Organic LETTERS

Letter

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Facile Base-Mediated Redox Transformation: An Efficient Strategy for the Synthesis of α-Acyloxyphosphoryl Compounds

Yalei Zhao,[†] Tieqiao Chen,*[,†] Daoqing Han,[§] Chang-Qiu Zhao,*[,‡] and Li-Biao Han*[,†,§]

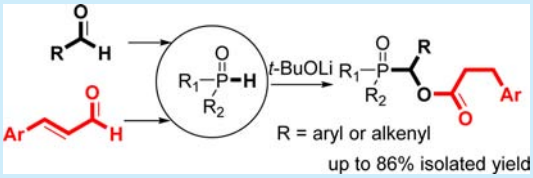
[†]State Key Laboratory of Chemo/Biosensing and Chemometrics, College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, China

[‡]College of Chemistry and Chemical Engineering, Liaocheng University, Liaocheng, Shandong 252059, China

[§]National Institute of Advanced Industrial Science and Technology (AIST), Tsukuba, Ibaraki 305-8565, Japan

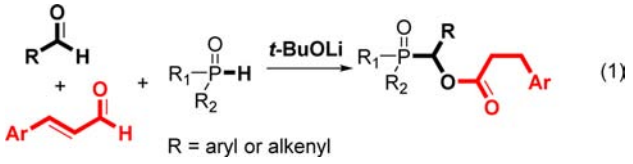
Supporting Information

ABSTRACT: An efficient one-pot synthesis of α-acyloxyphosphoryl compounds from aldehydes and hydrogen phosphoryl compounds has been developed using a facile base-mediated redox strategy. This redox transformation is applicable to synthesize a wide range of valuable α-acyloxyphosphoryl compounds with high atom- and step-economic efficiency.



α-Acyloxyphosphoryl compounds are regarded as important bioactive molecules and are widely applied in agrochemistry due to their antibiotic, pharmacogenetic, and pharmacological properties.[1] These compounds are also useful intermediates in organic synthesis.[2] Generally, α-acyloxyphosphoryl compounds are prepared by a two-step process: hydrophosphorylation of an aldehyde and subsequent esterification with a carboxylic acid.[3] However, the corresponding carboxylic acids need preactivation with stoichiometric activating reagents, and this procedure suffers from low atom-[4a,b] and step-economic[4c,d] efficiency.

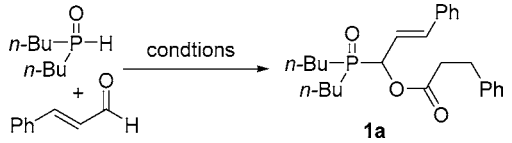
The redox functionalization of unsaturated aldehydes is emerging as a powerful methodology for the synthesis of carboxylic acid derivatives because of the high redox economy.[4e,f,8a] This transformation[5−8] usually is mediated by transition-metal complexes,[6] *N*-heterocyclic carbene (NHC) compounds,[7] or the combination of cyanide compounds (TMSCN or NaCN) and base.[8] Herein, we report an efficient one-pot synthesis of α-acyloxyphosphoryl compounds using a facile base-mediated redox strategy: the redox esterification of unsaturated aldehydes with hydrogen phosphoryl compounds (eq 1). Worth noting is that this redox functionalization of unsaturated aldehyde is mediated only by a simple base. Compared to conventional procedures, this transformation also features high atom- and step-economic efficiency and is applicable to prepare a wide range of α-acyloxyphosphoryl compounds.



