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New and Efficient Synthesis of (*E*)-4-Diethoxyphosphonyl-2-methyl-2-butenal and of Ethyl (*E*)-4-Diethoxyphosphonyl-2-methyl-2-butenoate, Important Building Blocks in Retinoid Chemistry.

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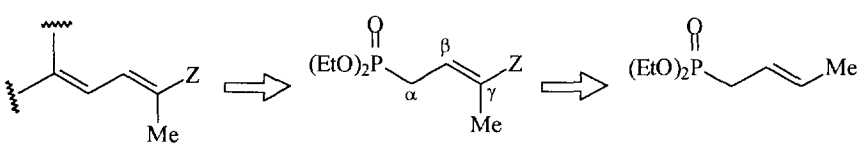
Abstract : Lithiated anion of diethyl α-trimethylsilyl-crotylphosphonate, *in-situ* generated from readily available diethyl crotylphosphonate, reacts smoothly with ethyl formate or ethyl chloroformate to give the title compounds **1** or **2**, respectively, in high isolated yield.

The direct formation of a functionalized diene by three-carbon chain elongation of a carbonyl compound is an important reaction in retinoid chemistry[1]. Phosphonoaldehyde **1** (in a protected form) or phosphonoester **2** appear to be very useful reagents, for this transformation under the Horner-Wadsworth-Emmons (HWE) conditions. However, although their unsubstituted or β-methylated analogues have been often used as HWE reagents in polyene syntheses[2,3], γ-methylated phosphonates **1** or **2** are rarely cited in the literature. Dioxolane derivative of **1**, obtained by phosphonylation of the corresponding ω-bromodioxolane, was recently used by Duhamel *et al.* in polyunsaturated aldehyde synthesis[4]. On the other hand, phosphonoester **2** was prepared in three steps from ethyl 2-methyl-3-butenoate and its use as C_5 building block in carotenoid synthesis was claimed[5]. Pursuing our work on use of diethoxyphosphonyl allylic anions as synthons[6], we decided to study a direct synthesis of **1** and **2** from the readily available diethyl crotylphosphonate **3**[7] (Scheme 1).

