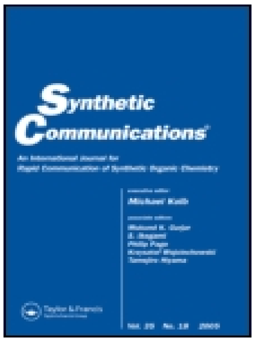

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Synthetic Communications
An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

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To cite this article: A. Johan H. Labuschagne , Johan S. Malherbe , Cornelius J. Meyer & David F. Schneider (2002) PHOSPHONIUM YLIDE-CATALYZED CYCLOTRIMERIZATION OF ETHYL PROPYNOATE, Synthetic Communications, 32:2, 297-304, DOI: 10.1081/SCC-120002015

To link to this article: http://dx.doi.org/10.1081/SCC-120002015

SYNTHETIC COMMUNICATIONS, 32(2), 297–304 (2002)

PHOSPHONIUM YLIDE-CATALYZED CYCLOTRIMERIZATION OF ETHYL PROPYNOATE

A. Johan H. Labuschagne,* Johan S. Malherbe,
Cornelius J. Meyer, and David F. Schneider[†]

Chemistry Department, University of Stellenbosch,
Stellenbosch 7602, South Africa

ABSTRACT

The cyclotrimerization of ethyl propynoate (**2**) to yield aromatic triesters is shown to proceed *via* consecutive [2 + 2] cycloadditions of ethoxycarbonylmethylenetriphenylphosphonium ylide (**1**) to three moles of (**2**), followed by cyclization and elimination of (**1**).

During our effects directed at the synthesis of cross-conjugated diesters we had occasion to synthesize the phosphonium ylide (**3**). Our synthetic method comprised the nucleophilic addition of the phosphonium ylide (**1**) to ethyl propynoate (**2**) under very mild conditions, and produced the ylide (**3**) in high yield.[1–3] In a subsequent paper by Barluenga and co-workers[4] it was pointed out that the formation of the phosphonium ylide (**3**) should be regarded as a [2 + 2] cycloaddition between the ylide (**1**) and ethyl propynoate (**2**) followed by ring opening, rather than a true Michael addition.[5–7]

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*Deceased.

[†]Corresponding author.

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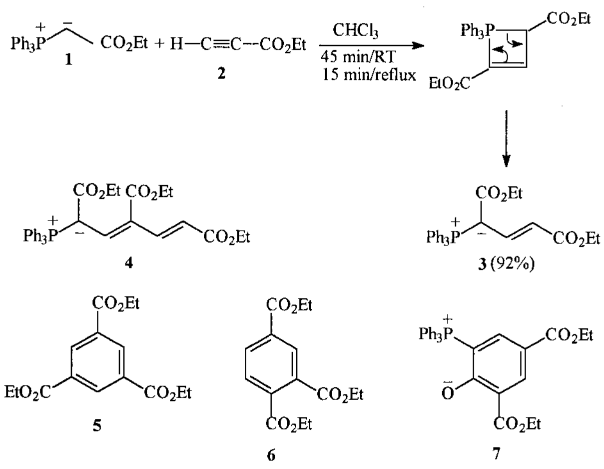


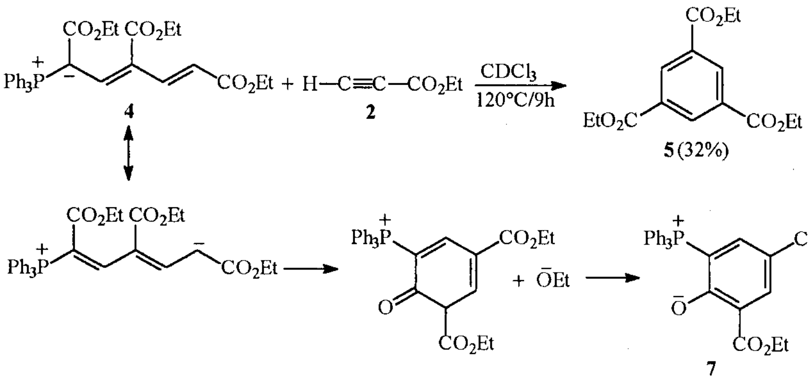
However, we found that when the above synthesis was conducted under slightly more drastic reaction conditions (60°C, 16 h) in the presence of an excess of ethyl propynoate (**2**) (3 molar equivalents), the phosphonium ylide (**4**) was produced in an isolated yield of 55% at the expense of (**3**). When this condensation was performed in a sealed tube (60°C, 120 h) we noticed that the aromatic triesters (**5**) and (**6**) developed in the reaction mixture as secondary reaction products, while the phosphonium ylide (**4**) was isolated in a significantly lower yield (~5%).

