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A ONE-POT GENERATION OF α-CHLORO-α-LITHIO ALKANEPHOSPHONATES. A NEW PREPARATIVE ROUTE TO 1,2- EPOXYALKANEPHOSPHONATES.

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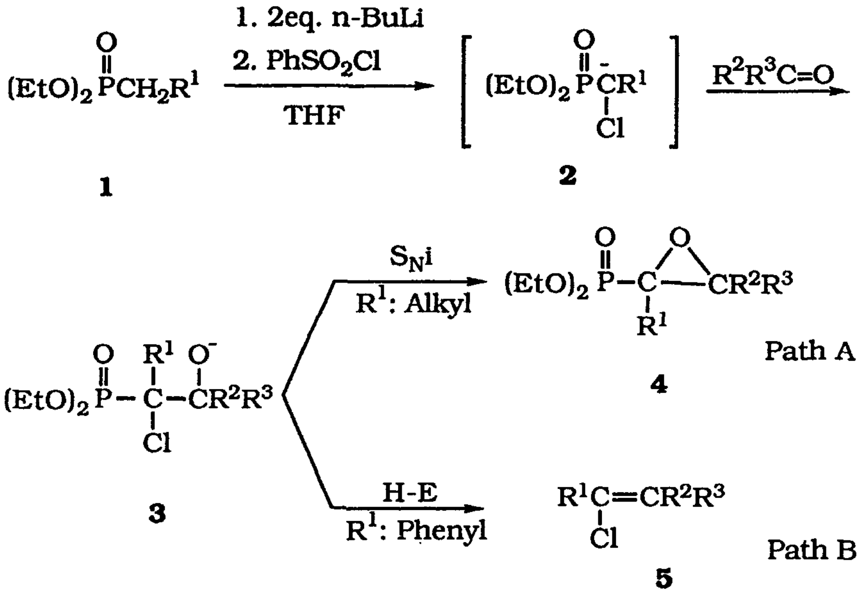
ABSTRACT: Reaction of lithio anion derived from diethyl alkanephosphonate in the presence of 2 eq. of n-BuLi with benzenesulfonyl chloride gives directly the corresponding diethyl-1-chloro-1-lithioalkanephosphonate, which reacts *in situ* with carbonyl compounds followed by intramolecular substitution reaction to give 1,2-epoxyalkanephosphonates.

The numerous synthetic routes to 1,2-epoxyalkane phosphonates have been reported.[1] Previous studies on 1,2-epoxyalkanephosphonates have been concerned with either their potential as synthetic intermediates[2] or the mechanism of the reaction of dialkylphosphonates with α-halo ketones.[3] Owing to the discovery of Fosfomycin ((1R,2S)-(-)-(1,2-

Scheme



Epoxypropyl)phosphonic acid) isolated from fermentation broth of streptomyces fradiae, 1,2-epoxyalkanephosphonates have biological significance.[4]

Here we wish to report a one-step synthesis of various 1,2-epoxyalkanephosphonates. Our new direct route uses the benzenesulfonyl chloride as a chlorenium ion source[5] and the α-chloro-α-phosphonyl carbanions as a key intermediates.

A general reaction procedure is as follows: To a stirred solution of diethyl alkanephosphonate (1 mmol) in dry THF (3 ml) is added n-butyllithium (2.2 mmol, 1.6 M in hexane) at

-78 °C under nitrogen atmosphere. After being stirred for 30 min at same temperature, benzenesulfonyl chloride (1 mmol) and carbonyl compound (1 mmol) are added successively and the mixture is allowed to warm with stirring to room temperature. Stirring is continued at room temperature for 15 h, sat. NH_4Cl solution (10 ml) is added, and the mixture is extracted with ether (3 x 20 ml). The combined organic layer is dried with $MgSO_4$, the solvent is removed under reduced pressure and the product is purified by column chromatography on silica gel (ethylacetate/hexane = 1/1).

As shown in Scheme, carbanionic species **2** are generated through the chlorination of α-lithioalkanephosphonates with benzenesulfonyl chloride in the presence of two equivalents of n-BuLi. The chlorination proceeds rapidly at -78 °C for 1 min, which is easily monitored by TLC. The addition reaction of **2** to carbonyl compound is followed by intramolecular substitution reaction to give 1,2-epoxyalkanephosphonate **4** . The results are summarized in table.

