

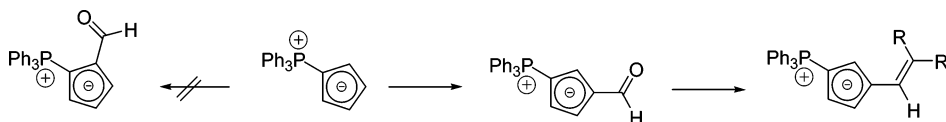
A Re-Evaluation of the Electrophilic Substitution Reactions of the Ramirez Ylide

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Received July 8, 2007



Cyclopentadienylidetriphenylphosphorane (the Ramirez ylide), unexpectedly and contrary to a number of earlier reports, has been shown to be like pyrrole in undergoing electrophilic substitution on the cyclopentadienide ring at either the 3- or the 2-position, depending on the electrophile. Formylation under Vilsmeier conditions and addition of tetracyanoethylene occurs at the 3-position, while activated acetylenes and the nitrosyl electrophile substitute at the 2 position. The 3-formylated product was reduced to the 3-methyl derivative and it also reacted under Knoevenagel conditions to give a number of novel condensation products. The results of single-crystal X-ray crystallographic analyses are given for four of the compounds studied, and a careful 2D NMR analysis of all of the compounds was performed in order to develop a reliable method for the unambiguous assignment of the regiochemistry of adduct formation.

Introduction

We have recently reported¹ that 1,3,5,6-tetrasubstituted azulenes can be prepared by sequential reaction of the Ramirez ylide² (**1**) with 2 equiv of dialkyl acetylenedicarboxylate via the *E*-configured vinyl adducts **2** (Scheme 1).

In investigating the scope of this azulene synthesis and as part of our study of its mechanism, we sought to prepare adducts analogous to **2**, bearing a hydrogen on the C α of the alkene with geminal substitution on the β -carbon. We proposed to make these via the key compound triphenylphosphonium 2-(formyl)cyclopentadienylide **3** (Scheme 2), a literature compound reported by Yoshida and co-workers³ as being formed under Vilsmeier conditions from the Ramirez ylide. We also envisaged

that **3** could be used as a source of further substitution on the azulene, for example, by its reduction to a methyl group.

However, azulene formation was not observed when adducts that were synthesized from the formylated product of **1** were reacted with a further equivalent of alkyne. This, therefore, cast doubt on the original structural assignment of **3**. We now report that **1** reacts with certain electrophiles to give products substituted instead at the 3-position. Derivatives prepared from one such product, triphenylphosphonium 3-(formyl)cyclopentadienylide, are also presented, as well as the characterization of a number of the key compounds by X-ray crystallography. An NMR method for the correct structural assignment of both 2- and 3-substituted compounds in the absence of X-ray crystallography is also demonstrated.

Results and Discussion

Our attempts to prepare compound **3** following the literature method (addition of **1** to an excess of Vilsmeier reagent at -15 to -10 °C) yielded a solid that gave similar spectroscopic data to that reported.³ However, a product of diformylation was also routinely found as a contaminant under these conditions (sometimes as the only product; see below), and we were able

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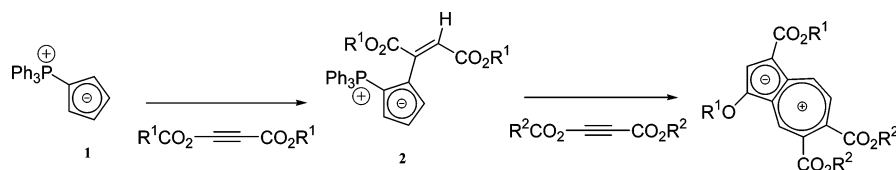
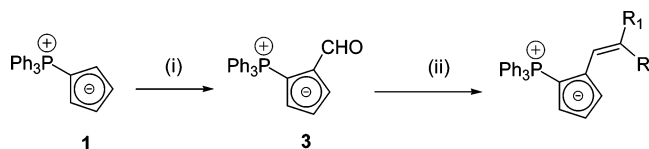
[‡] National University of Ireland, Maynooth.