The formation of the aforementioned reaction products under the respective reaction conditions was interpreted by us as an indication that an ylide-catalyzed cyclotrimerization of ethyl propynoate (**2**) was operative under these circumstances. In order to shed more light on this unusual reaction mode, the condensation of the ylide (**3**) with ethyl propynoate (**2**) was investigated in more detail.

When the pure phosphonium ylide (**3**) and three molar equivalents of ethyl propynoate (**2**) in chloroform were heated (40°C/117 h) in a sealed tube, the aromatic triesters (**5**) (22%) and (**6**) (6%), the phosphonium ylide (**4**) (56%) and the aromatic phosphobetaine (**7**) (9%) were isolated as pure compounds from the reaction mixture by separation on a chromatotron.

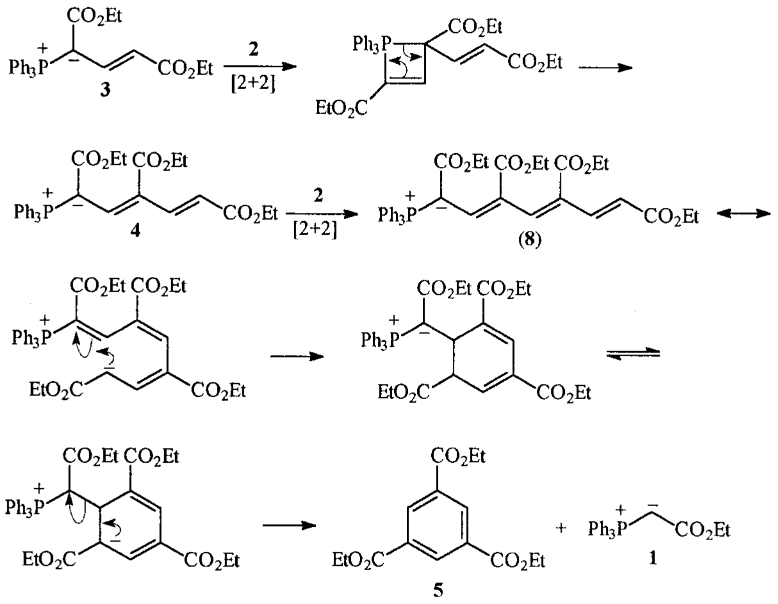
A pure crystalline sample of the phosphonium ylide (**4**) and one molar equivalent of ethyl propynoate (**2**) in deuteriochloroform were heated (120°C/9 h) in a sealed NMR tube, and the course of the reaction continuously monitored by ^{1}H NMR analysis. Under these circumstances the aromatic triester (**5**) was indeed produced, albeit in modest yield, but no NMR evidence could be found that the isomeric triester (**6**) was formed in a detectable quantity.

Since we have shown that both the phosphonium ylide (**4**) and the aromatic phosphobetaine (**7**) were formed during the condensation of the ylide (**3**) with an excess (3 molar equivalents) of ethyl propynoate (**2**) in a sealed tube, the formation of the betaine (**7**) can be rationalized as the result of intramolecular cyclization of (**4**).