(1)

Our initial investigations commenced with examining the reactivity of dibutylphosphine oxide with cinnamaldehyde, and the obtained results are compiled in Table 1. After an extensive screening, *t*-BuOLi was found to be an efficient base for the

Table 1. Redox Esterification of Cinnamaldehyde with Dibutylphosphine Oxide[a]



1a

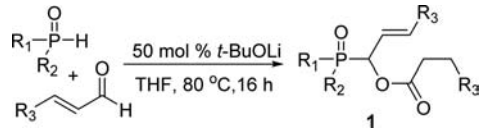
run	base	solv	temp (°C)	yield[b] (%)
1	none	THF	25	0
2	100 mol % Et_3N	THF	25	0
3	20 mol % NaOH	THF	25	5
4	20 mol % NaOBu-*t*	THF	25	21
5	20 mol % KOBu-*t*	THF	25	23
6	20 mol % LiOBu-*t*	THF	25	27
7	20 mol % LiOBu-*t*	THF	50	39
8	20 mol % LiOBu-*t*	THF	66	51
9	20 mol % LiOBu-*t*	THF	80	59
10	40 mol % LiOBu-*t*	THF	80	74
11	50 mol % LiOBu-*t*	THF	80	86
12	100 mol % LiOBu-*t*	THF	80	61
13	50 mol % LiOBu-*t*	DMF	80	36
14	50 mol % LiOBu-*t*	dioxane	80	73
15	50 mol % LiOBu-*t*	MeCN	80	27
16	50 mol % LiOBu-*t*	toluene	80	27
17	50 mol % LiOBu-*t*	hexane	80	5

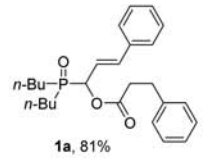
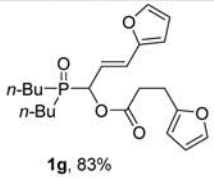
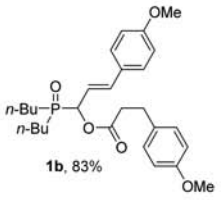
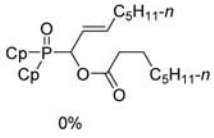
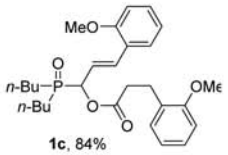
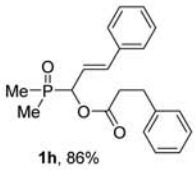
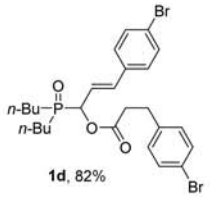
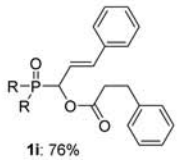
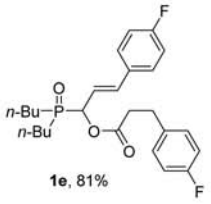
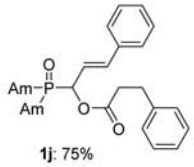
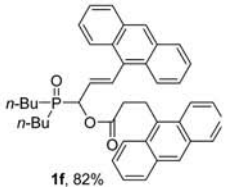
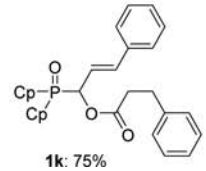
[a]Reaction conditions: under N_2 atmosphere, 0.2 mmol of dibutylphosphine oxide, 0.42 mmol of cinnamaldehyde, base, and 0.4 mL of solvent were charged into a 10 mL glass tube. The mixture was stirred for 16 h at the temperature indicated. [b]^{31}P NMR yield using trimethylphosphate as an internal standard.

Received: October 13, 2014
Published: November 14, 2014

   dx.doi.org/10.1021/ol503014f | *Org. Lett.* 2014, 16, 6152−6155

Table 2. Redox Esterification of Unsaturated Aldehydes with Hydrogen Phosphoryl Compounds[a]

