Pergamon

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Tetrahedron Letters 44 (2003) 5811–5814

TETRAHEDRON LETTERS

A facile synthesis of 1,2-oxaphospholenes and stereoselective conversion into oxaphospholanes

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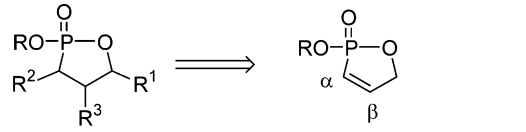
Received 3 May 2003; revised 3 June 2003; accepted 5 June 2003

Abstract—Treatment of α-acylallylphosphonates with *m*-CPBA in the presence of $MgSO_4$, afforded 1,2-oxaphosphol-3-enes 2-oxides and the subsequent cuprate addition produced 1,2-oxaphospholanes stereoselectively.

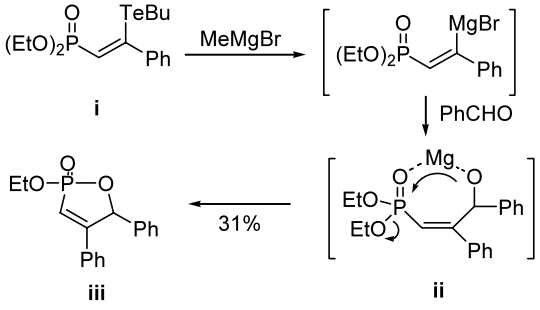
Heterocyclic compounds that contain phosphorus atoms have drawn attention to synthetic chemists[1] due to their association with various biological activities and unusual properties.[2] Recently, 1,2-oxaphospholane 2-oxides (**I**) attracted much attention as sugar surrogates since analogues with phosphorus atoms replacing the anomeric carbons could potentially serve as carbohydrate mimics.[3] For this end, several synthetic methods, have been developed to prepare a variety of oxaphospholanes during last decade.[4]



1,2 oxaphospholane 2-oxide (**I**) 1,2-oxaphosphol-3-ene 2-oxide (**II**)

We became interested in developing versatile synthetic methods for stereoselective preparation of oxaphospholanes with various substitution patterns, and we identified 1,2-oxaphospholene 2-oxide (**II**) as the divergent point for the preparation of **I**. Oxaphospholenes would serve not only as the starting point for various substituted oxaphospholanes,[5] but could also serve as good carbohydrate mimics. There have been only few reports of the preparation of oxaphospholenes[6] and the double bond in the 1,2-oxaphospholene ring did not show much reactivity toward nucleophilic reagents as only the reduction products were obtained from the reaction with dimethylcuprate or sodium naphthalenide.[7] Therefore, we envisaged a facile synthetic methodology to prepare oxaphospholene (**II**) with extra electron-withdrawing group at the α-position to increase the reactivity of 1,2-oxaphospholenes toward nucleophiles.[8]

Herein, we disclose a facile way to synthesize various 1,2-oxaphospholenes containing carbonyl group at the α-position of phosphorus and their reactivity toward nucleophiles. The new synthetic strategy was based on our recent finding of the synthesis of 1,2-oxaphospholenes (Scheme 1)[9] and regioselective preparation of acylallylphosphonates.[10] During the preparation of 3-hydroxy-1-alkenylphosphonate (**ii**) through transmetallation of 2-organyltelluro-1-alkenylphosphonate (**i**) with Grignard reagent, followed by addition of benzaldehyde, we obtained oxaphospholene (**iii**) instead of 3-hydroxy-1-alkenylphosphonate (**ii**) that was presumed to undergo intramolecular transesterification reaction to form oxaphospholene (**iii**). The low yield might be attributed to the isomerization of the double bond during condensation reaction since 3-hydroxy-1-alkenylphosphonate with *trans*-olefin could not cyclize under basic condition.[11]



Scheme 1.

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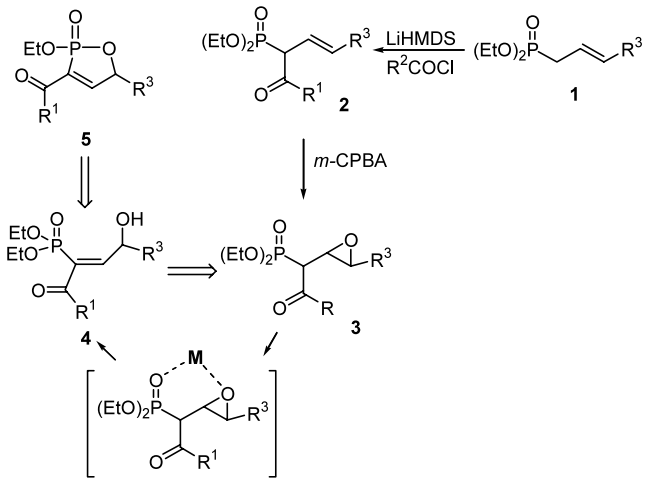
doi:10.1016/S0040-4039(03)01395-9