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(1) Higham, L. J.; Kelly, P. G.; Corr, D. M.; Müller-Bunz, H.; Walker, B. J.; Gilheany, D. G. *Chem. Commun.* **2004**, 684–685.

(2) Ramirez, F.; Levy, S. *J. Am. Chem. Soc.* **1957**, 79, 67–69.

(3) Yoshida, Z.; Yoneda, S.; Murata, Y.; Hashimoto, H. *Tetrahedron Lett.* **1971**, 1523–1526.

SCHEME 1. Azulene Synthesis from Ramirez Ylide ($R^1/R^2 = \text{CH}_3, \text{C}_2\text{H}_5, \text{and } (\text{CH}_3)_3\text{C}$)SCHEME 2. Proposed Route to Geminal-Substituted Adducts^a ($R/R^1 = \text{Carbonyl, Ester, or Cyano Groups}$)^a

^a Reagents and conditions: (i) POCl_3/DMF ($-15\text{ }^\circ\text{C}$), (ii) activated methylene compound using Knoevenagel conditions.

to show that formylation had in fact given the 3-substituted isomer **4**. This was because the compound formed could be subsequently reacted (Scheme 3) with dimethyl malonate under Knoevenagel conditions to give **5**, the structure of which was established by X-ray crystallography (Figure 1). Similar reaction with methyl cyanoacetate gave the analogous adduct **6** with the nitrile group syn to the ring, again established by X-ray (Figure 1).⁴ The structural parameters of compounds **5** and **6** compare well with our previous work⁵ and that of others.⁶

To a certain extent it is understandable that the original workers misassigned the structure of compound **4**, because it was consistent with the results with some other electrophiles (see below) and was not ruled out by the ^1H NMR spectrum. However, it is notable in hindsight that the presence of ^{31}P coupling to the three cyclopentadienylidene protons serves to complicate matters and would make such an analysis difficult. Furthermore, it is important to note that there is occasionally a $^4J_{\text{HH}}$ coupling observed between H2 and H4 and H5 in the 3-substituted compounds—a feature noted previously⁷—depending on the threshold value employed in the NMR processing package. In the ^1H – ^1H COSY spectra, the magnitude of this coupling appears less than the $^3J_{\text{HH}}$ coupling between H4 and H5. However, this smaller coupling has the potential to be misleading if used as the sole method of analysis; the phenomenon presumably owes its origins to the high degree of delocalization in the compounds.

In order to provide an accurate and straightforward method for the secure assignment of the products obtained when **1** reacts with a variety of electrophiles (in lieu of samples suitable for X-ray crystallographic analysis), we compared the ^1H – ^1H COSY NMR spectra of compound **5** (proven here to be

substituted at the 3-position), with that of triphenylphosphonium 2-(Z-(α,β -dicarbomethoxyvinyl)cyclopentadienylidene **7**, which we have previously confirmed as substituted at the 2-position, also by virtue of an X-ray crystal structure.⁵ Figure 2 illustrates that, as expected, the coupling patterns for the cyclopentadienylidene protons of the two compounds are very different. H5 and H3 both couple to H4 for **7**, whereas for **5**, only H4 and H5 couple strongly together (see Supporting Information for further comment).

When the formyl ylide **4** prepared by us is subjected to the same analysis, we find that the NMR is consistent with substitution at the 3- and not the 2-position; by way of confirmation, a ^1H NOE experiment (with variable mixing times; see Supporting Information) showed a correlation between H4 and H5, and another between H2, H4 and the aldehyde proton. A ^1H – ^{31}P correlation showed cross-peaks for each of the cyclopentadienylidene protons with the phosphorus resonance at 14.2 ppm, although the correlation is weaker for H4 (these spectra are reproduced in the Supporting Information). These additional NMR experiments for structural confirmation were important, because use of the COSY analysis alone can be misleading, as it may show coupling between all the ring protons in certain cases; for instance, in the reaction of **1** with tetrahalo-*p*-benzoquinones to give 3-substituted ring products, both $^3J_{\text{HH}}$ and $^4J_{\text{HH}}$ coupling were observed.⁷ Two other intriguing NMR phenomena are encountered when analyzing these systems: (i) there are occasionally no observable correlations between certain 5-membered ring protons with any carbon in the HSQC NMR and (ii) extreme broadening of some resonances in the ^{13}C NMR hindered their identification.⁸

