$LiAlH_4$-Induced Reductive Dephosphonylation of α,α-Dialkyl Triethyl β-Phosphonyl Esters: Mechanistic Study and Synthetic Application

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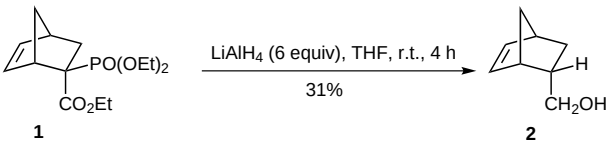
Abstract: Treatment of α,α-dialkyl triethyl β-phosphonyl esters with $LiAlH_4$ in CH_2Cl_2–THF caused the one-pot dephosphonylation and reduction to yield the corresponding primary alcohols bearing a controllable β secondary carbon center. Mechanistic study has revealed that the $LiAlH_4$-induced dephosphonylation should occur first with the assistance of the carboxylate group, and the hydrogen source of the resultant new C–H bond is $LiAlH_4$.

Key words: reductive dephosphonylation, β-phosphonyl esters, C–P bond cleavage, lithium aluminum hydride, primary alcohols

The cleavage of a phosphonyl group is an important process in synthetic chemistry.[1] During the previous study on the Diels–Alder reaction of 2-phosphono-2-alkenoates,[2] we serendipitously discovered that treatment of phosphoryl ester **1** derived from the cycloaddition between triethyl 2-phosphonoacrylate and cyclopentadiene with lithium aluminum hydride ($LiAlH_4$) caused the one-pot dephosphonylation–reduction to afford *endo*-{bicyclo[2.2.1]hept-5-en-2-yl}methanol (**2**)[3,4] as an useful synthetic intermediate[5] (Scheme 1). This so far undisclosed result attracted our attention because the reactions of phosphonates with $LiAlH_4$ in ethereal solutions usually produce the corresponding primary phosphines (RPH_2).[6] A literature search revealed that the reductive dephosphonylation of the phosphonates bearing a β-carbonyl moiety is rare and difficult to be achieved in practice.[1,7] Among few documented methods, Oh's group once reported a dephosphonylating operation on β-keto phosphonates, which involved treating the metal enolates of these substrates with $LiAlH_4$ in THF followed by quenching the reaction mixture with aqueous H_2SO_4 solution to yield dephosphonylated ketones.[8] For this transformation, the results from deuterium-labeled experiments suggest that the cleavage of the P–C bond is not caused by the attack of a hydride on the α- or γ-carbon atoms. However, the detailed mechanism of dephosphonylation has remained to be obscure. Apart from this, Amedjkouh's group reported a related methodology for transferring the cyclic β-iminophosphonates into amines by $LiAlH_4$, and the dephosphonylation upon the reduction was proposed to occur via the rearrangement of a lithiated phosphonyl amide intermediate.[9] To our knowledge, the $LiAlH_4$-mediated reductive dephosphonylation has never been reported on β-phosphonyl ester system. In this regard, we decided to carry out a close examination on the reaction in Scheme 1 for exploring a mechanistic rationale and a synthetic route to highly substituted primary alcohols.

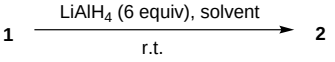


1 2

Scheme 1 Reaction of **1** with $LiAlH_4$ in THF

In THF, the reaction in Scheme 1 only produced 31% of **2** along with complex mixtures. For improving the yield, we initially examined several other solvents. As outlined in Table 1, the reactions performed in diethyl ether or 1,2-dimethoxyethane afforded **2** in the comparable yields (29% and 27%) as in THF (Table 1, entries 1 and 2), while a better conversion (48%) was obtained by employing dichloromethane (CH_2Cl_2) as a solvent (Table 1, entry 3). Nevertheless, it took much longer time for $LiAlH_4$ to disperse homogeneously in CH_2Cl_2 than in the tested ethereal solvents, and consequently, a prolonged reaction time (8 h) was required for the reaction to complete. On this basis, we further screened a few co-solvents of CH_2Cl_2 with THF, diethyl ether, and 1,2-dimethoxyethane, respectively, in different ratios (Table 1, entries 4–8), and found that

