosphere. Chemicals were obtained from commercial sources and used directly without further treatment. ^{1}H NMR spectra were recorded at

400 MHz (Bruker Avance 400 apparatus) using $CDCl_3$ as solvent. The chemical shifts δ are reported in ppm with TMS as internal standard. The structures of all products were confirmed by comparing their ^{1}H NMR data with those reported in the literature. The Supplemental Materials contains sample ^{1}H NMR of **3a**-**3s** (Figures S1–S19).

General procedure for the thioacetalization reaction in EL

A 25 mL round bottom flask was charged with the aldehyde **1** (1.0 mmol) and the thiol **2** (2.0 mmol) and EL (2 mL). The resulting mixture was stirred at rt for 12 h (TLC). Upon completion, water (5 mL) was added, and the resulting suspension was extracted with ethyl acetate (3 × 10 mL). The combined organic phases were further washed with water (3 × 5 mL). The organic solution was then dried with anhydrous Na_2SO_4. After filtration, the organic solvent was removed under reduced pressure. The residue was subjected to silica gel column chromatography to provide pure products with elution of mixed petroleum ether and ethyl acetate (v/v = 200 : 1).

1-[Bis(ethylthio)methyl]-4-chlorobenzene (**3a**).[13] ^{1}H NMR: δ 7.39 (d, J = 8.4 Hz, 2 H), 7.29 (d, J = 8.8 Hz, 2 H), 4.89 (s, 1 H), 2.63–2.47 (m, 4 H), 1.22 (t, J = 7.6 Hz, 6 H).

1-[Bis(ethylthio)methyl]benzene (**3b**).[13] ^{1}H NMR: δ 7.44 (d, J = 7.2 Hz, 2 H), 7.32 (t, J = 7.6 Hz, 2 H), 7.25 (t, J = 7.6 Hz, 1 H), 4.92 (s, 1 H), 2.64–2.47 (m, 4 H), 1.21 (t, J = 7.6 Hz, 6 H).

1-[Bis(ethylthio)methyl]-4-methylbenzene (**3c**).[16] ^{1}H NMR: δ 7.33 (d, J = 8.0 Hz, 2 H), 7.13 (d, J = 8.0 Hz, 2 H), 4.91 (s, 1 H), 2.64–2.47 (m, 4 H), 2.33 (s, 3 H), 1.22 (t, J = 7.6 Hz, 6 H).

1-[Bis(ethylthio)methyl]-4-methoxybenzene (**3d**).[13] ^{1}H NMR: δ 7.37 (d, J = 8.8 Hz, 2 H), 6.85 (d, J = 8.8 Hz, 2 H), 4.91 (s, 1 H), 3.79 (s, 3 H), 2.63–2.46 (m, 4 H), 1.22 (t, J = 7.6 Hz, 6 H).

1-[Bis(ethylthio)methyl]-4-bromobenzene (**3e**).[13] ^{1}H NMR: δ 7.45 (d, J = 7.6 Hz, 2 H), 7.33 (d, J = 8.4 Hz, 2 H), 4.88 (s, 1 H), 2.64–2.46 (m, 4 H), 1.22 (t, J = 7.6 Hz, 6H).

1-[Bis(ethylthio)methyl]-4-cyanobenzene (**3f**).[13] ^{1}H NMR: δ 7.64 (d, J = 8.4 Hz, 2 H), 7.58 (d, J = 8.4 Hz, 2 H), 4.94 (s, 1 H), 2.66–2.48 (m, 4 H), 1.23 (t, J = 7.6 Hz, 6 H).

1-[Bis(ethylthio)methyl]-4-nitrobenzene (**3g**).[13] ^{1}H NMR: δ 8.20 (d, J = 8.8 Hz, 2 H), 7.63 (d, J = 8.8 Hz, 2 H), 4.98 (s, 1 H), 2.66–2.51 (m, 4 H), 1.24 (t, J = 7.6 Hz, 6 H).

1-[Bis(ethylthio)methyl]-2-chlorobenzene (**3h**).[15] ^{1}H NMR: δ 7.75 (d, J = 8.0 Hz, 1 H), 7.33 (d, J = 8.0 Hz, 1 H), 7.28 (t, J = 7.6 Hz, 1 H), 7.18 (t, J = 7.2 Hz, 1 H), 5.49 (s, 1 H), 2.68–2.49 (m, 4 H), 1.24 (t, J = 7.6 Hz, 6 H).