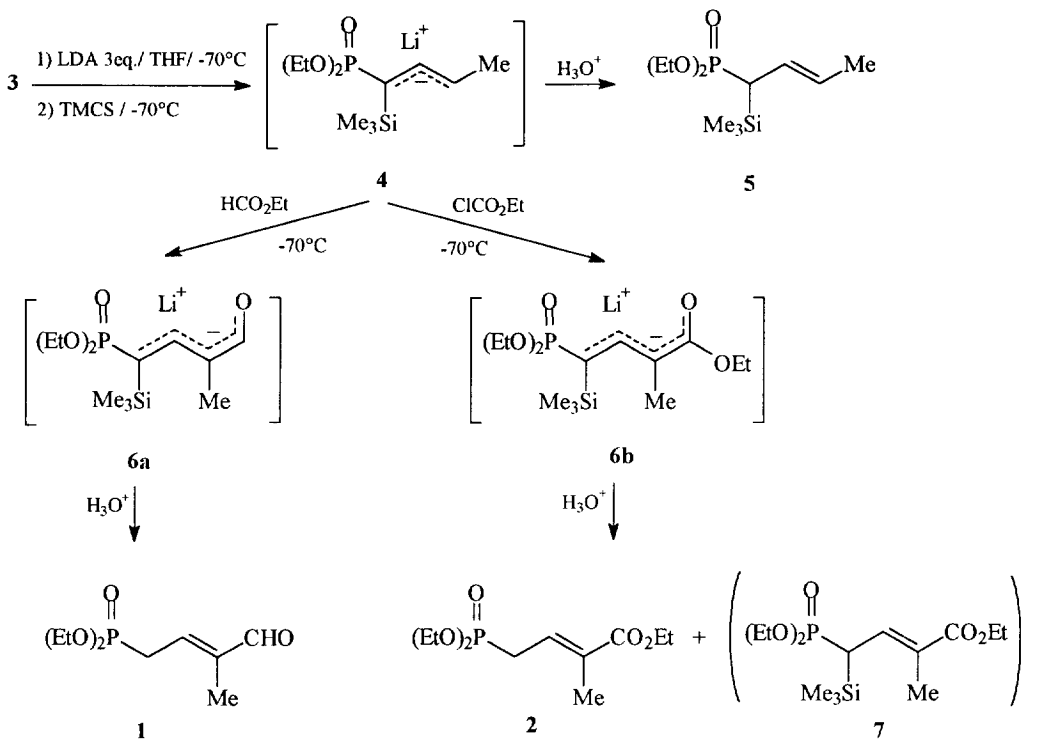


1 : Z = CHO
2 : Z = CO_2Et

3

Scheme 1

Whereas strict γ-regioselectivity was observed in trimethylsilylation of the lithiated anion of diethyl allylphosphonate[8], diethyl 2-pentenylphosphonate was α-silylated under the same conditions[8c]. We expected similar α-regioselectivity of silylation for the γ-methylated phosphonate **3**. Actually, treating phosphonate **3** with a three-fold excess of lithium diisopropylamide (LDA) in THF at -70°C, followed by addition of trimethylchlorosilane (TMCS) at the same temperature, gave quantitatively anion **4** [^{31}P NMR (THF), δ = 48.1 ppm], which could be hydrolyzed into α-silylated phosphonate **5**[9] (Scheme 2). Moreover, anion **4** reacted with ethyl formate at -70°C to give oxanion **6a** [^{31}P NMR (THF), δ = 43.5 ppm], which led to phosphonoaldehyde **1**[10], as the sole product, isolated in 78% yield, after acidic hydrolysis. The (*E*)-configuration of **1** was unambiguously established[11]. Attemps made in order to isolate intermediate α-silylated phosphonoaldehyde were unsuccessful, obviously owing to the fast desilylation, which occured during hydrolysis[12].



Scheme 2

The γ-regioselective reactivity of anion **4** was confirmed in its reaction with ethyl chloroformate : anion **6b** [^{31}P NMR (THF), δ = 41.1 ppm] was quantitatively formed at -70°C, in few minutes. Subsequent acidic hydrolysis gave a crude mixture composed of phosphonoester **2** and of α-trimethylsilylated phosphonoester **7**[13]. All efforts made in order to isolate **7** failed : upon fractional distillation or chromatographic separation, **7** underwent fast desilylation, giving **2**. Consequently, purification of the crude mixture by distillation or chromatography furnished phosphonoester **2**[14], in very good yield, as the sole product, isolated in its (*E*)-configuration[15].

In brief, the straight advantage of transient introduction of the bulky trimethylsilyl group lies in the γ-selective orientation of the nucleophilic reactivity of anion **4** towards the two electrophilic reagents used in this work. Conversely, lithiated derivative of starting phosphonate **3** showed exclusive α-regioselectivity in its reaction with ethyl formate[16] or ethyl chloroformate[17].

In conclusion, we propose, in this letter, a new, expeditive and efficient synthesis of two attractive phosphonates **1** and **2**, useful building blocks in retinoid chemistry.

References and Notes

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7. **3** was prepared from triethyl phosphite and (*E*)-crotyl bromide, by Arbuzov reaction, in 88% isolated yield [$bp_{2.5}$ = 82-83°C; ^{31}P NMR ($CDCl_3$), δ = 26.8 ppm].

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9. Physical and analytical data of **5** : $bp_{0.6}$ = 93°C (87% yield). ^{31}P NMR ($CDCl_3$), δ = 28.4 ppm. ^{1}H NMR ($CDCl_3$, 200 MHz) [δ_{ppm}, (J_{Hz})] : 0.1, s, 9H ($C\underline{H}_3Si$); 1.3, t (7), 6H ($C\underline{H}_3CH_2O$); 1.7, m, 3H ($C\underline{H}_3C\gamma$=); 2.1, dd (23.0 & 9.5), 1H (<u>H</u>CP); 4.1, m, 4H ($CH_3C\underline{H}_2O$); 5.4, m, 2H (<u>H</u>Cβ=Cγ<u>H</u>).

$^{13}C\{^{1}H\}$ NMR ($CDCl_3$) [δ_{ppm}, (JHz)] : -2.5, s, ($\underline{C}H_3Si$); 15.8, d (6.4), ($\underline{C}H_3CH_2O$); 17.7, d (2.2), ($\underline{C}H_3C\gamma$=); 33.0, d (127), ($\underline{C}HP$); 60.0 & 61.0, 2xd (6.6 & 6.9), ($CH_3\underline{C}H2O$); 121.8, d (10.6), (=$\underline{C}\beta$); 126.4, d (15.5), (=$\underline{C}\gamma$).