Table 1 Evaluation of Solvent Effect on the Formation of **2**



Entry	Solvent	Time (h)	Yield (%)[a]
1	Et_2O	4	29
2	1,2-dimethoxyethane	4	27
3	CH_2Cl_2	8	48
4	CH_2Cl_2–THF (1:1)	2	75
5	CH_2Cl_2–Et_2O (1:1)	2	53
6	CH_2Cl_2–1,2-dimethoxyethane (1:1)	2	63
7	CH_2Cl_2–THF (2:1)	2	54
8	CH_2Cl_2–THF (1:2)	2	70

[a] Yield is for isolated, chromatographically pure product.

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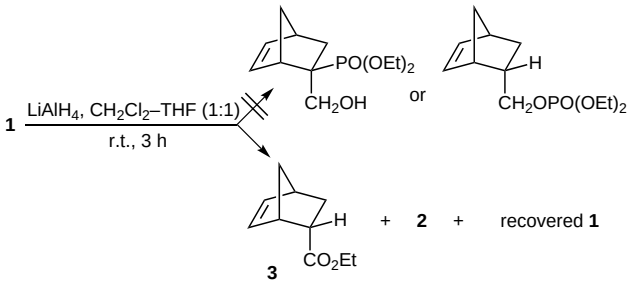
all of these co-solvents resulted in higher yields (53–75%) than each solvent used alone. Among which, the best result was received from CH_2Cl_2 and THF in a ratio 1:1 (v/v), affording **2** in 75% isolated yield after two hours at room temperature (Table 1, entry 4). Thus the reaction conditions in entry 4 are tentatively considered to be our choice to effect the formation of **2**.

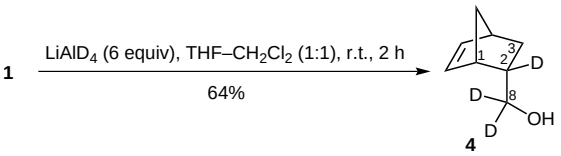
We originally thought that the dephosphonylation might be initiated by the reduction of the carboxylate group into an alkoxide intermediate, and the subsequent addition of the resulting oxide to the P=O bond could induce the cleavage of C–P bond in a Horner–Emmons-like process. To verify this, we treated **1** with one and two equivalents, respectively, of $LiAlH_4$ in CH_2Cl_2–THF. However, both reactions did not provide any trace of hydroxyl phosphonate or phosphate resulting from the reduction of the ester group, but rather produced the *endo*-norbornenyl ester **3**[10] exclusively in 23% yield or together with **2** in 48% yield, plus 65% and 5% of recovered **1** (Scheme 2). In contrast to our original assumption, these results unambiguously demonstrate that the dephosphonylation should take place prior to the reduction of the ester group. Once formed, ester **3** can be quickly reduced into **2** by excess of $LiAlH_4$.



$LiAlH_4$ (1 equiv)	23%	–	65%
$LiAlH_4$ (2 equiv)	48%	19%	5%

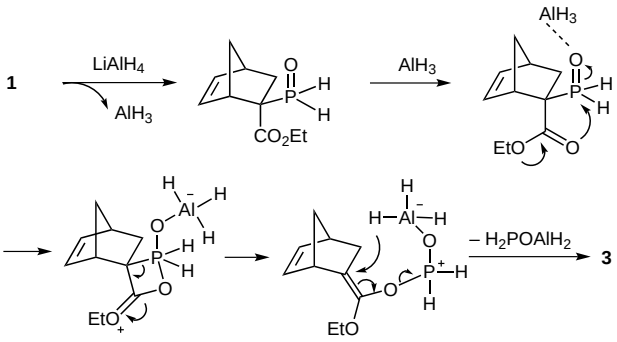
Scheme 2 Evaluation of effect of amount of $LiAlH_4$

