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Fe-Catalyzed Bisphosphorylation of Amino-2-en-1-ones with Trialkyl Phosphites

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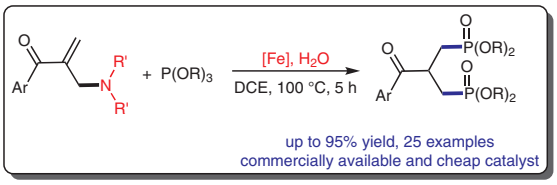

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Abstract A facile bisphosphorylation of amino-2-en-1-ones with trialkyl phosphites mediated by iron is developed. The reaction is considered to go through two Michael addition progresses. A variety of amino-2-en-1-ones are bisphosphorylated in high yields with functional group tolerance. In addition, the protocol of introduction of two different phosphates into one molecule is successful through a cascade reaction.

Key words iron, bisphosphorylation, amino-2-en-1-ones, cascade reaction.

Alkyl phosphonates are an important class of organic compounds widely found in pharmaceuticals and materials.[1] As a consequence, a variety of methods to prepare these compounds have been developed.[2] Among them, nucleophilic substitutions of halide phosphonates,[3] Michaelis–Arbuzov rearrangement of alkyl halides with trialkyl phosphites,[4] and nucleophilic additions of phosphites into alkenes were well investigated to deliver the alkyl phosphonates.[5] In addition, the substitution of quaternary ammonium salts by trialkyl phosphites toward the alkyl phosphonates has also been developed recently,[6] but the pre-functionalization (salification) of the tertiary amines in this method is needed. More recently, the direct phosphorylation of tertiary amines has received much attention, due to the abundant existence of the substrates. For example, Tian developed an elegant method for the catalyst-free C(sp^3)–N bond cleavage of allylic sulfonamides to form alkyl phosphonates under room temperature.[7] We have also disclosed an efficient and operational protocol to enable the construction of alkyl phosphonates via selective monophosphorylation and bisphosphorylation of amino-2-en-1-ones in the absence of external catalyst or additive.[8] In this reaction, the selectivity of monophosphorylation or bisphosphorylation was controlled by both the acidities and nucleophilicities of phosphorus sources. Dialkyl phosphites delivered the monophosphonated productions, and phosphine oxides offered the bisphosphonated products. However, the bisphosphoric acid derivatives have not been obtained through this strategy. We envisioned that the more nucleophilic reagents than phosphine oxides such as trialkyl phosphites would react with amino-2-en-1-ones with the acid as a catalysis.[9] Herein, we reported an iron-catalyzed bisphosphorylation of amino-2-en-1-ones using trialkyl phosphites as nucleophiles.[10] This method enables the facile synthesis of double the phosphoric acid derivatives.

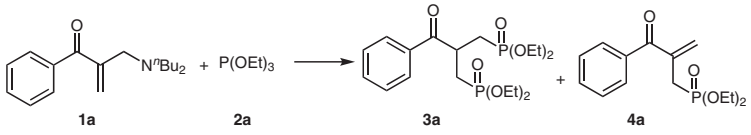
Considering the dialkyl phosphites could activate the amino-2-en-1-ones, and the trialkyl phosphites can be hydrolyzed to dialkyl phosphites under water. We first chose wet $ClCH_2CH_2Cl$ (DCE) as a solvent, **1a** (0.3 mmol) and triethyl phosphites (0.9 mmol) as model reactants under air conditions to start our investigation. Interestingly, the reaction delivered the bisphosphorylated product in 37% yield along with 53% of monophosphorylated product at 100 °C for 5 h (Table 1, entry 1). Inspired by this, 20 mol% H_2O were added into the reaction, and the selectivity of the reaction was increased, but the overall yields decreased to 74% (Table 1, entry 2), further increasing the loading of water to 1.0 equivalent, the yield of bisphosphorylated product **3a** was raised to 55% (Table 1, entry 3). The Brønsted acids such as HOAc, CF_3COOH, and TsOH could not promote the reaction (Table 1, entries 4–6). Then, Lewis acids were tested, we found the reactions performed well. When $AlCl_3$ was employed into the phosphorylation reaction, **3a** was obtained in 75% yield, with 10% yield of **4a** (Table 1, entry 7). $ZnCl_2$ gave the similar result, while $FeCl_3$ was an inferior catalyst in the reaction (Table 1, entries 8 and 9). Interestingly, when $FeCl_3{\cdot}6H_2O$ (20 mol%) was applied into the phosphorylation reaction, the selectivity was dramatically improved, furnishing **3a** with 85% yield and a trace amount of **4a** (Table 1, entry 10). The high selectivity and yield of the reac-

tion probably resulted from the dual role of the catalyst (catalysis and hydrolysis). Inspired by this, a variety of Lewis acid hydrates were tested, $Fe(NO_3)_3{\cdot}9H_2O$ gave the desired product in 95% yield along with trace of **4a** (Table 1, entry 11). Other nitrates such as, $Al(NO_3)_3{\cdot}6H_2O$, $Bi(NO_3)_3{\cdot}5H_2O$, and $Al_2(SO_4)_3{\cdot}18H_2O$ presented well catalytic feature in this transformation (Table 1, entries 12–14). The effect of solvent on the reaction was screened. Toluene afforded the bisphosphorylated product in moderate yield (Table 1, entry 15). CH_3CN is a good solvent in this transformation, which resulted in the desired product in 89% yield (Table 1, entry 16).