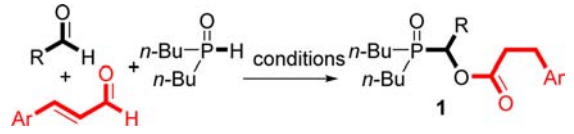


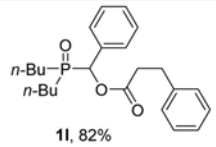
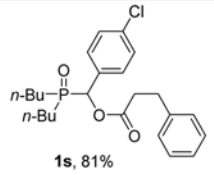
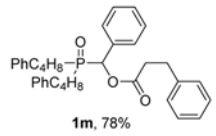
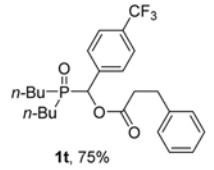
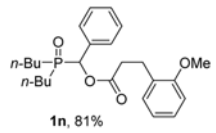
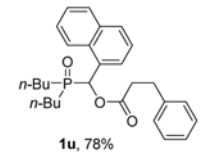
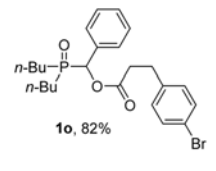
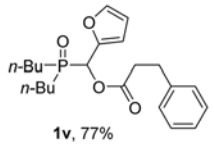
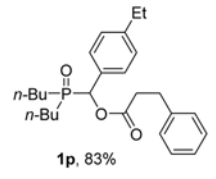
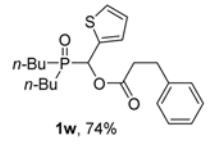
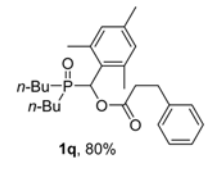
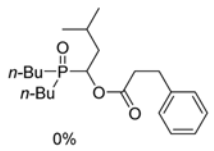
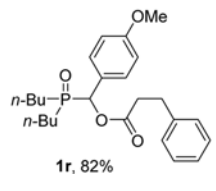
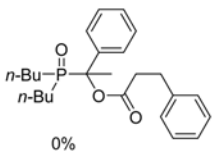
run	yield[b]	run	yield[b]
1	 **1a**, 81%	7	 **1g**, 83%
2	 **1b**, 83%	8	 0%
3	 **1c**, 84%	9	 **1h**, 86%
4	 **1d**, 82%	10[c]	 **1i**: 76%
5	 **1e**, 81%	11[d]	 **1j**: 75%
6	 **1f**, 82%	12[e]	 **1k**: 75%

[a]Reaction conditions: under N_2 atmosphere, 0.2 mmol of hydrogen phosphoryl compounds, 0.42 mmol of cinnamaldehyde, 0.1 mmol of *t*-BuOLi, and 0.4 mL of THF were charged into a 10 mL glass tube. The mixture was stirred at 80 °C for 16 h. [b]Isolated yield. [c]R = 4-phenylbutyl. [d]Am = 3-pentyl. [e]Cp = cyclopentyl.

present redox transformation (Table 1, runs 1−6). Thus, the redox esterification of cinnamaldehyde with dibutylphosphine oxide took place smoothly at room temperature in the presence of 20 mol % *t*-BuOLi, generating the corresponding *α*-

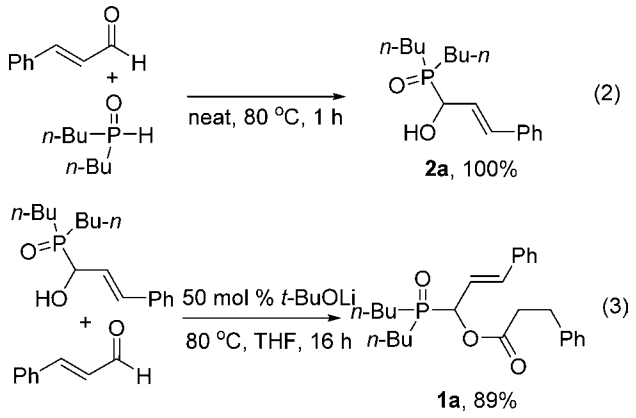
Table 3. One-Pot Synthesis of *α*-Acyloxyphosphoryl Compounds from Two Different Aldehydes Using a Redox Strategy[a]