1-[Bis(ethylthio)methyl]-3-nitrobenzene (**3i**).[16] ^{1}H NMR: δ 8.24 (s, 1 H), 8.05 (d, J = 10.4 Hz, 1H), 7.75 (d, J = 7.6 Hz, 1 H), 7.45 (t, J = 8.0 Hz, 1 H), 4.93 (s, 1 H), 2.62–2.42 (m, 4 H), 1.16 (t, J = 7.2 Hz, 6 H).

2-[Bis(phenylthio)methyl]furan (**3j**).[17] ^{1}H NMR: δ 7.37–7.32 (m, 5 H), 7.24–7.21 (m, 6 H), 6.20 (dd, 1 H, J = 3.2 Hz, 1.6 Hz), 6.13 (d, 1 H, J = 3.2 Hz).

2-(4-Chlorophenyl)-1,3-dithiolane (**3k**).[16] ^{1}H NMR: δ 7.43 (d, 2 H, J = 8.4 Hz), 7.25 (d, 2 H, J = 8.4 Hz), 5.57 (s, 1 H), 3.48–3.40 (m, 2 H), 3.34–3.28 (m, 2 H).

2-Phenyl-1,3-dithiolane (**3l**).[13] ^{1}H NMR: δ 7.51 (d, J = 7.6 Hz, 2 H), 7.32–7.22 (m, 3 H), 5.63 (s, 1 H), 3.52–3.44 (m, 2 H), 3.37–3.29 (m, 2 H).

2-(4-Methoxyphenyl)-1,3-dithiolane (**3m**).[18] ^{1}H NMR: δ 7.46 (d, J = 8.4 Hz, 2 H), 6.84 (d, J = 9.2 Hz, 2 H), 5.64 (s, 1 H), 3.79 (s, 3 H), 3.52–3.46 (m, 2 H), 3.38–3.31 (m, 2H).

2-(3,4-Dimethoxyphenyl)-1,3-dithiolane (**3n**).[14] ^{1}H NMR: δ 7.11 (s, 1 H), 7.05 (d, J = 10.4 Hz, 1 H), 6.78 (d, J = 8.4 Hz, 1H), 5.64 (s, 1 H), 3.90 (s, 3 H), 3.87 (s, 3 H), 3.53–3.47 (m, 2 H), 3.39–3.32 (m, 2 H).

1-[Bis(*n*-propylthio)methyl]-4-chlorobenzene (**3o**).[14] ^{1}H NMR: δ 8.12 (d, J = 8.8 Hz, 2 H), 7.55 (d, J = 8.4 Hz, 2 H), 4.84 (s, 1 H), 2.56–2.41 (m, 4 H), 1.51–1.43 (m, 2 H), 1.35–1.26 (m, 2 H), 0.81 (t, J = 7.2 Hz, 6 H).

1-[Bis(*n*-propylthio)methyl]-4-nitrobenzene (**3p**).[14] ^{1}H NMR: δ 7.39 (d, J = 8.4 Hz, 2 H), 7.29 (d, J = 7.6 Hz, 2 H), 4.84 (s, 1 H), 2.60–2.46 (m, 4 H), 1.56–1.49 (m, 2 H), 1.41–1.32 (m, 2 H), 0.88 (t, J = 7.6 Hz, 6 H).

1-[Bis(phenylthio)methyl]ethane (**3q**).[19] ^{1}H NMR: δ 7.45 (d, J = 7.4, 4 H), 7.30–7.19 (m, 6 H), 4.35 (t, J = 6.8 Hz, 1 H), 1.91–1.84 (m, 2 H), 1.12 (t, J = 7.2 Hz, 3 H).

1-[Bis(phenylthio)methyl]benzene (**3r**).[13] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.32 (m, 6 H), 7.23–7.17 (m, 9 H), 5.43 (s, 1 H).