When the amount of $Fe(NO_3)_3{\cdot}9H_2O$ was reduced to 10 mol% , a slight decrease of the yield was detected (Table 1, entry 17). Meanwhile, the study of the temperature showed that the reaction performed poor when the temperature was decreased to 80°C (Table 1, entry 18).

With the optimized conditions in hand, the substrate scope of this transformation was investigated (Scheme 1). The effect of substituted groups on the reaction was examined. The substrate with a methyl on the benzene (**1b**) delivered the expected product **3b** in 83% yield. 2,4-Dimethyl ketone **1c** enabled the conversion with a good yield. When the benzyl was switched to naphthyl, the reaction performed well, giving the desired product in 80% yield. The reactants with methoxy-substituted benzenes performed well in the reaction system, for instance, **1f** furnished the corresponding product in 95% yield. Other electron-donating groups decorated on the benzene ring such as **1g**, **1h**, and **1i** were tolerated in this reaction, furnishing the corresponding products in good yields, respectively. On the other hand, an electron-withdrawing group such as nitro group has a negative effect on the transformation, which gave the desired product in 55% yields (**3j**). Br-, Cl- and F-bearing benzene substrates could also furnish the desired products in fair yields (**3k–n**). Moreover, the protocol is also applicable to heterobenzene, for instance, **1o** could deliver **3o** in 96% yield. The scope of phosphites was examined in this bisphosphorylation reaction. Trimethyl phosphite led to the

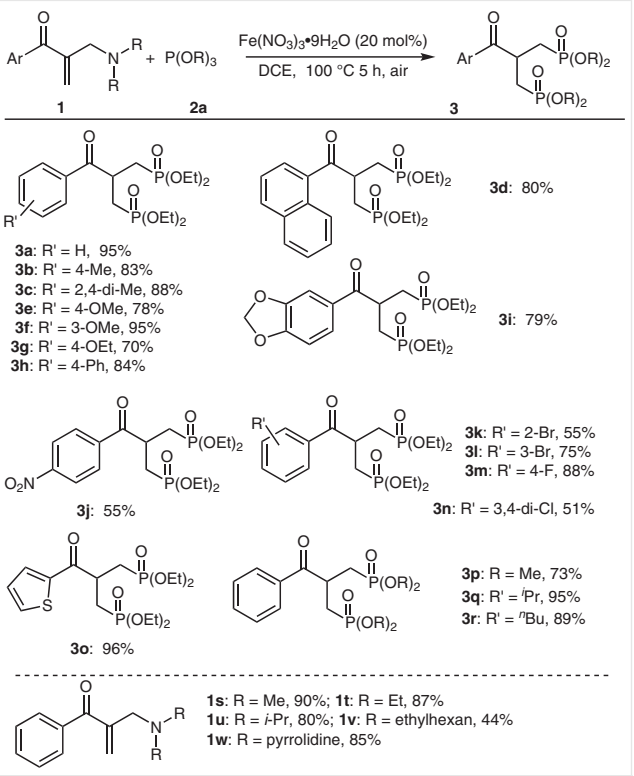
Table 1 The Optimization of the Reaction[a]