According to the substituent $\mathbf{R^1}$, the reaction path is different as shown in Scheme. In the case of phosphonates **1** possessing an α–alkyl group, desired 1,2-epoxyalkane phosphonates were obtained via the intramolecular substitution reaction of β-oxyanion of phosphonates **3** (path A). However, it is noteworthy that when the anion **2** derived

Table. Preparation of 1,2-epoxyalkanephosphonates(4) and vinyl chlorides(5).

Run	R^1	R^2	R^3	Product	Yield(%)[a]
1[b]	Me	Ph	H	4	58
2	Me	$4\text{-}ClC_6H_4$	H	4	80
3	Me	PhCH=CH	H	4	45
4	Me	$CH_3(CH_2)_4CH_2$	H	4	45
5	Me	Ph	Ph	4	70
6	Me	Ph	Me	4	70
7	Et	$4\text{-}MeOC_6H_4$	H	4	67
8	Et	Ph	Ph	4	57
9	$PhCH_2$	Ph	Ph	4	30
10	Ph	Ph	H	5	55
11	Ph	$4\text{-}ClC_6H_4$	H	5	35

[a] Isolated yield, [b] Ref. 1a

from $\mathbf{R^1}$ = Ph was treated in a same manner with carbonyl compound, no 1,2-epoxyalkanephosphonates were obtained. Instead Horner-Emmons reaction proceeded and the corresponding vinyl chlorides **5** were formed as the sole product within 1 h at room temperature (path B). This result is in accord with the fact that efficient Wittig elimination can be brought about if the intermediate is activated at the α-position to the phosphorus atom by an electron-stabilizing group.[6]

In conclusion, we have synthesized 1,2-epoxy alkanephophonates from diethyl alkanephosphonates using benzenesulfonyl chloride as a chlorenium ion source.

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7. All compounds gave satisfactory spectral data.

Run **2** ; ^{1}H NMR ($CDCl_3$) δ 1.23-1.40 (6H, m),1.76 (3H, s), 4.00-4.73 (4H, m), 5.05-5.30 (1H, m), 7.27 (4H, m); IR (film) 1230 (P=O) cm^{-1}; Mass (70 eV) m/z (%) 304 (M$^+$,1.7),77 (100.0).

Run **3** ; ^{1}H NMR ($CDCl_3$) δ 1.05-1.70 (9H, m),3.40 (1H, t), 3.75-4.30 (4H, m), 6.40-7.40 (7H, m); IR (film) 1254 (P=O) cm^{-1}; Mass (70 eV) m/z (%) 296 (M$^+$,3.3),115 (100.0).

Run **4** ; ^{1}H NMR ($CDCl_3$) δ 0.91-1.82 (22H, m), 4.17 (5H, m); IR (film) 1246 (P=O) cm^{-1}.

Run **5** ; ^{1}H NMR ($CDCl_3$) δ 1.00-1.61 (9H, m), 3.34-4.33 (6H, m), 7.17-7.80 (10H, m); IR (film) 1254 (P=O) cm^{-1}.

Run **6** ; ^{1}H NMR ($CDCl_3$) δ 0.97-1.77 (9H, m), 2.04 (3H, d), 4.00-4.60 (4H, m), 7.22 (5H, s); IR (film) 1230 (P=O) cm^{-1}; Mass (70eV) m/z (%) 284 (M$^+$,0.7), 121 (100.0).

Run **7** ; ^{1}H NMR ($CDCl_3$) δ 0.88-2.30 (11H, m), 3.93 (3H, s), 4.04-4.63 (4H, m), 4.87-5.23 (1H, m), 6.83-7.67 (4H, m); IR (film) 1244 (P=O) cm^{-1}; Mass (70 eV) m/z (%) 314 (M$^+$,2.9),121 (100.0).

Run 8 ; ^{1}H NMR ($CDCl_3$) δ 0.90-2.62 (11H, m), 3.47-4.50 (4H, m), 7.20-7.83 (10H, m); IR (film) 1240 (P=O) cm^{-1}.

Run 9 ; ^{1}H NMR ($CDCl_3$) δ 1.21-1.43 (6H, m), 4.02-4.70 (4H, m), 5.02-5.31 (1H, m), 7.30 (10H, m); IR (film) 1240 (P=O) cm^{-1}.

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