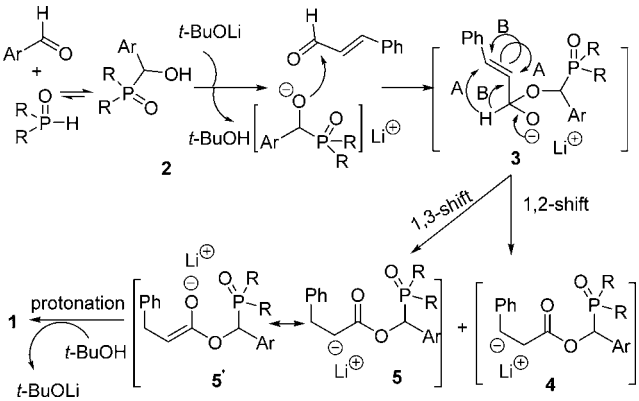
run	yield[b]	run	yield[b]
1	 **1l**, 82%	8	 **1s**, 81%
2[c]	 **1m**, 78%	9	 **1t**, 75%
3	 **1n**, 81%	10	 **1u**, 78%
4	 **1o**, 82%	11	 **1v**, 77%
5	 **1p**, 83%	12	 **1w**, 74%
6	 **1q**, 80%	13	 0%
7	 **1r**, 82%	14	 0%

[a]Reaction conditions: under N_2 atmosphere, 0.2 mmol of hydrogen phosphoryl compounds and 0.2 mmol of aldehyde were heated neat in a 10 mL sealed glass tube at 80 °C for 1 h, then 0.24 mmol of cinnamaldehyde, 0.1 mmol of *t*-BuOLi and 0.4 mL of THF were added. The mixture was stirred at 80 °C for 16 h. [b]Isolated yield. [c]Bis(4-phenylbutyl)phosphine oxide was used instead of dibutylphosphine oxide.

dx.doi.org/10.1021/ol503014f | *Org. Lett.* 2014, 16, 6152−6155



Scheme 1. Proposed Mechanism for the Redox Esterifications of Unsaturated Aldehydes with Hydrogen Phosphoryl Compounds



acyloxyphosphoryl compound **1a** in 27% yield (Table 1, run 6). Further studies reveal that this reaction is temperature dependent (Table 1, runs 7−9). Under similar reaction conditions, the yield of **1a** increased to 39% at 50 °C (Table 1, run 7). While the temperature was elevated to 80 °C, **1a** was produced in 59% yield (Table 1, run 9). To our delight, 86% yield of α-acyloxyphosphoryl compound **1a** was obtained in the presence of 50 mol % *t*-BuOLi (Table 1, run 11). However, a further increase of the amount of base did not improve the yield of **1a** (Table 1, run 12). As to the solvent, this reaction proceeded readily in THF and dioxane but poorly in DMF, MeCN, toluene, and hexane. This result probably was contributed to the difference in solubility of *t*-BuOLi in these solvents (Table 1, runs 11 and 13−17).[9]

Under the optimized reaction conditions, this redox strategy was widely applicable to the preparation of various α-acyloxyphosphoryl compounds **1** from unsaturated aldehydes and hydrogen phosphoryl compounds. As shown in Table 2, various aromatic conjugated aldehydes underwent redox esterification with dibutylphosphine oxide in the current system to produce the corresponding α-acyloxyphosphoryl compound **1** efficiently. Thus, cinnamaldehydes bearing an electron-donating group (*p*-MeO and *m*-MeO) were successfully converted to the expected **1b** and **1c** in 83% and 84% yields, respectively (Table 2, runs 2 and 3). The redox esterification of cinnamaldehydes with halogen atoms like Br and F was achieved in the current base-mediated system to yield the desired products **1d** and **1e** in high yields. The resulting products would be further functionalized via cross-coupling reaction (Table 2, runs 4 and 5). The multiaromatic cyclic conjugated aldehydes also underwent redox reaction readily with dibutylphosphine oxide, furnishing **1f** in 82% yield (Table 2, run 6). Worth noting is that a heterocycle group, as exemplified by a furan group, also was successfully introduced into the α-acyloxyphosphoryl skeleton using the present base-mediated redox strategy (Table 2, run 7). However, aliphatic conjugated aldehyde worked poorly under similar reaction conditions due to severe polymerization (Table 2, run 8).