We also found that the IR spectrum of **4** showed a carbonyl band at 1632 cm^{-1} (cf. the 1640 cm^{-1} reported).³ Freeman and Lloyd⁹ have suggested that the carbonyl stretch can distinguish between 2- and 3-substitution in the acetyl derivatives; the former leads to a lowering of the $\nu(\text{CO})$ absorption as a result of the resonance canonical structure, whereby a negative charge on the oxygen atom takes part in an intramolecular association with the heteronium atom. A 3,5-diformylated derivative (phenyls at the 2- and 4-positions) was reported in the same paper as having two carbonyl stretches at 1622 and 1645 cm^{-1} and the 3,4-diformylcyclopentadienylidene made by us (see below) has a $\nu(\text{CO})$ absorption at 1647 cm^{-1} , so it appears this method has some validity. It should also be noted that the UV spectra of **4** determined by us does differ somewhat from that reported in that we did not find a band at 370 nm. We attribute this to contamination by decomposition products, well-known in the case of the parent Ramirez ylide.

The misassignment of the structure of compound **4** (and some other structures; see below) is quite unfortunate, because both these authors and subsequent workers have relied on it in trying to understand electrophilic substitution of the Ramirez ylide. Thus Yoshida and co-workers went to considerable lengths in

(4) Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 272186 (**5**), 272187 (**6**), 633415 (**8**) and 633413 (**9**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

(5) Higham, L. J.; Kelly, P. G.; Muller-Bunz, H.; Gilheany, D. G. *Acta Crystallogr. C* **2004**, *60*, o308–o311.

(6) See, for instance, (a) Huy, N. H. T.; Compain, C.; Ricard, L.; Mathey, F. *J. Organomet. Chem.* **2002**, *650*, 57–58. (b) Ammon, H. L.; Wheeler, G. L.; Watts, P. H., Jr. *J. Am. Chem. Soc.* **1973**, *95*, 6158–6163. (c) Holy, N. L.; Baenziger, N. C.; Flynn, R. M.; Swenson, D. C. *J. Am. Chem. Soc.* **1976**, *98*, 7823–7824.

(7) Pons, M.; Pérez Pla, F.; Valero, R.; Hall, C. D. *J. Chem. Soc., Perkin Trans.* **1996**, *2*, 1011–1019.

(8) A full listing of these issues is given in the Supporting Information.

(9) Freeman, B. H.; Lloyd, D. *Tetrahedron* **1974**, *30*, 2257–2264.

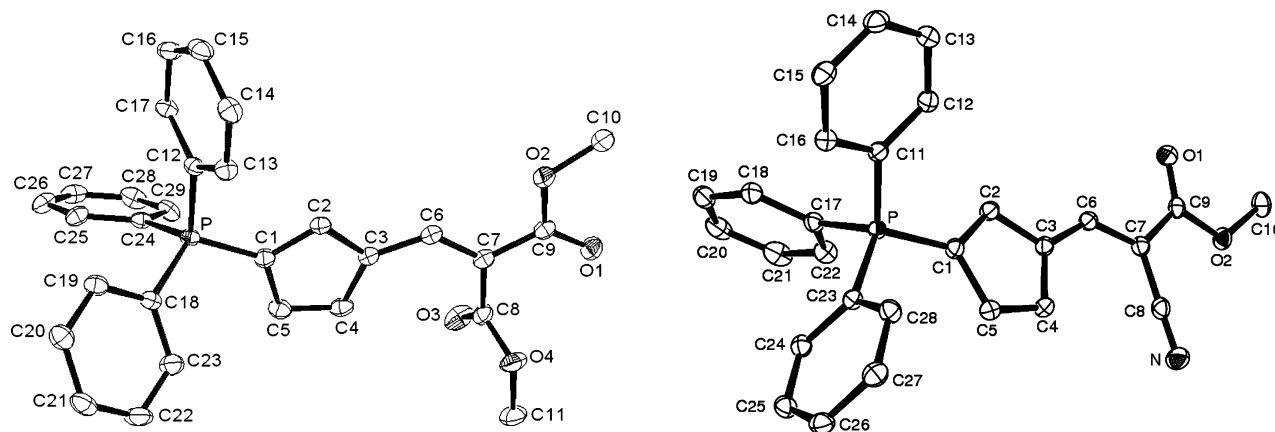


FIGURE 1. The X-ray crystal structures of compounds 5 (left) and 6.