To investigate the mechanism in a more direct manner, we further conducted an isotopic labeling experiment with $LiAlD_4$. Interestingly, the reaction furnished compound **4** incorporated by three deuterium atoms at C-2 and C-8 positions as the single *endo* isomer (Scheme 3). In comparison of its ^{1}H NMR spectrum with that of **2**, the original signals of the C-2 methine proton at δ = 2.34–2.25 ppm and the C-8 methylene protons at δ = 3.40 and 3.26 ppm disappeared, while the splitting pattern of the C-3 *endo* proton at δ = 0.53 ppm changed from ddd (J = 11.6, 4.4, 2.6 Hz) into dd (J = 11.6, 2.6 Hz). On its ^{13}C NMR spectrum, the C-2 and C-8 peaks at δ = 41.0 and 65.7 ppm were, respectively, displayed as a triplet (J = 20.1 Hz) and a quintet (J = 21.6 Hz) resulting from the splitting by the deuterium nucleus. We also observed that the aqueous workup of the reaction with $LiAlH_4$ (1 equiv) by D_2O did not give any deuterium-labeled product but afforded **3** in 25% yield, plus 61% of recovered **1**. These results demonstrate that the hydrogen source of the resultant new C–H bond comes from $LiAlH_4$ instead of protic solution, which has remarkably distinguished our protocol from the previously reported dephosphonylation of β-keto phosphonates.[8]



Scheme 3 Deuterium-labeled reaction with $LiAlD_4$

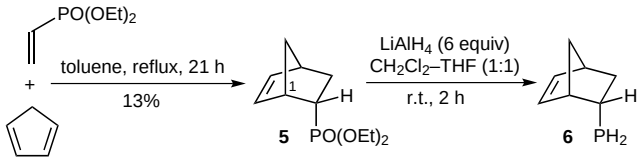
Based on the aforementioned results, we propose a possible pathway for the dephosphonylation as depicted in Scheme 4. Since one equivalent of $LiAlH_4$ was not enough to completely convert **1** into **3**, it is possible that **1** would be first reduced into a phosphine oxide at the expense of the reducing agent. With the coordination by released aluminum hydride (AlH_3), the P=O bond would then experience a nucleophilic attack by the carbonyl oxygen atom to furnish a transient four-membered cyclic intermediate. Subsequent cleavage of P–C bond would give the formation of a phosphoenol-type complex. From which, the delivery of a hydride from the aluminium complex to the β-position from the less hindered *exo* side would trigger consecutive double-bond migration and elimination to furnish ester **3**. This mechanism well explains the selective formation of **3** as the *endo* product as well as the origin of the C-2 hydrogen, which, as we see, would be hardly explained without considering the participation of the ester group.



Scheme 4 Proposed mechanism for dephosphonylation

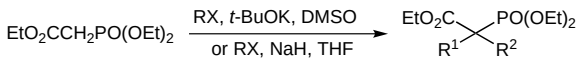
In an attempt to further clarify the role of the carboxylate moiety, we also synthesized norbornenyl phosphonate **5**[11] through the cycloaddition of diethyl vinylphosphonate[12] with cyclopentadiene and allowed it to react with $LiAlH_4$ under the developed conditions. In the absence of the carboxylate group, the reaction merely followed the reductive pattern of normal phosphonates[6] to give the formation of phosphine **6**[13] (Scheme 5), thus again validating the crucial role that the carboxylate group played on the dephosphonylation. Furthermore, it is noteworthy that at least six equivalents of $LiAlH_4$ were required to ensure a regular formation of **2**, and the use of less amounts, for ex-

ample, four or five equivalents, usually led to the inconsistent yields.