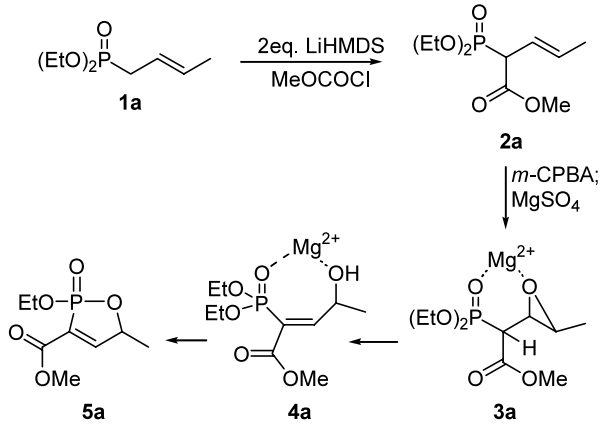


Scheme 2.

From these observations, we envisioned that 3-hydroxy-1-alkenylphosphonate **4** would make the key intermediate for the preparation of oxaphospholene **5** bearing various electron-withdrawing groups at the α-position (Scheme 2). **4** Could be obtained from **3** through stereoselective opening of the epoxide ring. The epoxide **3** would be readily obtained through epoxidation reaction of acylallylic phosphonate **2**. Also, acylallylic phosphonates **2** can be obtained from the reaction of the anion of allylphosphonate, **1** with chloro alkylformate or acid chloride in good yield. Stereoselectivity in the epoxidation of **2**[12] would not affect the formation of the desired olefin stereochemistry of **4** as the geometry the phosphonate in the ring-opening of epoxide, **3** would control the stereochemical outcome.[13] Formation of the desired (*Z*)-isomer **4** would be crucial for the successful construction of the oxaphospholene since the other isomer could not form the oxaphospholene ring and will form lactone ring instead when R^1 is an alkoxy group.[14] A selective chelation of a Lewis acid with the phosphonate oxygen atom and the oxygen atom of the epoxide during the epoxide opening reaction was anticipated[15] for the formation of the desired isomeric olefin **4** as the major product.

When allylic phosphonate **2a** was treated with *m*-CPBA, only the oxaphospholene, **5a** was obtained in 25% yield instead of the expected epoxide **3a** (Scheme 3).

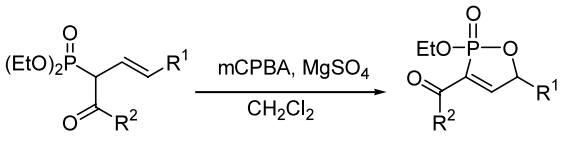
It was also found out that neither **5a** nor **3a** could be isolated unless $MgSO_4$ was used as the drying agent during the workup process and no major product could be isolated without the presence of $MgSO_4$. Based on this observation, it was presumed that the epoxide **3a** was not stable enough to be isolable and chelation of two oxygen atoms of the epoxide ring and phosphonate by Mg^{2+} directly transformed **3a** into **5a** presumably via stereoselective opening of the epoxide of **3a** into the (Z)-allylic alcohol **4a** followed by transesterification.



Scheme 3.

To further promote the formation of the oxaphospholene to a practical level during the epoxidation reaction of **2a**, various Lewis acids were added to the epoxidation reaction. Most Lewis acids failed to promote the formation of the oxaphospholene except $MgSO_4$. The yield of oxaphospholene **5a** improved dramatically with the addition of one equivalent of $MgSO_4$. Several examples of the transformation were summarized in Table 1. The reaction worked equally well with esters (**5a**–**e**, **5h**), and carbonyl compounds (**5f**, **5g**, **5i**).[16] In all cases, diastereomeric oxaphospholenes were obtained without any sign of selectivity regardless of substitution patterns. The stereochemistry and ratio of two diastereoisomers were determined based on the ^1H NMR and NOE analysis of the two isomers of **5g** that were isolated separately.

Table 1.



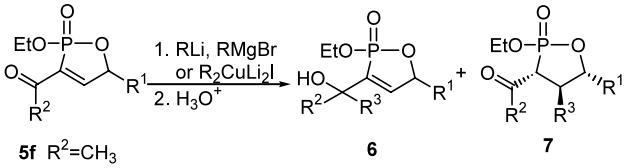
product	R^1	R^2	*cis*:*trans* ratio[a]	yield(%)[b]
5a	Me	OMe	50:50	75
5b	Me	OEt	38:62	78
5c	Me	O^{n}Bu	34:66	80
5d	Me	O^{i}Bu	37:63	70
5e	Me	OBz	38:62	65
5f	Me	Me	48:52	85
5g	Me	^{i}Pr	46:54[c]	85
5h	Et	OMe	45:55[d]	70
5i	Et	Me	45:55	80

[a] The ratio was determined by ^1H NMR and the stereochemistry was determined through NOE analysis. [b] combined yield for *cis*/*trans*-isomers. [c] ratio of the isolated isomers. [d] The ratio was determined by ^{31}P NMR analysis.