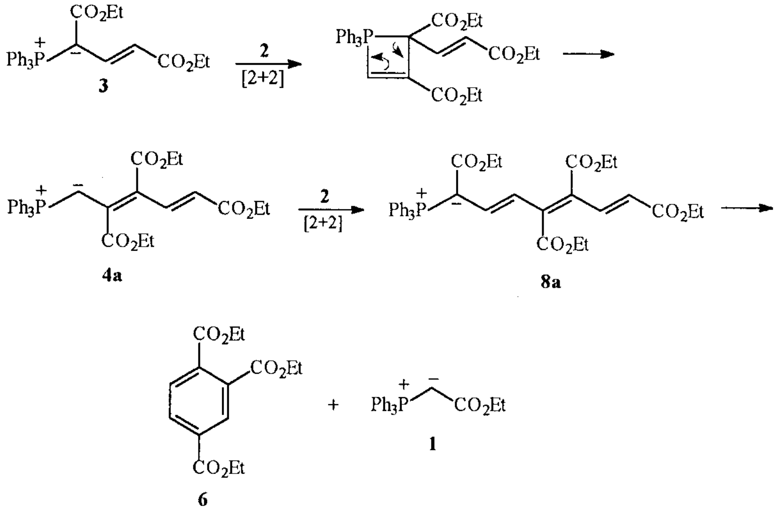


In order to substantiate the proposed ylide-catalyzed cyclotrimerization of ethyl propynoate (**2**), the pure phosphonium ylide (**3**) and ten molar equivalents of the acetylenic ester (**2**) in deuteriochloroform were heated at 60°C for several days in a sealed NMR tube. ^{1}H NMR monitoring of the reaction mixture after 72, 144, 216 and 379 h at 60°C revealed that the aromatic triesters (**5**) and (**6**) were present in combined yields of 120% (63 : 37), 146% (66 : 34), 175% (67 : 33) and 184% (64 : 36), respectively, calculated on the basis of one molar equivalent of the phosphonium ylide (**3**) as starting material. Work-up of the reaction mixture followed by separation on a chromatotron, yielded the pure aromatic triesters (**5**) (127%) and (**6**) (36%) as the most important reaction products.

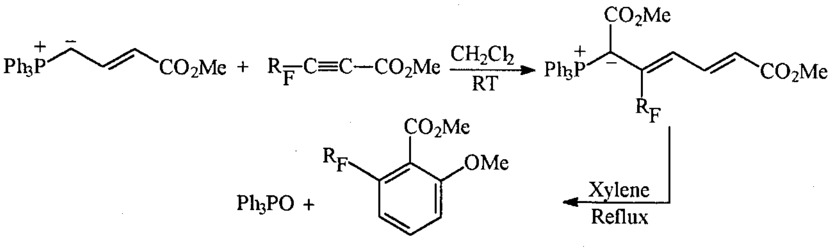
This experiment clearly demonstrated that the phosphonium ylide (**1**), or the ylide (**3**) as a primary condensation product, acted as a catalyst which promoted the cyclotrimerization of ethyl propynoate (**2**) to yield the aromatic triesters (**5**) and (**6**). We, therefore, suggest that consecutive [2 + 2] cycloadditions of three moles ethyl propynoate (**2**) led to the formation of the ylides (**3**), (**4**) and (**8**) of which (**3**) and (**4**) were characterized as reaction intermediates. Intramolecular cyclization of the phosphonium ylide (**8**), followed by elimination of the ylide (**1**) for further utilization in the catalytic cycle, may lead to the formation of the aromatic triester (**5**) as the major condensation product.



Formation of the isomeric triester (**6**) may likewise proceed *via* the formation of the phosphonium ylides (**4a**) and (**8a**) as reaction intermediates, followed by intramolecular cyclization of (**8a**).



Ding and co-workers[8–12] have extensively investigated the potential of the reaction of triphenylphosphoranylidenebutenoates with 2-perfluoroalkynoates for the synthesis of perfluoroalkyl, polysubstituted benzenoids and naphthoates *via* intramolecular Wittig condensations, e.g.



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The enhanced electrophilic character of the ester carbonyl group, due to the activating effect of the perfluoroalkyl substitutent, most probably facilitated the intramolecular Wittig condensation under these conditions. The authors mentioned, however, that an unidentified byproduct was formed with a decrease in the yield of the polysubstituted benzenoid (**9**) when an excess of perfluoroalkynoate was used. Similar Wittig-type cyclizations of structurally related arsonium ylides to produce tetrasubstituted benzenes were recently communicated.[13]

EXPERIMENTAL

All operations were carried out in an argon atmosphere. Merck silica gel 60 (particle size 0.063–0.200 mm) and silica gel 60 PF254 with calcium sulphate were used for column chromatography and separations on the chromatotron, respectively. NMR spectra were recorded for solutions in deuteriochloroform on a *Varian VXR 300* instrument, and mass spectra were taken on a *Varian Mat 311 A* spectrometer. Multiplicities were confirmed by APT and SFORD experiments, while HETCOR experiments were performed to interpret more complex spectra.

