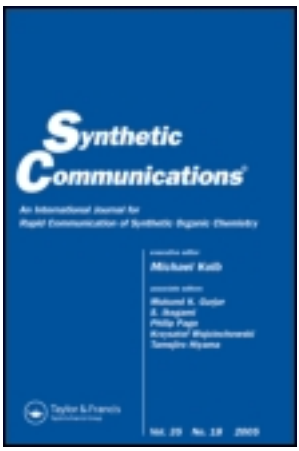


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

tert-Butyl 3-Carboxyethyl-3-phosphonodiethylpropionate. A Novel Reagent for Stobbe-Like Condensations

W. Martin Owton [a] , Peter T. Gallagher [a] & Antonio Juan-Montesinos [a]

[a] Eli Lilly & Co. Ltd., Lilly Research Centre, Erl Wood Manor, Windlesham, Surrey, GU20 6PH, Great Britain

Published online: 23 Sep 2006.

To cite this article: W. Martin Owton , Peter T. Gallagher & Antonio Juan-Montesinos (1993) tert-Butyl 3-Carboxyethyl-3-phosphonodiethylpropionate. A Novel Reagent for Stobbe-Like Condensations, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 23:15, 2119-2125, DOI: 10.1080/00397919308018605

To link to this article: http://dx.doi.org/10.1080/00397919308018605

SYNTHETIC COMMUNICATIONS, 23(15), 2119-2125 (1993)

tert-BUTYL 3-CARBOXYETHYL-3-PHOSPHONODIETHYLPROPIONATE. A NOVEL REAGENT FOR STOBBE-LIKE CONDENSATIONS.

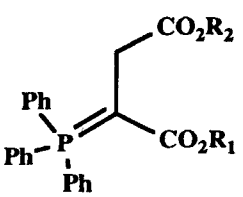
W. Martin Owton*, Peter T. Gallagher and Antonio Juan-Montesinos

Eli Lilly & Co. Ltd., Lilly Research Centre, Erl Wood Manor,

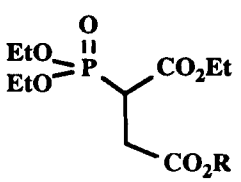
Windlesham, Surrey GU20 6PH, Great Britain.

Abstract: *tert*-Butyl-3-carboxyethyl-3-phosphonodiethylpropionate was prepared and reacted with a range of aldehydes to give, after hydrolysis, itaconic half esters.

The condensation of succinate esters with aldehydes or ketones, known as the Stobbe reaction, gives itaconate half-esters. However the reaction yields are variable and a number of other products can arise[1]. To improve the selectivity and yield of this reaction we sought an activated succinate ester. A number of such reagents are known in the literature, but none met our precise need.



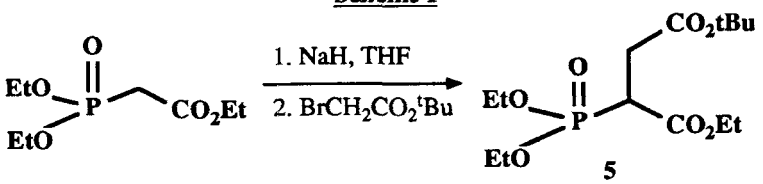
1. R_1= Me R_2= H
2. R_1= Et R_2 = Et
3. R_1= Me R_2= ^{t}Bu



4. R = Et
5. R = ^{t}Bu

The phosphoranes **1**[2], **2**[3], and **3**[4] react with aldehydes, but do so only sluggishly and require multiple equivalents of reagent[5]. The phosphonate **4** reacts with aldehydes in good yields[6], however it is not possible to selectively hydrolyse the products to the half esters we required. We therefore prepared the mixed ^{t}butyl/ethyl phosphonosuccinate **5** according to Scheme I and investigated its reaction with a range of aldehydes.

Scheme I



5

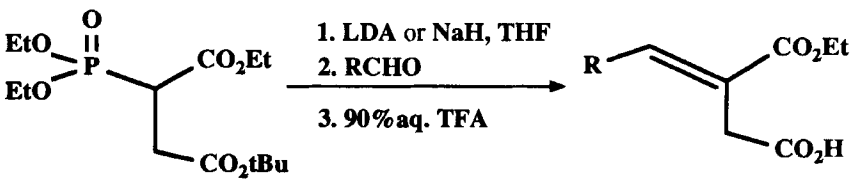
The anion of 5, created with LDA or NaH, undergoes the expected reaction with aldehydes in THF to give ethyl-*t*-butyl itaconates. The crude product esters are unstable to column chromatography on silica gel, therefore the crude products were cleaved with TFA/H_2O(9:1)[7] to give the desired half-esters in good to excellent yield (Table I).

The geometry of the product double bond is predominantly as drawn (Scheme II),with only minor amounts of the other isomer detectable by ^{1}H NMR.The double bond geometry was established by n.O.e experiments on the product mixture derived from reaction of 5 with benzaldehyde. Irradiation of the major olefinic proton (7.78ppm) produced weak enhancements of the allylic methylene (3.42ppm) and the methylene of the ethyl ester (4.22ppm). Irradiation of the allylic methylene (major & minor produced a weak effect on the olefinic proton of the major product and a strong n.O.e. to the signal of the minor product (6.98ppm).