1-(Bis(phenylthio)methyl)-4-methylbenzene (**3s**).[25] ^{1}H NMR: δ 7.51 (d, J = 7.6, 4 H), 7.39 (d, J = 7.2Hz, 2 H), 7.32–7.17 (m, 6 H), 7.04 (d, J = 7.6Hz, 2 H), 5.43 (s, 1 H), 2.26 (s, 3 H).

Funding

This work was financially supported by the Natural Science Foundation of Jiangxi Province (20142BAB213007).

References

1. Rostrup-Nielsen, J. R. *Sci.* **2005**, 308, 1421-1422.
2. Shams, S. S.; Zhang, L. S.; Hu, R.; Zhang, R.; Zhu, J. *Mater. Lett.* **2015**, 161, 476-479.
3. Huber, G. W.; Iborra, S.; Corma, A. *Chem. Rev.* **2006**, 106, 4044-4098.
4. Pereira, C. S. M.; Silva, V. M. T. M.; Rodrigues, A. E. *Green Chem.* **2011**, 13, 2658-2671.
5. Wei, L.; Chen, X.; Liu, Y.; Wan, J.-P. *Chin. J. Org. Chem.* **2016**, 36, 954-961.
6. Wan, J.-P.; Zhong, S.; Xie, L.; Cao, X.; Liu, Y.; Wei, L. *Org. Lett.* **2016**, 18, 584-587.
7. Sartori, G.; Ballini, R.; Bigi, F.; Bosica, G.; Maggi, R.; Righi, Paolo. *Chem. Rev.* **2004**, 104, 199-250.
8. Luh, T.-Y. *Acc. Chem. Res.* **1991**, 24, 257-263.
9. Luh, T.-Y.; Lee, C.-F. *Eur. J. Org. Chem.* **2005**, 3875-3885.
10. Chou, C.-M.; Chen, W.-Q.; Chen, J.-H.; Lin, C.-L.; Tseng, J.-C.; Lee, C.-F.; Luh, T.-Y. *Chem. Asian J.* **2006**, 1-2, 46-55.
11. Takeda, T.; Fujiwara, T. *Rev. Heteroatom Chem.* **1999**, 21, 93-115.
12. Corey, E. J.; Seebach, D. *Angew. Chem. Int. Ed.* **1965**, 4, 1075-1077.
13. Wu, Y.-C.; Zhu, J. *J. Org. Chem.* **2008**, 73, 9522-9524.
14. Saraswathy, V. G.; Sankararaman, S. *J. Org. Chem.* **1994**, 59, 4665-4670.
15. Liu, Y. *Phosphorus Sulfur Silicon Relat. Elem.* **2016**, 191, 679-682.
16. Hajipour, A. R.; Pourmousavi, S. A.; Ruoho, A. E. *Synth. Commun.* **2008**, 38, 2548-2566.
17. Madabhushi, S.; Mallu, K. K. R.; Chinthala, N.; Beeram, C. R.; Vangipuram, V. S. *Tetrahedron Lett.* **2012**, 53, 697-701.
18. Naik, S.; Gopinath, R.; Goswami, M.; Patel, B. K. *Org. Biomol. Chem.* **2004**, 2, 1670-1677.

19. Kumar, A.; Rao, M. S.; Rao, V. K. *Aust. J. Chem.* **2010**, 63, 135140.
20. Yadav, J. S.; Reddy, B. V. S.; Pandey, S. K. *Synth. Commun.* **2002**, 32, 715-719.
21. (a)Huang, L.-F.; Lee, C.-F.; Tseng, J.-C.; Luh, T.-Y. *Synlett* **2006**, 3173-3175. (b)Leung, M.-K.; Luh, T.-Y. *Sci. Synth.* **2007**, 30, 221-349
22. Yu, J.-S.; Wu, W.-B.; Zhou, F. *Org. Biomol. Chem.* **2016**, 14, 2205-2209.
23. Liu, Y.; Huang, B. *Phosphorus Sulfur Silicon Relat. Elem.* **2016**, 191, 926-929.
24. Liu, Y.; Wang, H.; Zhang, J.; Wan, J.-P.; Wen, C. *RSC Adv*. **2014**, 4, 19472-19475.
25. Zhang, H.; Wang, H.; Yang, H.; Fu, H. *Org. Biomol. Chem.* **2015**, 13, 6149-6153.