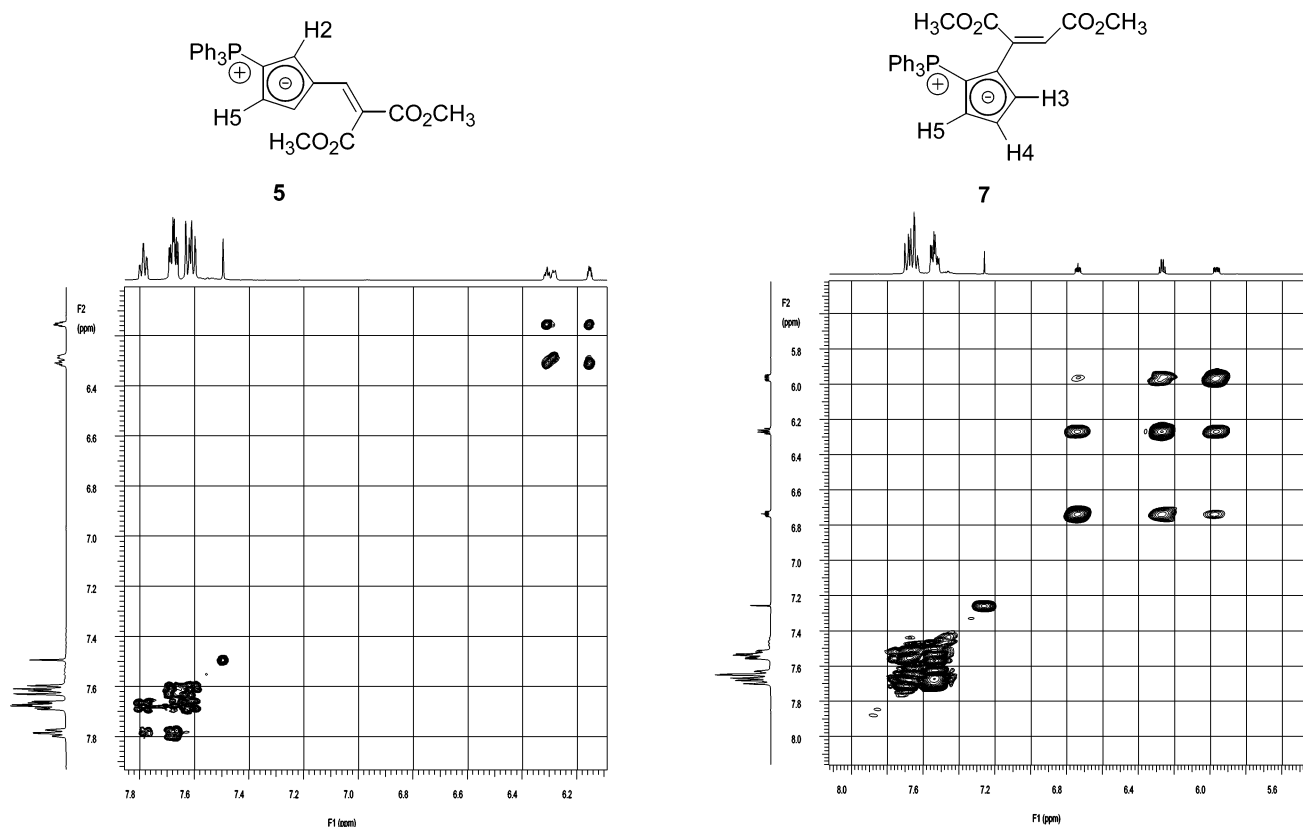


FIGURE 2. ^1H COSY NMR analysis of 5 and 7. The spectra illustrate the distinct coupling patterns observed for 5 (H4 and H5 coupling, shown left) and 7 (H3, H4 and H5 couple together).

a subsequent paper¹⁰ to understand which is the most susceptible position on the 5-membered ring to electrophilic substitution. Among a number of models studied (reaction indices including superdelocalizabilities, localization energies, and π -electron densities), electron transfer theory was used to rationalize the supposed preference for attack at the 2-position. This was despite steric considerations and HMO calculations on the electron densities at the different sites deeming the 2-position less favorable than C₁ or C₃.^{3,10} Lloyd and Singer instead speculated that 2-substitution may be due to a more favored transition state expected of the linear rather than cross-conjugated system.¹¹

(10) Yoshida, Z.; Yoneda, S.; Murata, Y. *J. Org. Chem.* **1973**, *38*, 3537–3541.