Table I

	R	YIELD (% w.r.t Aldehyde)
6	Ph	95
7	o-MeO-Ph	75
8	p-MeO-Ph	93
9	p-Me-Ph	77
10	p-F-Ph	77
11	m-NO_2-Ph	75
12	1-Naphthaldehyde	83
13	Furfuraldehyde	95
14	Thiophene-2-carboxaldehyde	95
15	Heptanal	80

Scheme II



These results demonstrate that the readily available *tert*-butyl-3-carboxy ethyl-3-phosphonodiethylpropionate offers a high yielding alternative to the classical Stobbe condensation. We feel that this reagent should prove useful in synthetic chemistry.

EXPERIMENTAL:

***tert*-Butyl 3-carboxyethyl-3-phosponodiethylpropionate (5).**

Triethylphosphonoacetate (49.28g,220 mmol) in dry THF (150ml) was added

dropwise with stirring under N_2 at 0^0C over 30 mins to hexane washed sodium hydride (11.075g,50% disp, 231 mmol) in dry THF (300ml). The reaction mixture was stirred and allowed to warm to room temperature overnight. *tert*-Butyl bromoacetate (45g, 231 mmol) was added dropwise at 0^0C over 30 mins and the reaction mixture was stirred and allowed to warm to room temperature. After 24 hours the reaction mixture was concentrated under reduced pressure and partitioned between water and ethyl acetate. The organic phase was collected, washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a pale yellow liquid (74.9g). This crude product was vacuum distilled to give F_1(120-132 ^{0}C, 0.08mm Hg, 16.3g) then F_2 (132 ^{0}C, 0.08mm Hg, 32.48g). Both fractions proved to be required product giving an overall yield of **5** of 48.78g (66% yield).

Typical procedure using LDA: Phosphonate **5** (3.0g, 8.875 mmol) was dissolved in dry THF (20ml) at 0^0C under N_2. LDA solution (1.5N in cyclohexane) (6 ml) was added. The reaction mixture was stirred at 0^0C for 20 mins then benzaldehyde (940 mg, 8.85 mmol) in THF (10ml) was added dropwise. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature overnight. After 18 hours water (5ml) was added and the solvent was removed under reduced pressure. The residue was partitioned between water and CH_2Cl_2. The organic phase was collected, dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure. The resulting oil was dissolved in trifluoroacetic acid/water (9:1) and stirred at room temperature for 90 mins. The solvent was removed under reduced pressure and CCl_4 was added, this to was removed under reduced pressure and the product was evaporated to dryness to give 2.15g dark oil. ^{1}H NMR showed this to be predominantly the required product with minor amounts of the other double bond isomer and deprotected **5**.

Typical procedure using Sodium Hydride: To a suspension of sodium hydride (50% disp, hexane washed) in dry THF (15ml) was added **5** (2.5g, 7.4 mmol) dropwise. The reaction mixture was stirred for 2 hours at 0^0C under N_2. 3-Nitrobenzaldehyde (1.09g, 7.2 mmol) was dissolved in dry THF at 0^0C under N_2. The anion solution was added dropwise with stirring to the aldehyde solution at 0^0C under N_2. The cooling bath was removed and the reaction mixture was stirred and allowed to warm to room temperature overnight. The reaction was worked up and the product hydrolysed as described in the LDA procedure above to give the required product as a yellow solid (1.73g). All final products were characterised by 300MHz ^{1}H NMR, IR and high resolution mass spectrometry.

***tert*-Butyl 3-carboxyethyl-3-phosphonodiethylphosphonate (5)**

^{1}H NMR δ($CDCl_3$) 1.30, 3H(t); 1.34, 6H(t); 1.43, 9H(s); 2.73, 1H(ddd); 2.99, 1H(ddd); 3.40, 1H(ddd); 4.13, 4H(m); 4.23, 2H(m).

IR 2982, 1733,1258,1151 cm^{-1}.

MH^+ calc. 339.1573 obs. 339.1559 deviation -4.05ppm.

(E)-4-Phenyl-3-carboxyethylbut-3-enoic acid (6)

^{1}H NMR δ(DMSO) 1.27 3H(t), 3.43 2H(s), 4.22 2H(q), 7.26-7.52 5H(m), 7.78 1H(s).

IR 1718, 1708 cm^{-1}.

MH^+ calc. 235.0970 obs. 235.0983 deviation +5.3ppm.

(E)-4-(2-Methoxyphenyl)-3-carboxyethylbut-3-enoic acid (7)

^{1}H NMR δ($CDCl_3$) 1.36, 3H(t); 3.52, 2H(s); 3.92, 3H(s); 4.31 ,2H(q); 6.93, 1H(bd); 7.00, 1H(dt); 7.29, 1H(bd); 7.38, 1H(dt); 8.01, 1H(s).

