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Tetrahedron Letters 44 (2003) 7933–7935

TETRAHEDRON LETTERS

A novel procedure for conversion of epoxides to α-hydroxyphosphonates with a trialkylphosphite mediated by $LiClO_4$

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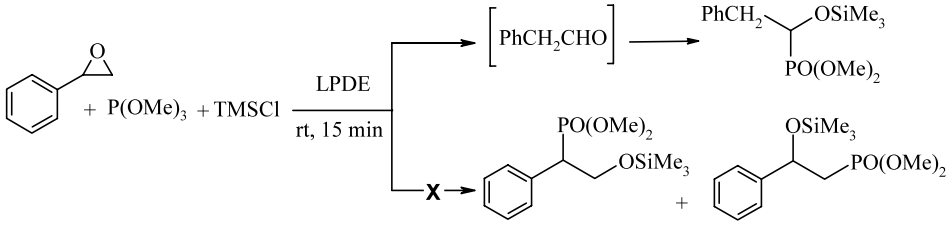
Received 19 July 2003; revised 21 August 2003; accepted 1 September 2003

Abstract—A new method has been developed for the direct conversion of epoxides to α-hydroxyphosphonates by the reaction of a trialkylphosphite with the epoxide in 5 M lithium perchlorate in diethyl ether (LPDE). The reaction is highly regioselective and efficient with excellent yields under mild and neutral conditions.

Phosphonic acids and their phosphonate derivatives are of great interest in synthetic organic chemistry due to their biological activities.[1] They are employed in synthetic operations leading to carbon–carbon bond formation[2] and as transition state analogues in production of antibody catalysts for a wide variety of reactions.[3] α-Hydroxyphosphonates, especially enantiomerically pure α-hydroxyphosphonates,[4] have been used for the preparation of α-substituted phosphonates such as α-halophosphonates, and are important intermediates in organic synthesis.[5,6] They have been used for the preparation of α-ketophosphonates,[7] 1,2-diketones from acid chlorides, α-aminophosphonates, and are widely used for pharmaceutical applications.[8] A number of synthetic methods for α-hydroxyphosphonates have been reported.[3,4,8] Although these methods are useful, to the best of our knowledge, there is no report in the literature on the conversion of epoxides to α-hydroxyphosphonates. Epoxides are attractive starting materials in organic synthesis, due to their high reactivity[9] and easy access. There are many reports on Lewis acid catalyzed ring-opening reactions of epoxides with carbon,[10] nitrogen,[11] phosphite,[12] oxygen[13] and other nucleophiles[14] in the literature.

Recently, concentrated solutions of lithium perchlorate in diethyl ether (LPDE) have gained importance as versatile reaction media for various organic transformations at room temperature, which are otherwise difficult to carry out under mild conditions. Several organic reactions are faster in this medium compared with other solvents. Moreover, high chemo-, regio-, and stereoselectivities have been observed in this medium. The mild Lewis acidity of the lithium ion in donor solvents such as diethyl ether is responsible for these selectivities.[15] In continuation of our interest in the application of etheral solutions of lithium perchlorate,[16] as well as in the chemistry of phosphonate derivatives,[17] herein we



Scheme 1.

Keywords: epoxide; α-hydroxyphosphonates; trialkylphosphite; lithium perchlorate.
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0040-4039/$ - see front matter © 2003 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2003.09.002

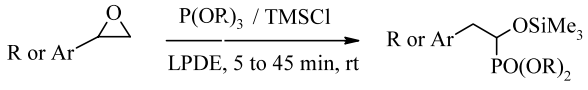
describe a simple and new protocol for the direct conversion of epoxides to α-hydroxyphosphonates by reaction with trialkylphosphites in a 5 M solution of LPDE under neutral conditions. It has been well established that epoxides rearrange to produce carbonyl compounds[15] using 5 M LPDE under neutral reaction conditions. Thus, when an epoxide was reacted with an equimolar amount of trimethylsilyl chloride (TMSCl) and a trialkylphosphite in 5 M LPDE, the α-hydroxy phosphonate was produced as the sole product. In the presence of $LiClO_4$/TMSCl, the epoxide would appear to rearrange faster than nucleophilic addition to the epoxide (Scheme 1).