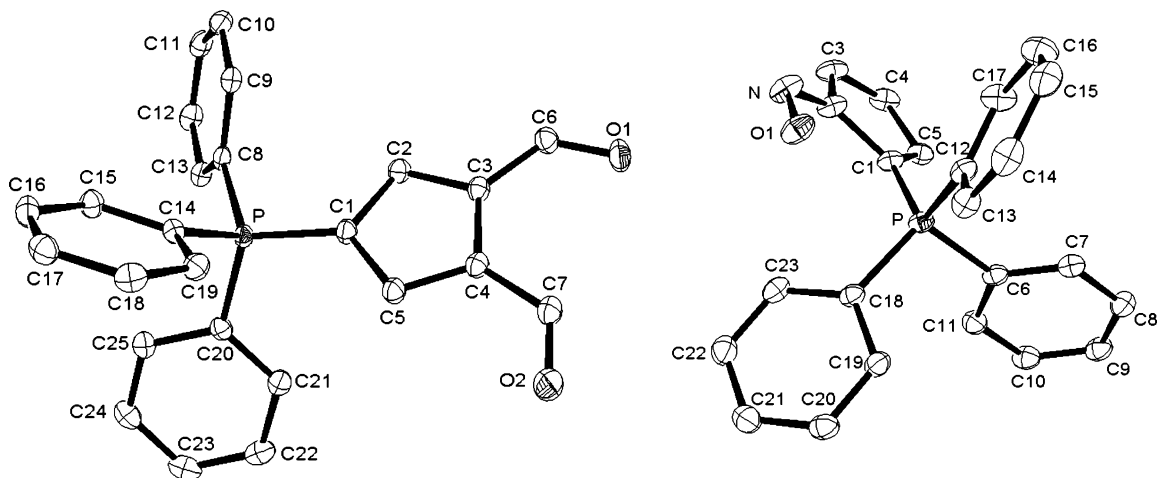
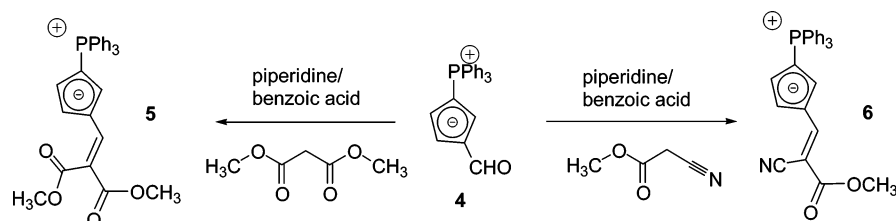
(11) Lloyd, D.; Singer, M. I. *C. Chem. Ind.* **1971**, 786.

Electrophilic substitution at the 3-position on the cyclopentadienylidene ring of **1** has been reported for azasulfonium salts¹² and recently with tungsten phosphinidene reagents, with the latter placement accounted for on steric grounds.^{6a} Addition reactions at the 3-position with mercury(II) iodide,^{6c} iodine, and thallium(III) trifluoroacetate¹³ have also been described, the reaction outcomes noted as surprising and again attributed to sterics; a recent theoretical study suggests both the 2- and 3-positions are the preferred sites of protonation.¹⁴ Taken with

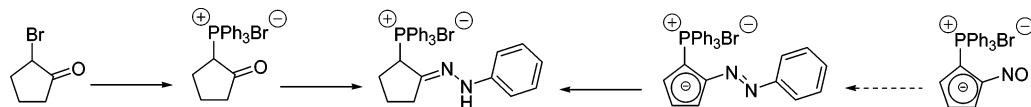
(12) (a) Schlingensief, K. H.; Hartke, K. *Tetrahedron Lett.* **1977**, *14*, 1269–1272. (b) Schlingensief, K. H.; Hartke, K. *Liebigs Ann. Chem.* **1978**, 1754–1764.