With the successful preparation of oxaphospholene system, we turned our attention to the reactivity of the synthesized oxaphospholenes toward nucleophilic reagents. The *cis*-isomer of **5f**, *cis*-isomer of **5g**, and *trans*-isomer of **5g** were treated with organometallic reagents and the result is summarized in Table 2. With alkyl lithiums (entries 1 and 2) or Grignard reagents (entries 3 and 4), both the 1,2- and 1,4-addition products were observed. On the other hand, cuprate addition reaction produced exclusively the 1,4-addition products, the α,β,γ-trisubstituted oxaphospholanes, (entries 5–8) in good yield with complete stereoselectivity.[17]

The relative stereochemistry of the oxaphospholanes, **7e** and **7f** was determined unambiguously by the NOE experiment (Scheme 4). The methyl groups on the oxaphospholane ring showed strong NOE with all the adjacent protons and no NOE with each other.

Table 2.

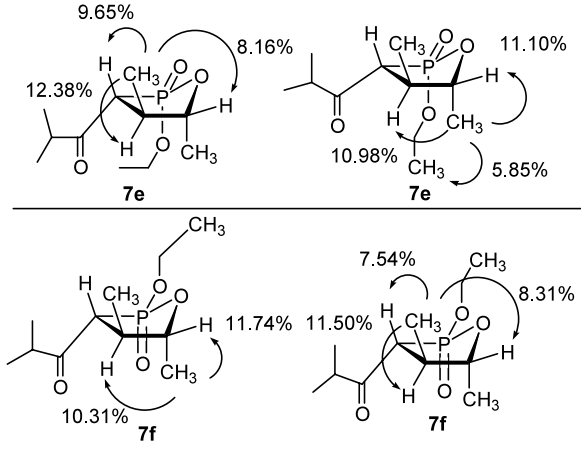


5f R^2=CH_3
5g R^2=^{i}Pr

6 **7**

entry	starting material	organometallic reagents	products (ratio)[a]	yield(%)
1	**5f**[c]	CH_3Li	**6a:7a** (50:50)	85
2	**5f**[c]	nBuLi	**6b:7b**(14: 86)	80
3	**5f**[c]	CH_3MgBr	**6a:7a**(47:53)	86
4	**5f**[c]	MgBr	**6c:7c**(30:70)	74
5	**5f**[c]	$(CH_3)_2CuLi$	only **7a**	80
6	**5f**[c]	$(nBu)_2CuLi$	only **7b**	92
7	**5g**[c]	$(CH_3)_2CuLi$	only **7e**	83
8	**5g**[d]	$(CH_3)_2CuLi$	only **7f**	80

[a] The ratio was determined by ^{1}H NMR analysis.
[b] Total yield of **6** and **7** after chromatography.
[c] *cis*-isomer. [d] *trans*-isomer.



Scheme 4. NOE result of **7e** and **7f**.

Apparently, the stereoselectivity was controlled by the stereochemistry of the existing methyl group rather than the stereochemistry of the phosphorus center as the dialkyl cuprate was added to the unsaturated system from the opposite side of R^1 and the resulting enolate was again quenched from the opposite side of R^3 to produce all *trans* arrangements of alkyl and carbonyl groups around the ring.

In summary, a facile one step synthesis of oxaphospholenes with extra electron-withdrawing groups at the α-position was developed by a simple treatment of acylallyl phosphonates with *m*-CPBA in the presence of one equivalent of $MgSO_4$. Furthermore, the functionalization of the oxaphospholenes was successfully carried out with high stereoselectivity, which will be applicable to a divergent synthesis of oxaphospholanes with various substitution patterns.

Acknowledgements

We thank Dr. Dong Young Oh for guidance and helpful discussion during the project.