IR 1718, 1715 cm^{-1}.

MH^+ calc. 265.1076 obs. 265.1063 deviation -4.9ppm.

(E)-4-(4-Methoxyphenyl)-3-carboxyethylbut-3-enoic acid (8)

^{1}H NMR δ($CDCl_3$) 1.37, 3H(t); 3.63, 2H(s); 3.86, 3H(s); 4.30, 2H(q); 6.96, 2H(d);

7.37 2H(d), 7.88 1H(s).

IR 1734, 1706 cm^{-1}.

MH^+ calc. 265.1076 obs. 265.1071 deviation -1.97ppm.

(E)-4-(4-Methylphenyl)-3-carboxyethylbut-3-enoic acid (9)

^1H NMR δ($CDCl_3$) 1.35, 3H(t); 2.38, 3H(s); 3.58, 2H(s); 4.31, 2H(q); 7.23, 2H(d); 7.29, 2H(d); 7.90, 1H(s).

IR 1711, 1698 cm^{-1}.

MH^+ calc. 249.1127 obs. 249.1132 deviation +2.23ppm.

(E)-4-(4-Fluorophenyl)-3-carboxyethylbut-3-enoic acid (10)

^1H NMR δ(DMSO) 1.28, 3H(t); 3.43, 2H(s); 4.22, 2H(q); 7.31, 2H(dd); 7.50, 2H(dd),; 7.78, 1H(s).

IR 1731, 1719 cm^{-1}.

MH^+ calc. 253.0876 obs. 253.0853 deviation -9.34ppm.

(E)-4-(3-Nitrophenyl)-3-carboxyethylbut-3-enoic acid (11)

^1H NMR δ(DMSO) 1.35, 3H(t); 3.49, 2H(s); 4.32, 2H(q); 7.63, 1H(m); 7.76, 1H(bd); 7.92, 1H(s); 8.22, 1H(bd); 8.29, 1H(t).

IR 1736, 1732, 1532, 1353 cm^{-1}.

MNH_4^+ calc. 297.1087 obs. 297.1111 deviation +8.2ppm.

(E)-4-(1-Naphthyl)-3-carboxyethylbut-3-enoic acid (12)

^1H NMR δ(DMSO) 1.34, 3H(t); 3.30, 2H(s); 2.29, 2H(q); 7.49, 1H(d); 7.60, 3H(m); 7.90, 1H(m); 8.01, 2H(m); 8.26, 1H(s).

IR 1712, 1696 cm^{-1}.

MH^+ calc. 285.1127 obs. 285.1123 deviation -1.43ppm.

(E)-4-(2-Furyl)-3-carboxyethylbut-3-enoic acid (13)

^1H NMR δ($CDCl_3$) 1.33, 3H(s); 3.92, 2H(s); 4.27, 2H(q); 6.50, 1H(dd); 6.69, 1H(d); 7.64, 1H(d); 7.65, 1H(s).

IR 1709 1698 cm^{-1}.

MNH_4^+ calc. 242.1028 obs. 242.1020 deviation -3.5ppm.

(E)-4-(2-Thienyl)-3-carboxyethylbut-3-enoic acid (14)

^1H NMR δ($CDCl_3$) 1.36, 3H(t); 3.80, 2H(s); 4.32, 2H(q); 7.16, 1H(dd); 7.25, 1H(d); 7.59, 1H(d); 8.06, 1H(s).

IR 1704, 1629 cm^{-1}.

MH^+ calc. 241.0534 obs. 241.0530 deviation -1.5ppm.

(E)-3-Carboxyethyldec-3-enoic acid (15)

^1H NMR δ($CDCl_3$) 0.90, 3H(t); 1.32, 3H(t); 1.2-1.5, 8H(m); 2.19, 2H(m); 3.39, 2H(s); 4.22, 2H(q); 7.00, 1H(t).

IR 1715, 1700 cm^{-1}.

MH^+ calc. 243.1596 obs. 243.1576 deviation -8.3ppm.

The authors would like to thank Dr W. Prowse for his assistance in the n.O.e. experiments.

REFERENCES:

1. **Organic Reactions, 6, 1.**
2. Cameron, A.F, Duncanson, F.D., Freer, A.A., Armstrong V.W., Ramage R., **J. Chem. Soc. Perkin Trans. II, (1975), 1030.**
3. Awad, W.I., Kandile, N.D., Wassef, N.W., Mohamed, M.I., **J. Prakt. Chem., 331, (1989), 405.**
4. Rizzacasa, M.A., Sargant, M.V., **Aust. J. Chem. 40, (1987), 1737.**
5. Hughes, A.B., Sargant, M.V. **J. Chem. Soc. Perkin Trans. I, (1989), 449.**
6. Linke, S., Kurz, J., Lipinski, D., Gau.,**Liebigs Ann. Chem. (1980) 542.**
7. Comber, M.F., Sargant, M.V. **J. Chem. Soc. Perkin Trans. I, (1991), 2783.**

(Received in UK 3 March 1993)