1. 1,3,5-Triethoxycarbonylpenta-2,4-dienylidenetriphenylphosphonium Ylide (4): Ethoxycarbonylmethylenetriphenylphosphonium ylide (**1**) (2 g, 5.74 mmol) and ethyl propynoate (1.69 g, 17.2 mmol) in chloroform (50 cm^3) were stirred for 16 h at 60°C, the solvent evaporated under reduced pressure at 30°C and the residue chromatographed on silica gel. Elution with ether–petroleum ether (4:1) yielded 1,3,5-*triethoxycarbonylpenta-2,4-dienylidenetriphenylphosphonium ylide* (**4**) (1.71 g, 55%), m.p. 121.5°C (from ether); δ_H 0.92 (t, J_{HH} 7.1 Hz, 3H), 1.05 (t, J_{HH} 7.1 Hz, 3H), 1.25 (t, J_{HH} 7.1 Hz, 3H), 3.94 (q, J_{HH} 7.1 Hz, 2H), 3.99 (q, J_{HH} 7.1 Hz, 2H), 4.16 (q, J_{HH} 7.1 Hz, 2H), 6.40 (d, J_{HH} 15.7 Hz, =CH), 7.25 (d, J_{PH} 18.8 Hz, =CH), 7.71 (d, J_{HH} 15.8 Hz, =CH), 7.50–7.91 (m, arom.H, 15H); δ_C 14.09 (CH_3), 14.37 (CH_3), 14.50 (CH_3), 59.28 (CH_2), 59.35 (CH_2), 59.85 (CH_2), 63.70 (d, J_{PC} 115.7 Hz, P=C <), 109.98 (d, J_{PC} 14.4 Hz, =C <), 113.0 (=CH), 124.45 (d, J_{PC} 91.9 Hz, 3 × arom. C), 129.05 (d, J_{PC} 12.4 Hz, 6 × *m*-arom. C), 132.79 (d, J_{PC} 2.7 Hz, 3 × *p*-arom. C), 133.87 (d, J_{PC} 9.6 Hz, 6 × *o*-arom. C), 142.18 (=CH), 149.18 (d, J_{PC} 15.5 Hz, =CH), 167.51 (> C=O), 167.66 (> C=O), 167.71 (> C=O); M^+, 544.2023. Calcd. for $C_{32}H_{33}O_6P$: M, 544.2014; Found: C, 70.40; H, 6.10. Required: C, 70.58; H, 6.07.

2. Condensation of 1,3-Diethoxycarbonylallylidenetriphenylphosphonium Ylide (3) with Ethyl Propynoate (2) in a Molar Ratio of 1 : 3: The phosphonium ylide (**3**) (4.46 g, 10 mmol) and ethyl propynoate (**2**) (3 g, 30 mmol) in chloroform (15 cm^3) were heated for 117 h at 40°C in a glass pressure vessel, the solvent evaporated under reduced pressure at 30°C and the residue chromatographed on silica gel. Elution with ether–petroleum ether (2 : 3), ether–petroleum ether (4 : 1) and ethanol–ether (3 : 1), respectively, yielded the following three fractions:

(a) *1,3,5-triethoxycarbonylbenzene* (**5**)[3] (0.64 g, 22%), m.p. 135°C (from ether–petroleum ether)[3]; Found: C, 61.10; H, 5.80. Calcd. for $C_{15}H_{18}O_6$: C, 61.22; H, 6.12; *1,2,4-triethoxycarbonylbenzene* (**6**) (0.17 g, 6%), b.p. 150°C (air-bath temp.)/0.05 mm Hg; δ_H 1.38 (t, J 7.0 Hz, 6H), 1.41 (t, J 7.0 Hz, 3H), 4.40 (q, J 7.1 Hz, 4H), 4.42 (q, J 7.1 Hz, 2H), 7.74 (dd, J 8.0 and 0.6 Hz, H_6), 8.20 (dd, J 8.0 and 1.7 Hz, H_5), 8.40 (dd, J 1.7 and 0.5 Hz, H_3); δ_C 14.07 (CH_3), 14.12 (CH_3), 14.28 (CH_3), 61.69 (CH_2), 61.94 (CH_2), 62.0 (CH_2), 128.87 (arom. C), 130.11 (arom. C), 131.99 (arom. C), 132.13 (arom. C), 132.72 (arom. C), 136.29 (arom. C), 164.99 (> C=O), 166.61 (> C=O), 167.14 (> C=O); M^+, 294.1099. Calcd. for $C_{15}H_{18}O_6$: M, 294.1103; Found: C, 61.05; H, 6.0. Required: C, 61.22; H, 6.12;