Scheme 5 Preparation and reduction of phosphonate **5** by $LiAlH_4$

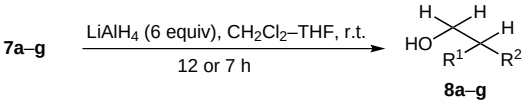
After completing the mechanistic study, we then turned our attention to exploring the synthetic utility of the new protocol. The generation of compounds with the controlled creation of an alkylated carbon center is of considerable use in synthetic chemistry with numerous approaches having been developed to attend this goal.[14] For example, the synthetic sequence involving the regioselective alkylation of β-keto esters followed by the hydrolysis and decarboxylation has been realized as a useful strategy for preparing the alkylated ketones in a regiocontrolled manner.[14b] In light of the efficient formation of **2**, we envisioned that the combination of the selective alkylation of a phosphonoacetate with the reductive dephosphonylation would provide a convenient entry into primary alcohols bearing a controllable β secondary carbon center. To demonstrate this, we first carried out the alkylation on triethyl phosphonoacetate with a range of selected alkylating agents including 5-bromo-1-pentene, 1,5-dibromopentane,[15] 1,6-dibromohexane, 1-iodopropane, allyl bromide, 4-bromo-1-butene, iodoethane,[16] benzyl bromide, iodomethane, 2-(bromomethyl)naphthalene, and iodocyclohexane to synthesize substrates **7a**–**h** (Scheme 6). The good anion-stabilizing capability of the phosphonyl moiety[1] allowed the alkyl groups to be conveniently introduced either in a single step to afford **7a**–**c**, or in a stepwise manner to give the unsymmetrically substituted precursors **7d**–**h**. Upon the treatment with $LiAlH_4$ in CH_2Cl_2–THF in a 1:1 ratio, most of the substrates (**7a**, **c**–**e**,**g**,**h**) were smoothly converted into the expected alcohols (**8a**,**c**–**e**,**g**,**h**) in synthetically useful yields (52–77%, Table 2, entries 1, 3–5, 7, and 8) except for **7b** and **7f**, and from which, the desired products **8b** and **8f** were only produced in 31% and 26% yield, respectively. Nevertheless, the better conversions (60% and 41%) were obtained with changing the ratio of the co-solvent into 2:1 (CH_2Cl_2–THF, v/v) (Table 2, entries 2 and 6).[17] As such, both solvent systems (CH_2Cl_2–THF = 1:1 and 2:1) are suggested to be practically attempted.



7a $R^1 = R^2$ = 4-pentenyl, 81%
7b $R^1 = R^2 = -(CH_2)_n-$, n = 5, 70%
7c $R^1 = R^2 = -(CH_2)_n-$, n = 6, 23%
7d R^1 = *n*-Pr, R^2 = allyl, 84%
7e R^1 = *n*-Pr, R^2 = 3-butenyl, 88%
7f R^1 = Et, R^2 = Bn, 95%
7g R^1 = 2-naphthyl, R^2 = Me, 83%
7h R^1 = Et, R^2 = cyclohexyl, 31%

Scheme 6 Preparation of α,α-dialkyl triethyl β-phosphonyl esters

Table 2 $LiAlH_4$-Promoted Reductive Dephosphonylation of α,α-Dialkyl Triethyl β-Phosphonyl Esters



Entry[a]	Substrate	Product **8**	Yield (%)[d]
1[b]	**7a**	**8a** $R^1 = R^2$ = 4-pentenyl	52
2[c]	**7b**	**8b** $R^1 = R^2 = (CH_2)_n$, n = 5	60
3[b]	**7c**	**8c** $R^1 = R^2 = (CH_2)_n$, n = 6	67
4[b]	**7d**	**8d** R^1 = *n*-Pr, R^2 = All	70
5[b]	**7e**	**8e** R^1 = *n*-Pr, R^2 = 3-butenyl	60
6[c]	**7f**	**8f** R^1 = Et, R^2 = Bn	41
7[b]	**7g**	**8g** R^1 = 2-naphthyl, R^2 = Me	69
8[b]	**7h**	**8h** R^1 = Et, R^2 = cyclohexyl	77