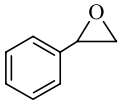
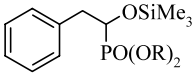
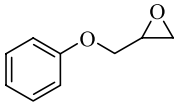
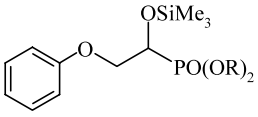
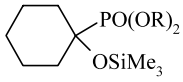
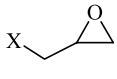
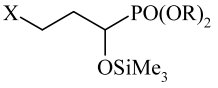
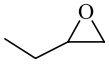
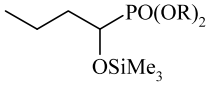
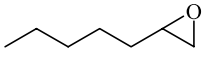
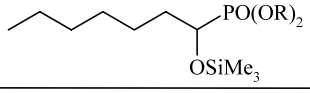
In order to optimize the reaction conditions, we investigated the stoichiometry of the reaction. α-Hydroxyphosphonate formation was observed almost quantitatively by stirring the epoxide (1 equiv.), trimethylsilyl chloride (1.1 equiv.) and trialkylphosphite (1.2 equiv.) at room temperature for 15–45 min. The yield of the α-hydroxyphosphonate was reduced drastically and the formation of undesired products was observed in the absence of trimethylsilyl chloride. To show the generality and scope of the LPDE promoted α-hydroxyphosphonate synthesis, the reaction was examined with various structurally diverse epoxides and trialkylphosphite. These results are summarized in Table 1.[18,19] The data in Table 1 clearly shows that different epoxides were successfully converted into α-hydroxyphosphonates in high yields at room temperature with high regioselectivity and short reaction times. The reactions were clean and the products were obtained without the formation of any side-products, such as the direct nucleophilic addition products that are normally observed under the influence of Lewis acids.

In conclusion, we present a straightforward LPDE mediated methodology for the conversion of epoxides to α-hydroxyphosphonates by reaction with a trialkylphosphite using inexpensive and readily available reagents under very mild conditions. The present procedure provides a novel, efficient and simple methodology for the preparation of α-hydroxyphosphonates. Furthermore $LiClO_4$ is not expensive and is stable to moisture so that it can be recovered and reused after activation.

Further investigations to broaden the scope, synthetic applications and mechanistic aspects are now underway in our laboratories.

Table 1. LDPE-promoted synthesis of α-hydroxyphosphonates from epoxides



Entry	Epoxide	Phosphite	Product		Yield (%)[a,b]	
1		$P(OMe)_3$ $P(OEt)_3$			R = Me R = Et	92[17] 88[17]
2		$P(OMe)_3$ $P(OEt)_3$			R = Me R = Et	85[14] 84[14]
3		$P(OMe)_3$ $P(OEt)_3$			R = Me R = Et	72[17] 70[17]
4		$P(OMe)_3$ $P(OEt)_3$		X = Br	R = Me R = Et	78[5b] 80[5b]
		$P(OMe)_3$ $P(OEt)_3$		X = Cl	R = Me R = Et	76[1] 74[1]
5		$P(OMe)_3$ $P(OEt)_3$			R = Me R = Et	82[5] 84[5a]
6		$P(OMe)_3$ $P(OEt)_3$			R = Me R = Et	80[5b] 80[5b]

[a]Isolated yields. [b]Literature references for each compound.

Caution: Although we did not have any accident while using $LiClO_4$, it is advisable to dry lithium perchlorate in a fume hood using a suitable lab-shield.

Acknowledgements

We are grateful to the Sharif University of Technology Research Council for financial support of this research. We also thank 'Volkswagen-Stiftung, Federal Republic of Germany' for financial support towards the purchase of chemicals.

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18. **Typical procedure**: A mixture of the epoxide (2 mmol), trimethylphosphite or triethylphosphite (2.4 mmol), TMSCl (2.2 mmol) and 3 mL of 5 M $LiClO_4$ in diethyl ether were placed in a 50 mL flask under argon and stirred at room temperature for 15–45 min. After the reaction was complete, CH_2Cl_2 (15 mL) was added and the resulting precipitated $LiClO_4$ was separated by filtration. The organic layer was washed with water (2×15 mL), dried over $MgSO_4$, and the solvent was removed. Almost pure product was obtained, further purification was carried out by column chromatography on basic alumina eluting with ethyl acetate/hexane, if needed. All compounds were characterized on the basis of spectroscopic data (IR, NMR, MS) and by comparison with those reported in the literature.
19. *Dimethyl 1-(trimethylsiloxy)-2-phenylethanephosphonate*: Oil; IR (CH_2Cl_2): 1490, 1462, 1258, 1041, cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 0.25 (s, 9H), 2.94–2.99 (m, 1H), 3.10–3.27 (m, 1H), 3.72–3.84 (m, 6H), 4.10–4.16 (m, 1H), 7.24–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 53.1 (d, $J_{cp}=6.9$ Hz), 54.2 (d, $J_{cp}=6.8$ Hz), 59.1 (d, $J_{cp}=162.2$ Hz), 128.6, 129.3, 132.1, 134.2.
Dimethyl 1-(trimethylsiloxy)-1-cyclohexylphosphonate: Oil; IR (CH_2Cl_2): 1661, 1253, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 0.23 (s, 9H), 1.12–1.78 (m, 10H), 3.67 (d, 6H, $J=10.4$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.4 (d, $J_{cp}=10.2$ Hz), 26.9, 32.8 (d, $J_{cp}=2.3$ Hz), 53.2 (d, $J_{cp}=7.2$ Hz), 71.1 (d, $J_{cp}=161.2$ Hz).