(b) *1,3,5-triethoxycarbonylpenta-2,4-dienylidenetriphenylphosphonium ylide* (**4**) (3.02 g, 56%); (c) the third fraction was subjected to further purification by chromatographic separation on a chromatotron with ethanol–dichloromethane (3 : 7) as eluent to yield *2,4-diethoxycarbonyl-6-triphenylphosphoniumphenoxide* (**7**) (0.42 g, 9%), m.p. 206°C (from ether); δ_H 1.26 (t, J 7.1 Hz, 3H), 1.33 (t, J 7.1 Hz, 3H), 4.20 (q, J 7.1 Hz, 2H), 4.32 (q, J 7.1 Hz, 2H), 7.49–7.69 (m, arom. C, 15H), 7.63 (dd, J_{PH_5} 15.9 Hz, $J_{H_3H_5}$ 2.65 Hz, H_5), 8.69 (dd, $J_{H_3H_5}$ 2.5 Hz and J_{PH_3} 0.6 Hz, H_3); δ_C 14.40 (CH_3), 14.52 (CH_3), 60.03 (2 × CH_2), 107.02 (d, J_{PC} 101.3 Hz, C_6), 110.88 (d, J_{PC} 16.0 Hz, C_4), 121.18 (d, J_{PC} 7.1 Hz, C_2), 121.94 (d, J_{PC} 92.4 Hz, 3 × arom.C), 129.39

(d, J_{PC} 12.8 Hz, 6 × *m*-arom. C), 133.28 (d, J_{PC} 3.0 Hz, 3 × *p*-arom. C), 133.98 (d, J_{PC} 10.2 Hz, 6 × *o*-arom. C), 141.45 (d, J_{PC} 1.7 Hz, C_3), 143.19 (d, J_{PC} 12.5 Hz, C_5), 166.21 (> C=O), 166.24 (> C=O), 176.75 (d, J_{PC} 5.8 Hz, C_1); M^+, 498.1584. Calcd. for $C_{30}H_{27}O_5P$: M, 498.1596; Found: C, 71.75; H, 5.2. Required: C, 72.29; H, 5.42.

3. Condensation of 1,3,5-Triethoxycarbonylpenta-2,4-dienylidenetriphenylphosphonium Ylide (4) with one Molar Equivalent of Ethyl Propynoate (2): The phosphonium ylide (**4**) (50 mg, 0.1 mmol) and ethyl propynoate (**2**) (10 mg, 0.1 mmol) in deuteriochloroform (0.5 cm^3) were heated in a sealed NMR tube at 120°C while the progress of the reaction was continuously monitored by NMR analysis. After 9 h at 120°C NMR analysis showed that 1,3,5-*triethoxycarbonylbenzene* (**5**)[3] (32%) was present in the reaction mixture while ethyl propynoate (**2**) was totally consumed at that stage. No NMR or TLC evidence could be found that 1,2,4-triethoxycarbonylbenzene (**6**) was formed in a detectable quantity under these circumstances.

4. Phosphonium Ylide-Catalyzed Cyclotrimerization of Ethyl Propynoate (2): Ethyl propynoate (**2**) (0.98 g, 10 mmol) and 1,3-diethoxycarbonylallylidenetriphenylphosphonium ylide (**3**) (0.45 g, 1 mmol) in deuteriochloroform (1.0 cm^3) were heated for several days at 60°C in a sealed NMR tube. ^1H NMR monitoring of the composition of the reaction mixture after 72, 144, 216 and 379 h at 60°C revealed the presence of mixtures of *1,3,5-triethoxycarbonylbenzene* (**5**) and *1,2,4-triethoxycarbonylbenzene* (**6**) in combined yields of 120% (63 : 37), 146% (66 : 34), 175% (67 : 33) and 184% (64 : 36), respectively. The reaction mixture was subjected to filtration through a silica gel column and the residue from the 5% ether–dichloromethane eluate was separated on a chromatotron with 10–20% ether–petroleum ether as eluent to yield the *aromatic triesters* (**5**) (376 mg, 127%) and **(6)** (104 mg, 36%) as pure compounds.

ACKNOWLEDGMENTS

We thank Mr HSC Spies for the NMR spectra and many helpful discussions and Ms V Truter for the mass spectra. Technical assistance by Mr MC de Jongh and his staff is gratefully acknowledged.

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Received in the UK December 4, 2000

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