[a] Reactions of **7a**,**c**–**h** were conducted for 12 h, whereas reaction of **7b** was performed for 7 h at r.t.
[b] CH_2Cl_2–THF in a ratio of 1:1 (v/v) was used.
[c] CH_2Cl_2–THF in a ratio of 2:1 (v/v) was used.
[d] Isolated yield.

As compared with **1**, we also noted that much longer times (7–12 h) were required for these precursors, especially for the acyclic phosphonates, to attend the completion of the reactions. In accordance with our proposed mechanism (Scheme 4), we postulate that the rigid bicyclic skeleton of **1** can force the carbonyl and the phosphonyl groups to inherently stay in a co-plane during the transition state, to therefore facilitate the formation of the proposed cyclic intermediate. For the acyclic precursors, however, only the eclipsed intermediary conformer (Figure 1) can achieve the co-planarity to form the cyclic oxaphosphetane intermediate. We think that the higher energy level associated with this conformation should account for longer reaction times observed for these substrates.

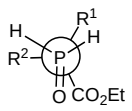


Figure 1 Eclipsed intermediary conformer required for reaching the cyclic intermediate

In summary, we have disclosed a novel $LiAlH_4$-promoted reductive dephosphonylation operation[18] on β-phosphonyl esters. Substantive evidences have been provided to support that the dephosphonylation should occur first with the assistance of the carboxylate group and $LiAlH_4$ is the hydrogen source of the resultant new C–H bond, which

make our procedure to be unique to previously reported dephosphonylation methods. Moreover, the convenient preparation of a variety of primary alcohols from readily accessed α,α-dialkyl β-phosphonyl esters in a controllable fashion has further underscored the value of the protocol.

Acknowledgment

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(17) Such solvent effect was not observed for other substrates.
(18) **Formation of 2 (Table 1, Entry 4) as a Typical Procedure for the LiAlH$_4$-Mediated Reductive Dephosphonylation**
To a stirred suspension of LiAlH$_4$ (95%, 169 mg, 4.23 mmol) in dry CH_2Cl_2 (5 mL) and THF (5 mL) precooled at 0 °C in an ice bath, a solution of **1** (213 mg, 0.705 mmol) in CH_2Cl_2–THF (5 mL, v/v = 1:1) was added dropwise in 2 min via a syringe under a nitrogen atmosphere. The ice bath was then removed and stirring was continued for an additional 2 h at r.t. The reaction mixture was recooled in an ice bath and cautiously quenched with 5% NaOH aq solution (2 mL). The resulting pale grey suspension was diluted with CH_2Cl_2 (30 mL) and successively washed with H_2O (2 × 8 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (hexane–EtOAc = 5:1) to afford 66 mg (75%) of **2** with the NMR spectral data agreeing well with the literature.[3] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.15 (dd, *J* = 5.7, 3.0 Hz, 1 H), 5.96 (dd, *J* = 5.7, 2.9 Hz, 1 H), 3.40 (dd, *J* = 10.4, 6.5 Hz, 1 H), 3.26 (dd, *J* = 10.4, 8.9 Hz, 1 H), 2.93 (br s, 1 H), 2.81(br s, 1 H), 2.34–2.25 (m, 1 H), 1.82 (ddd, *J* = 11.6, 9.2, 3.9 Hz, 1 H), 1.45 (dm, *J* = 8.2 Hz, 1 H), 1.27 (br d, *J* = 8.6 Hz, 2 H), 0.53 (ddd, *J* = 11.6, 4.4, 2.6 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.5, 132.1, 66.5, 49.5, 43.6, 42.2, 41.7, 28.8.