(13) Roberts, R. M. G. *Tetrahedron* **1980**, *36*, 3295–3300.

(14) Laavanya, P.; Krishnamoorthy, B. S.; Panchanatheswaran, K.; Manoharan, M. *J. Mol. Struct. (THEOCHEM)* **2005**, *716*, 149–158.

FIGURE 3. The X-ray crystal structure of **8** and **9**.SCHEME 3. Reaction of the 3-Substituted Isomer **4** with Diethyl Malonate and Methyl Cyanoacetate

SCHEME 4. Verification Method Used by Yoshida et al. to Support Substitution in the 2-Position



our results, it is now clear that ylide **1** is much more like pyrrole than had been previously thought. We were intrigued as to why 3-substitution occurs under Vilsmeier conditions. One possibility is that this is a situation of thermodynamic versus kinetic control. Strong evidence for reversibility of addition at the 3-position was found by Pons et al. in reactions with tetrahalobenzoquinones.⁷ Unfortunately, it was difficult to study this possibility. While no other formylated product was present in the crude reaction mixture, this does not rule out the possibility that an initially formed 2-substituted Vilsmeier intermediate rapidly rearranges to the 3-isomer. The use of milder reaction conditions merely lowered the yield while the use of even slightly more forcing conditions gives substantial amounts of a diformylated compound, which is the exclusive product with excess Vilsmeier reagent. This had also been reported by Yoshida and co-workers and assigned as the 2,5-diformylated cyclopentadienylidene. The IR, UV, and melting point data of the compound obtained by us correlates with that reported. However, again the ¹H NMR suggests a different substitution pattern with one doublet (³J_{HP} = 4.47 Hz) for the two 5-membered ring protons, an NOE between the 5-membered ring protons and a phenyl ring, and an NOE between the aldehyde protons and the ring protons only. This strongly suggests the 3,4-substitution pattern of compound **8**, which was confirmed by an X-ray crystallographic study (Figure 3).

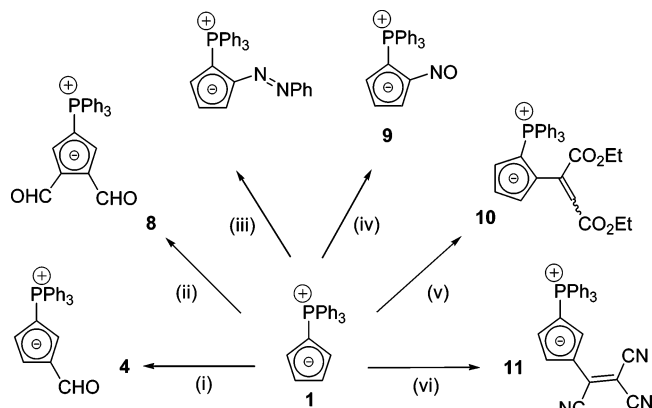
We turned then to other electrophilic substitution reactions. Yoshida and co-workers¹⁰ also reported the 2-nitroso and 2-nitro

derivatives as well as 2-substituted compounds derived by reaction with benzaldehyde and maleimide. The authors converted the 2-nitroso compound to triphenylphosphonium (2-phenylazo)cyclopentadienylidene to support their assignment at the 2-position. The latter compound had been previously reported by Ramirez and Levy,¹⁵ who had made it through reaction of **1** with benzenediazonium chloride. They had also established its identity through its treatment with hydrobromic acid and reduction of the resultant hydrobromide to (2-phenylhydrazonocyclopentyl)triphenylphosphonium bromide, whose substitution pattern was in turn authenticated by its independent preparation from phenylhydrazine and (2-oxocyclopentyl)triphenylphosphonium bromide; see Scheme 4.

We repeated the nitrosation reaction according to the reported experimental procedure and found that this reaction did indeed lead to the 2-substituted derivative **9**, assignable by our described NMR studies and further characterized by X-ray crystallography (see Figure 3). Despite repeated attempts, we could not repeat the nitration reaction of **1**, nor the reported reactions of **1** with benzaldehyde or maleimide.