As for the hydrogen phosphoryl compounds, other secondary phosphine oxides are also efficient substrates for the present redox esterification of unsaturated aldehydes. Thus, in addition to dibutylphosphine oxide, the reaction of dimethylphosphine oxide ($Me_2P(O)H$) with cinnamaldehyde occurred smoothly under similar reaction conditions, giving the desired product **1h** in 86% yield (Table 2, run 9). Other secondary phosphine oxides, even the bulky ones like di-3-pentylphosphine oxide and dicyclopentylphosphine oxide, are found reactive to have efficient production of the corresponding α-acyloxyphosphoryl compounds **1** in good yields (Table 2, runs 10−12).

As demonstrated in eqs 2 and 3 (vide infra), we predicted that, by slightly tuning the reaction procedure, this base-mediated redox strategy could be applied to the synthesis of unsymmetrical α-acyloxyphosphoryl compounds **1** in one pot using two different aldehydes, extending the substrate scope of the current catalytic system. Indeed, this was the case. Thus, an equimolor ratio of dibutylphosphine oxide and benzaldehyde was heated neat at 80 °C for 1 h, followed by addition of 1.1 equiv of cinnamaldehyde, 50 mol % *t*-BuOLi, and solvent THF. The mixture was stirred at 80 °C for another 16 h to give the corresponding unsymmetrical α-acyloxyphosphoryl compound **1l** in 82% yield (Table 3, run 1). Following a similar reaction procedure, bis(4-phenylbutyl)phosphine oxide could also be converted to the expected product **1m** in good yield (Table 3, run 2). To our delight, other aromatic aldehydes, both with an electron-donating and electron-withdrawing group, all underwent hydrophosphorylation with dibutylphosphine oxide, and then redox esterification with various enals in the presence of *t*-BuOLi under similar reaction conditions, producing the corresponding valuable unsymmetrical α-acyloxyphosphoryl compounds **1** in good yields (Table 3, runs 3−12). However, when aliphatic aldehydes and ketones were employed as the substrates, only the hydrophosphorylative products were produced, and the subsequent redox esterification did not work (Table 3, runs 13 and 14).

In order to clarify the mechanism, control experiments were performed. An equivalent amount of dibutylphosphine oxide and cinnamaldehyde was heated at 80 °C for 1 h, and α-hydroxyphosphoryl compound **2a** was generated quantitatively (eq 2). Interestingly, the resulting **2a** can further react with cinnamaldehyde smoothly in the presence of 50 mol % *t*-BuOLi to give the α-acyloxyphosphoryl compound **1a** in 89% yield (eq 3). Thus, on the basis of these control experiments and Table 3, this redox reaction can be rationalized to take place via a tandem process involving (1) hydrophosphorylation of aldehydes to produce α-hydroxyphosphoryl compound **2**, (2) addition of **2** to another cinnamaldehyde in the presence of *t*-BuOLi, (3) isomerization of **3** via 1,2-shift or 1,3-shift to afford **4** or **5** (**5′**) by the aid of a base,[10] and (4) protonation of **4** or **5** (**5′**) with *t*-BuOH to give the corresponding α-acyloxyphosphoryl compound **1** (Scheme 1).

In conclusion, we disclosed an efficient one-pot synthesis of α-acyloxyphosphoryl compounds using a facile base-mediated

dx.doi.org/10.1021/ol503014f | Org. Lett. 2014, 16, 6152−6155

redox strategy. This redox esterification of unsaturated aldehydes with hydrogen phosphoryl compounds provides a straightforward protocol for the synthesis of α-acyloxyphosphoryl compounds with high atom- and step-economic efficiency.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, full spectroscopic data, and copies of ^{1}H, ^{31}P, and ^{13}C spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: chentieqiao@hnu.edu.cn.
*E-mail: literabc@hotmail.com.
*E-mail: libiao-han@aist.go.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support from NSFC 21373080, 20772055 and Fundamental Research Funds for the Central Universities (Hunan University).

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