10. Experimental procedure, physical and analytical data of **1** : A solution of **3** (1.92g, 0.01 mol) in THF (10mL) was added under argon at -70°C to a solution of LDA (0.03 mol) in THF (30mL). After 10 min, a solution of TMCS (1.2g, 0.01 mol) in THF (5mL) was added at -70°C and stirring continued for about 5 min, until anion **4** was quantitatively formed (as proved by ^{31}P NMR). Then a solution of ethyl formate (1.5g, 0.02 mol) in THF (10 mL) was added at -70°C and stirring continued for 60 min. The mixture was quenched at 0°C with water (30 mL). Aqueous layer was washed with ether (2x10 mL) and acidified (pH~1) with 4N HCl. After usual work-up, the crude product (85% yield) was purified by bulb to bulb distillation ($bp_{0.2}$ = 98°C) to give pure **1** (1.7g, 78% yield). ^{31}P NMR ($CDCl_3$), δ = 22.2 ppm. ^{1}H NMR ($CDCl_3$, 200 MHz) [δ_{ppm}, (JHz)] :1.3, t (7), 6H ($C\underline{H}_3CH_2O$); 1.7, d (3.5), 3H ($C\underline{H}_3C\gamma$=); 2.8, dd (23.5 & 8), 2H ($C\underline{H}_2P$); 4.0, qui (7), 4H ($CH_3C\underline{H}_2O$); 6.5, m, 1H ($\underline{H}C\beta$=); 9.4, s, 1H ($C\underline{H}O$). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$) [δ_{ppm}, (JHz)] : 9.4, d (6), ($\underline{C}H_3C\gamma$=); 16.3, d (6), ($\underline{C}H_3CH_2O$); 28.0, d (138.7), ($\underline{C}H_2P$); 62.3, d (6.7), ($CH_3\underline{C}H_2O$); 142.0, d (11.5), ($\underline{C}\gamma$=); 142.5, d (12.5), ($\underline{C}\beta$=); 192.7, d (3.4), ($\underline{C}HO$). MS : 220 (M^+), 191 (M^+-29), 111, 81, 55.

11. A NOE effect of about 19% was observed on the $\underline{H}C\beta$ signal, when $C\underline{H}O$ was irradiated. We gratefully thank Dr. N. Plé, who realized the NOE experiment.

12. Hydrolysis carried out with a mixture of DCl/D_2O led to a substantial incorporation (> 60%, as proved by ^{1}H NMR and MS spectral data) of deuterium atoms in α-position of phosphonoaldehyde **1**.

13. Experimental procedure analogous as that described in ref. 10 was used, except hydrolysis, which was performed at -70°C, with 4N HCl. The crude product was a mixture of **2** and **7**, in a ratio of ~ 60:40 as proved by ^{31}P NMR ($CDCl_3$) : δ = 23.4 and 25.3 ppm, respectively, and by ^{1}H NMR ($CDCl_3$) : in the spectrum of the mixture, significant distinct peaks were clearly assigned to **7**, namely [δ_{ppm}, (JHz)] : 0.15, s, ($C\underline{H}_3Si$); 1.8, d (4), ($C\underline{H}_3C\gamma$=); 2.6, dd (21 & 13), ($C\underline{H}P$)].

14. Bulb to bulb distillation ($bp_{0.1}$ = 110°C) or column chromatography purification (SiO_2, eluent : ether) of the crude mixture gave pure **2** (84% yield). ^{31}P NMR ($CDCl_3$), δ = 23.4 ppm. ^{1}H NMR ($CDCl_3$, 200 MHz) [δ_{ppm}, (JHz)] : 1.3, m, 9H ($C\underline{H}_3CH_2O$); 1.9, d (4), 3H ($C\underline{H}_3C\gamma$=); 2.7, dd (23.5 & 8), 2H ($C\underline{H}_2P$); 4.1, m, 6H ($CH_3C\underline{H}_2O$); 6.7, m, 1H ($\underline{H}C\beta$=). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$) [δ_{ppm}, (JHz)] : 12.1, d (2.5), ($\underline{C}H_3C\gamma$=); 14.0, s, ($\underline{C}H_3CH_2OC$); 16.0, d (6), ($\underline{C}H_3CH_2OP$); 27.0, d (139), ($\underline{C}H_2P$); 59.8, s, ($CH_3\underline{C}H_2OC$); 61.5, d (6.7), ($CH_3\underline{C}H_2OP$); 129.5, d (11.2), ($\underline{C}\beta$=); 131, d (13.9), ($\underline{C}\gamma$=); 166.3, d (3.5), ($\underline{C}O_2Et$). MS : 264 (M^+), 218 (M-46), 190, 162, 134, 82.

15. In the ^{1}H NMR spectrum of conjugated ester **2**, chemical shift at 6.7 ppm for $\underline{H}C\beta$ is characteristic of a *"cis"*arrangement between the ester moiety and $\underline{H}C\beta$; see for example : a) Kinstle, T.H.; Mandanas, B.Y., *Chem. Commun.* **1968**, 1699-1700. b) Tay, M.K.; About-Jaudet, E.; Collignon, N.; Teulade, M.P.; Savignac, P., *Synth. Commun.* **1988**, *18*, 1349-1362.

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