Yoshida and co-workers also reported that the reaction between **1** and diethyl acetylenedicarboxylate goes at the 2-position, which we have previously confirmed and shown to be a separable mixture of the *E*- and *Z*-vinyl adducts **10**,¹⁶ as shown by our X-ray crystallographic study on the dimethyl ester

(15) Ramirez, F.; Levy, S. *J. Org. Chem.* **1956**, *21*, 1333–2036.

SCHEME 5. Reaction of **1** with the Original Electrophiles Used and the Correct Assignments^a

^a Reagents and conditions: (i) POCl₃/DMF (−15 °C), (ii) POCl₃/DMF (25 °C), (iii) benzenediazonium chloride (0 °C), (iv) NaNO₂ in CH₃COOH, (v) C₂H₅CO₂CCO₂C₂H₅, (vi) (NC)₂C=C(CN)₂. Compounds **4** and **11** were originally assigned as substituted in the 2-position, while **8** was described as the 2,5-diformylated adduct.

analogues.⁵ However, reaction of **1** with tetracyanoethylene leads to the 3-substituted adduct **11**, which we have also characterized by X-ray crystallography.¹⁷ This contradicts the 2-substitution proposed by Yoshida and co-workers¹⁰ and also by Rigby et al.¹⁸ The NMR, IR, and melting point data obtained by us suggest that the compounds are the same.

The authenticated results for electrophilic substitution of Ramirez ylide are shown in Scheme 5. It appears that the position of substitution may depend on the bulk of the electrophile used. Thus in comparing similar strength electrophiles (alkyne vs alkene and NO⁺/N₂⁺ vs Vilsmeier) the more bulky react at the 3-position. However, we cannot say this with certainty, because these are not large differences in size and it is very noticeable that in all cases *the other isomer is not detected*, which would be expected in the case of small energy differences between the two alternatives. Furthermore, we have not been able to rule out the intervention of kinetic versus thermodynamic effects.

With the substitution pattern of **4** secure, the structures of our Knoevenagel condensation derivatives from diethylmalonate and 2,4-pentanedione are now established as **12** and **13**. We also prepared the methyl compound **14** via the tosyl hydrazone of **4** (see Scheme 6), after other reduction methods failed.¹⁹

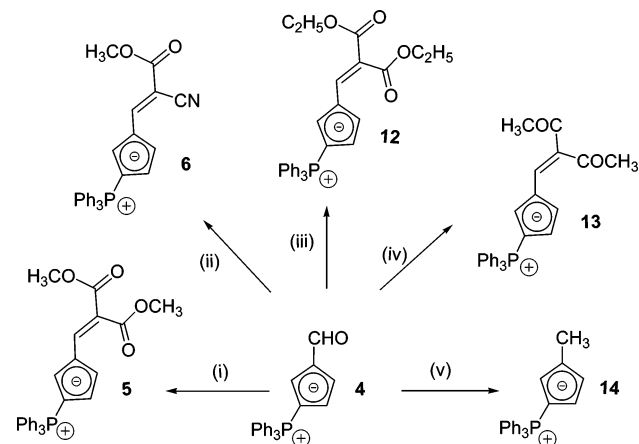
In summary, we have addressed the issue of the site of substitution in the parent formyl compound by showing the compound to be triphenylphosphonium 3-(formyl)cyclopenta-

(16) Under the reaction conditions employed by Yoshida, we found that a mixture of both the *E* and *Z* adducts was obtained. We have successfully modified the reaction conditions for **7** and **10** to facilitate the production of the *Z*-isomer only in both cases; see Supporting Information for details.

(17) This assignment, based on the ¹H–¹H COSY NMR analysis, was later verified by an X-ray crystallographic study. Although the substitution at the 3-position is confirmed, some disorder about the vinyl group itself precludes its inclusion here. The authors would be happy to supply the CIF to interested parties.

(18) (a) Rigby, C. W.; Lord, E.; Hall, C. D. *Chem. Commun.* **1967**, 714–716. (b) Rigby, C. W.; Lord, E.; Naan, M. P.; Hall, C. D. *J. Chem. Soc. B* **1971**, 1192–1197.