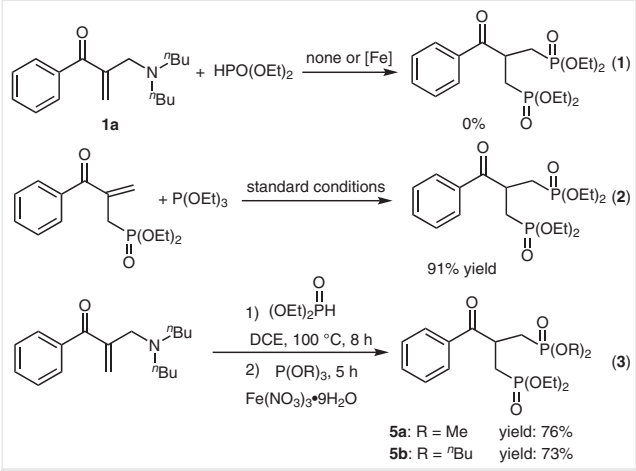
1a 2a 3a 4a

Entry	Acid (20 mol%)	Temp (°C)	Solvent	**3a**/**4a** (%)[b]
1	–	100	DCE	37:53
2	H_2O	100	DCE	56:18
3[c]	H_2O	100	DCE	55: 32
4	HOAc	100	DCE	60:28
5	CF_3COOH	100	DCE	45:21
6	TsOH	100	DCE	42:18
7	$AlCl_3$	100	DCE	75:10
8	$ZnCl_2$	100	DCE	72:13
9	$FeCl_3$	100	DCE	69:21
10	$FeCl_3{\cdot}6H_2O$	100	DCE	85:trace
11[d]	$Fe(NO_3)_3{\cdot}9H_2O$	100	DCE	95:trace
12	$Al(NO_3)_3{\cdot}6H_2O$	100	DCE	88:trace
13	$Bi(NO_3)_3{\cdot}5H_2O$	100	DCE	89:trace
14	$Al_2(SO_4)_3{\cdot}18H_2O$	100	DCE	91:trace
15	$Fe(NO_3)_3{\cdot}9H_2O$	100	toluene	65: 20
16	$Fe(NO_3)_3{\cdot}9H_2O$	100	CH_3CN	89:trace
17[e]	$Fe(NO_3)_3{\cdot}9H_2O$	100	DCE	86:trace
18[f]	$Fe(NO_3)_3{\cdot}9H_2O$	80	DCE	84:trace

[a] Reaction conditions: **1a** (0.3 mmol) and **2a** (3 equiv) mixed in solvent (2 mL) at 100 °C under N_2 for 5 h.
[b] Isolated yield.
[c] H_2O (1 equiv).
[d] 20 mol% of catalyst.
[e] 10 mol% of catalyst.
[f] 20 mol% of catalyst, at 80 °C.



Scheme 1 The scope of the substrates of the reaction



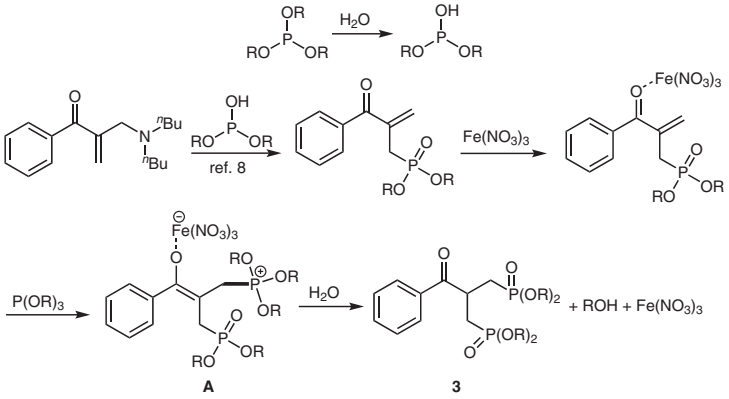
Scheme 2 Control experiments

corresponding product in 73% yield (**3p**), triisopropyl phosphite furnished **3q** in 95% yield, and tributyl phosphonite gave 89% yield of the expected product. Additionally, the impact of the amino group on the reaction was screened.

Substrates with dimethylamino, diethylamino, diisoproylamino, bis(2-ethylhexyl)amino, and pyrroldine instead of the dibutylamino group were applied into triethyl phosphite, the desired products were furnished in good yields, except **1v**, which may be due to the steric hindrance (**1s–w**).

To investigate the mechanism of this transformation, several control experiments were studied (Scheme 2). Firstly, **1a** was subjected to the reaction with diethyl phosphite rather than triethyl phosphite, and just the monophosphorylation product was found, even the $Fe(NO_3)_3{\cdot}9H_2O$ was employed into this reaction, the bisphosphorylation product was not found, suggesting that only trialkyl phosphite performs the bisphoaphorylation the reaction. Secondly, the monophosphorylation product was used as the substrate to be subjected to triethyl phosphite in the presence of catalyst under the standard conditions, the bisphosphorylation was obtained in 91% yield. This indicated that the reaction was carried out via a monophosphorylation procedure, followed by an acid-catalyzed phosphorylation (Scheme 2, eq. 2). To highlight this protocol, the unsymmetrical bisphosphorylation products were achieved in good yields by sequence (Scheme 2, eq. 3).

A plausible mechanism of this reaction was proposed according to the control experiments and preceding literatures.[7,8] As demonstrated in Scheme 3, a part of the trialkyl phosphites were hydrolyzed to form dialkyl phosphites,



Scheme 3 Plausible mechanism of the reaction

which activated the amino group of amino-2-en-1-ones to deliver the monophosphorylated products.[8] Then, Lewis acid activated the carbonyl group, and the nucleophile of trialkyl phosphite added to the alkene to form **A**. With the assistance of H_2O, the bisphosphorylated product was afforded.