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16. **Representative experimental procedure**: *m*CPBA (2 mmol, 0.334 g) and $MgSO_4$ (1 mmol, 0.12 g) were added to a solution of the phosphonate (1 mmol) in CH_2Cl_2 (5 ml). After the reaction mixture was stirred for 12 h, the reaction was quenched by addition of sodium bicarbonate (2 ml, 5 M aqueous solution). The resulting mixture was extracted with diethyl ether (20 ml×3). The combined organic extract was washed with water (3 ml×2), dried over magnesium sulfate and was concentrated. The residue was purified by flash chromatography using ethylacetate as the eluent to afford the oxaphospholene (65–85%) as a colorless oil.
17. **Spectroscopic data of selected products**: **5g** (*trans*) ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.15$ (d, $J=6.0$ Hz, 3H), 1.17 (d, $J=6.0$ Hz, 3H), 1.33 (t, $J=7.1$ Hz, 3H), 1.52 (d, $J=6.9$ Hz, 3H), 3.08 (m, 1H), 4.20–4.28 (m, 2H), 4.98–5.02 (m, 1H), 7.53 (dd, $J=1.6$ Hz, 41.7 Hz, 1H). NOE: 1.51–1.53 (4.98–5.02, 11.36%; 7.47–7.57, 4.77%), ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=16.2$, 18.3 (d, $J=6.5$ Hz), 20.4 (d, $J=2.3$ Hz), 38.3 (d, $J=4.7$ Hz), 63.7 (d, $J=6.3$ Hz), 75.8 (d, $J=6.6$ Hz), 131.2 (d, $J=153.9$ Hz), 156.8 (d, $J=25.6$ Hz), 199.0 (d, $J=16.0$ Hz). HRMS: m/z (M^+) for $C_{10}H_{17}O_4P$, calcd 232.0864, found 232.0867; **5g** (*cis*) ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.15$ (d, $J=5.6$ Hz, 3H), 1.17 (d, $J=5.6$ Hz, 3H), 1.34 (t, $J=7.1$ Hz, 3H), 1.47 (d, $J=6.9$ Hz, 3H), 3.07 (m, 1H), 4.23–4.31 (m, 2H), 5.05–5.09 (m, 1H), 7.51 (dd, $J=1.7$ Hz, 41.8 Hz, 1H). NOE: 1.46–1.47 (4.25–4.29, 4.07%; 5.05–5.10, 10.24%; 7.45–7.46, 3.50%) ^{13}C NMR (100 MHz, $CDCl_3$) $\delta=16.4$ (d, $J=5.8$ Hz), 18.4 (d, $J=6.4$ Hz), 20.1, 38.3 (d, $J=4.7$ Hz), 64.0 (d, $J=8.7$ Hz), 131.6 (d, $J=153.2$ Hz), 156.8 (d, $J=23.8$ Hz), 199.1 (d, $J=12.9$ Hz). HRMS: m/z (M^+) for $C_{10}H_{17}O_4P$, calcd 232.0864, found 232.0867; **7e** ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.98$ (d, $J=6.5$ Hz, 3H), 1.13 (d, $J=4.9$ Hz, 3H), 1.15 (d, $J=4.9$ Hz, 3H), 1.35 (t, $J=7.1$ Hz, 3H), 1.41 (d, $J=6.1$ Hz, 3H) 2.72–2.77 (m, 1H), 3.13 (dd, $J=6.0$ Hz, 23.2 Hz, 1H), 3.84–3.89 (m, 1H), 4.16–4.22 (m, 3H). NOE: 1.41 (2.72–2.77, 10.98%; 3.84–3.90, 11.10%; 4.18, 5.85%), 0.98 (2.70–2.77, 12.38%; 3.09–3.17, 9.65%; 3.84–3.88, 8.16%). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=16.2$ (d, $J=14.7$ Hz), 16.5 (d, $J=5.8$ Hz), 17.3, 18.5, 19.1 (d, $J=10.5$ Hz), 41.9, 53.9 (d, $J=107.1$ Hz), 62.8 (d, $J=6.9$ Hz), 79.7 (d, $J=6.1$ Hz), 205.5; **7f** ^{1}H NMR (400 MHz, $CDCl_3$) $\delta=0.95$ (d, $J=6.5$ Hz, 3H), 1.11 (d, $J=5.1$ Hz, 3H), 1.13 (d, $J=5.1$ Hz, 3H), 1.23 (t, $J=7.1$ Hz, 3H), 1.37 (d, $J=6.1$ Hz, 3H) 2.62–2.66 (m, 1H), 2.80–2.83 (m, 1H), 3.29 (dd, $J=11.8$ Hz, 25.1 Hz, 1H), 3.99–4.09 (m, 3H). NOE: 0.94–0.96 (2.62–2.66, 11.50%; 3.24–3.33, 7.54%; 4.03, 8.31%), 1.35–1.37 (2.63–2.64, 10.34%, 4.01–4.07, 11.74%) ^{13}C NMR (100 MHz, $CDCl_3$) $\delta=16.0$ (d, $J=15.0$ Hz), 16.3 (d, $J=5.7$ Hz), 17.0, 18.7, 19.4 (d, $J=8.0$ Hz), 41.8, 54.4 (d, $J=104.6$ Hz), 63.5 (d, $J=7.3$ Hz), 80.3 (d, $J=5.5$ Hz), 205.8.