(19) No reduction of **4** was observed in Wolf–Kishner, Clemmensen, or Meerwein–Verley–Ponndorf reactions or by employing sodium borohydride in refluxing ethanol.

SCHEME 6. The Derivatives Prepared from the 3-Substituted Formyl Ylide **4**^a

^a Reagents and conditions: (i–iv) utilized piperidine/benzoic acid/reflux reaction conditions; (i) dimethyl malonate, (ii) methyl cyanoacetate, (iii) diethyl malonate, (iv) 2,4-pentanedione, (v) (a) toluene sulfonylhydrazide/reflux, (b) NaBH₄/0 °C.

dienylide. For this and a number of other reactions with electrophilic reagents, ¹H–¹H COSY and ¹H NOE NMR analysis can be a very useful tool in the structural assignment of the products. In addition, we have prepared six new derivatives of the formylated compound (including the tosyl hydrazone), two of which were characterized by X-ray crystallography.

Our study shows that care must be taken when making structural assignments in this system, and papers^{3,10,11,18,20,21,22} detailing the purported 2-substituted adducts must be treated with caution.

In reference to our initial objective of preparing geminal-substituted vinyl adducts suitable as precursors for the preparation of novel azulenes (Scheme 1), we found that the 3-substituted compounds do not react with acetylenes to give azulenes, a now entirely expected result in light of our proposed mechanism.¹

Experimental Section

Please refer to the Supporting Information for detailed characterization data (full NMR, HRMS, and elemental analysis).

Triphenylphosphonium 3-(formyl)cyclopentadienylide (4**).** Phosphorus oxychloride (2.85 mL, 4.69 g, 30.6 mmol) was added over 10 min to a stirred suspension of **1** (10.0 g, 30.6 mmol) at −10 °C in *N,N*-dimethylformamide (50 mL, 47.2 g, 0.65 mol). The mixture became a brown solution, and after 20 min was poured onto ice/water (200 g), precipitating a pink solid. NaOH (10% w/v) was added until the mixture became alkaline to litmus and it was then stirred overnight. The pink solid was filtered, washed with water and cold diethyl ether (20 mL), and dried in vacuo. The solid can be recrystallized from toluene or ethyl acetate/chloroform.

Yield: 7.9 g (71%). Mp: 223–225 °C (lit.¹⁰ mp: 221–222 °C dec). ¹H NMR (dimethyl sulfoxide-*d*₆, 500 MHz): 9.60 (s, 1H,

(20) Yoneda, S.; Watanabe, M.; Yoshida, Z. *Bull. Chem. Soc. Jpn.* **1978**, 51, 2605–2608.

(21) Yoshida, Z.; Yoneda, S.; Murata, Y.; Hashimoto, H.; Murata, Y. *Tetrahedron Lett.* **1971**, 1527–1529.

(22) Yoshida, Z.; Yoneda, S.; Yato, T. *Tetrahedron Lett.* **1971**, 2973–2976.

aldehyde), 7.91 (m, 3H, H_{para}), 7.79 (m, 6H, H_{meta}), 7.74 (m, 6H, H_{ortho}), 6.72 (m, 1H, cyclopentadienylene H4), 6.68 (m, 1H, cyclopentadienylene H2), 6.30 (m, 1H, cyclopentadienylene H4) ppm. ³¹P NMR (dimethyl sulfoxide-*d*₆, 500 MHz): 6.7 ppm. HRMS: calcd for [MH]⁺ (C₂₄H₂₀PO) 355.1252, found 355.1265 (3.7 ppm). IR (KBr): ν_{max} 1630 (C=O) cm⁻¹. λ_{max} (log ϵ , CH₂-Cl₂): 277 (sh) (3.75), 304 (3.98) nm.

Acknowledgment. The authors thank the National University of Ireland, Maynooth, University College Dublin and

Enterprise Ireland for Scholarships (P.G.K. and D.M.C.) and the European Commission for a Marie Curie Development Host Fellowship HPMD-CT-2000-00053 (L.J.H.).

Supporting Information Available: Detailed experimental procedures, NMR spectra, and selected crystallographic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO7014104