In summary, we have developed an iron-catalyzed bisphosphorylation of amino-2-en-1-ones and trialkyl phosphites to prepare 1,3-diphosphoric acid derivatives under mild conditions.[11–13] This reaction is an effective supplement of the previous work to forge the alkyl 1,3-diphosphorus compounds. Additionally, unsymmetrical 1,3-diphosphonate esters were obtained by a sequential addition according to this strategy.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611803.

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(11) **2-[(Diethylamino)methyl]-1-phenylprop-2-en-1-one (1a)**
Ketone **1** (1 mmol) was mixed with silica gel (2.0 g) in a mortar. Then formaldehyde (0.18 g, 3 mmol, 37% in H_2O) and dialkylamine (2 mmol) were added and mixed. The mixture was placed into a flask with a cap and stirred for 5–7 h at room temperature. Then diethyl ether (20 mL) was added. After filtration and the removal of the solvent at the reduced pressure, the product was isolated. Further purification of the crude reaction mixture on silica gel column gave the pure product.

(12) **General Procedure for 3a**
To a 50 mL Schlenk tube with a stir bar added allylamine derivatives **1a** (81.9 mg, 0.3 mmol), triethyl phosphite (149.5 mg, 3 equiv), $Fe(NO_3)_3{\cdot}9H_2O$ (20 mol%), and DCE (2 mL), the mixture was stirred at 100 °C for 5 h and monitored by TLC. The solution was then evaporated under vacuum. The crude reaction mixture was purified by column chromatography on silica gel (pure EtOAc) to get product **3a**.^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 7.4 Hz, 2 H), 7.58 (t, *J* = 7.1 Hz, 1 H), 7.51 (t, *J* = 7.4 Hz, 2 H), 4.34 (ddd, *J* = 20.5, 13.9, 6.6 Hz, 1 H), 4.13–3.91 (m, 8 H), 2.44–2.32 (m, 2 H), 2.14–2.01 (m, 2 H), 1.24 (t, *J* = 7.0 Hz, 6 H), 1.14 (t, *J* = 7.0 Hz, 6 H) ppm.^{13}C NMR (101 MHz, $CDCl_3$): δ = 199.77, 199.68, 199.59, 135.05, 133.61, 128.92, 128.88, 77.32, 77.00, 76.68, 62.56, 62.49, 62.35, 62.29, 34.46, 34.43, 34.41,

28.95, 28.85, 27.53, 27.43, 16.24, 16.18, 16.10, 16.03 ppm.^{31}P NMR (243 MHz, $CDCl_3$): δ = 28.09 ppm. HRMS: *m/z* calcd for $C_{18}H_{31}O_7P_2$ $[M + H]^+$: 421.1540; found: 421.1541.

(13) **General Procedure for 5a**

To a 50 mL Schlenk tube with a stir bar added allylamine derivatives **1a** (81.9 mg, 0.3 mmol), diethyl phosphite (82.8 mg, 2 equiv), and DCE (2 mL), the mixture was stirred at 100 °C for 8 h. Then, trialkyl phosphite (1.5 equiv), $Fe(NO_3)_3{\cdot}9H_2O$ (20 mol%), and DCE (2 mL) were added. The mixture was stirred at 100 °C for 5 h and monitored by TLC. The solution was then evaporated under vacuum. The crude reaction mixture was purified by column chromatography on silica gel (pure EtOAc) to get the product. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 7.4 Hz, 2 H), 7.58 (t, *J* = 7.3 Hz, 1 H), 7.48 (t, *J* = 7.6 Hz, 2 H), 4.21–4.06 (m, 1 H), 4.00 (p, *J* = 7.3 Hz, 4 H), 3.62 (d, *J* = 10.9 Hz, 6 H), 2.43–2.23 (m, 2 H), 2.17–2.02 (m, 2 H), 1.24–1.16 (m, 6 H) ppm.^{13}C NMR (101 MHz, $CDCl_3$): δ = 199.91 (s), 135.59 (s), 133.51 (s), 128.73 (d, *J* = 13.8 Hz), 61.91 (t, *J* = 6.9 Hz), 52.39 (t, *J* = 6.5 Hz), 34.96 (t, *J* = 3.3 Hz), 29.65 (d, *J* = 12.6 Hz), 28.35 (dd, *J* = 20.7, 11.8 Hz), 27.05 (d, *J* = 11.1 Hz), 16.27 (t, *J* = 5.8 Hz) ppm. ^{31}P NMR (243 MHz, $CDCl_3$): δ = 30.78, 27.87 ppm. HRMS: *m/z* calcd for $C_{16}H_{27}O_7P_2$ $[M + H]^+$: 393.1227; found: 393.1227.