Sometimes, the Least Demanding Solution Is the Most Suitable: A Careful Survey of NMR Spectra of a Phosphonium Salt Accounted for Its “Unusual Wittig Reaction”

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Supporting Information

ABSTRACT: Careful product analysis in combination with appropriate supporting experiments unambiguously proves that in contrast to what was previously reported, generation of the phosphonium salt from a β-cyclocitral-derived allylic alcohol and PPh₃HBr takes place via a proton-driven elimination/addition path.

1. INTRODUCTION

In 2008, (E)-4-((3-ethyl-2,4,4-trimethylcyclohex-2-enylidene)-methyl)benzoic acid 1 was unexpectedly obtained by Das and Kabalka during their preparation of novel analogues of all-trans-retinoic acid by changing the flexible alkene backbone into a more rigid phenyl ring. This scaffold has been later widely utilized by the same group both in the context of an ongoing chemical biology project. Accordingly, the construction of a small library of structural analogues in the relevant biological profile of compound 2, coupled with its ready availability, led us to use this scaffold for the preparation of a phosphonium salt from a β-cyclocitral 3 along the pathway outlined in Scheme 1.

2. RESULTS AND DISCUSSION

In detail, the reaction of 4-formylbenzoic acid methyl ester with phosphorus ylides featuring the β-cyclocitral skeleton afforded compounds 6 in place of the planned regioisomeric dienes 5. Thus, different from their expectations, the phosphonium salts 9, not 7, were the precursors of the pivotal ylides for the Wittig olefination reaction.

The reaction of allylic alcohols with triphenylphosphine hydrobromide (PPh₃P-HBr) is a well-established method for the direct preparation of allyl triphenylphosphonium bromide salts. Notably, in the case of tertiary allyl alcohols acting as the substrates, the phosphonium salts, where the least hindered electrophilic carbons intercept the phosphate nucleophile, are usually observed as the major products. In the specific case of allylic alcohols 4, the formation of the two regioisomeric phosphonium salts 7 and 11 was anticipated. The former phosphonium salt resulted from the ipso substitution of bromide, whereas the latter phosphonium salt resulted from its allylic displacement (Scheme 2). Thus, 7 would have given the dienes 5, whereas 11, lacking in α-proton, would not have been exploitable in Wittig olefination. Thus, the authors are faced with an “unusual Wittig reaction”.

In the primary as well as in successive papers, the authors speculated that under basic conditions (n-BuLi or t-BuONa), the salt 11 could originate the pivotal ylide 10 for the “Wittig olefination” (Scheme 2). They envisioned that deprotonation at methylene beta carbon of 11 triggered a 1,2-phosphorus migration followed by an intermolecular proton shift giving ylides 10. The subsequent in situ reaction with the aromatic aldehyde led to the unexpected dienes 6. In support of the postulated mechanism, they reported the NMR spectral characterization of the “unusual Wittig salt” 11 (R = Me) that could be isolated as a yellow solid after recrystallization from methanol/ether (1:6).

In the context of an ongoing chemical biology project, we selected compound 6 (R = Me) as a scaffold from which to prepare a small library of guanidine derivatives. With the aim of...
arriving to the 1,3-diene system incorporating the β-cyclocitrall skeleton, we found it convenient to follow the Das protocol. Actually, reacting 4 (R = Me) with Ph₃P·HBr, after careful filtration on silica gel eluting with ethyl acetate, we obtained a white phosphonium bromide salt in optimal yield (96%). However, much to our surprise, its ¹H NMR was importantly different from the one reported by Das and his colleagues, which in our opinion was rather inconsistent. For example, the multiplicity and the integration of signals at δ 5.5−5.7 are in accord for two protons; the integration of aromatics is excessive (31H instead of 15H), whereas that of methylenes appears deficient. Conversely, the above inconsistencies were not observed in the ¹H NMR recorded for the phosphonium salt in our hands to which we assigned the formula that is the one of a “usual Wittig salt.”
From our point of view, no base-induced conversion of 11 to 10 was involved in the “anomalous Wittig reaction”. More simply, our findings suggest that the ylide 10 originates from the salt 9, whose formation requires two classical chemical steps, namely, acid-catalyzed 1,4-dehydration of 4, followed by the 1,4-addition of triphenylphosponium (Ph₃PH⁺) onto the resulting diene 12 (Scheme 3).

Scheme 3. Proposed Mechanism (This Work) for the Conversion of 4 into Phosphonium Salt 9

In this work, treatment of 4 with PPh₃HBr gave cleanly, after careful filtration on silica gel (EtOAc elution, 96% yield), a new white solid, which was unambiguously assigned as the phosphonium salt 9 (Scheme 3). The proton spectrum is depicted in Figure 2.

In order to definitively confirm the mechanism proposed above, we treated allylic alcohol 4 with hydrogen bromide in tert-butyl alcohol in the absence of triphenylphosphine, obtaining diene 12, which was isolated and fully characterized (Figure 3).

The subsequent exposure to triphenylphosphine hydrobromide in methanol afforded the phosphonium salt 9, thereby confirming our expectations (Scheme 4).

3. CONCLUSIONS

In conclusion, in this work, we provide convincing evidence that treatment of allylic alcohol 4 with PPh₃HBr does not afford the phosphonium salt 11, as reported by Das and Evans, but the isomeric salt 9. Therefore, rationalization of the outcome of the Wittig reaction associated with such a phosphonium salt involves neither 1,2-P migrations nor 1,4-H⁺ shifts but simply an acid-promoted elimination and a regioselective addition to a protonated 1,3-diene. This latter mechanism is supported by strong analytical data such as monodimensional and bidimensional ¹H NMR spectra and appropriate corollary experiments.

4. EXPERIMENTAL SECTION

4.1. General Information. β-cyclocitral was purchased from commercial sources (Sigma-Aldrich, Milan, Italy). All other reagents and solvents were of the highest quality available or were freshly distilled. Melting points (uncorrected) were measured with a Buchi–Tottoli apparatus, and ¹H, ¹³C, ³¹P, and bidimensional NMR spectra were recorded on a

Figure 2. ¹H NMR spectra of phosphonium salt 9.
Varian 400 MHz instrument unless otherwise noted. Chemical shifts are given in parts per million (δ) relative to the solvent, and coupling constants are in hertz. The abbreviations used are as follows: s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, m = multiplet, td = triple doublet, dt = double triplet, and ddd = double double doublet. Mass spectrometry (MS) analyses were performed on ESI Micromass ZMD 2000. High-resolution MS (HRMS) spectra were recorded using an ESI-Q-TOF mass spectrometer (Agilent Technologies). Infra-red spectra were recorded on a PerkinElmer FT-IR Spectrum 100 spectrometer. Flash chromatography was carried out on a silica gel (Merck, 230−400 mesh). High-performance liquid chromatography analysis was performed by Beckman system gold 168 using a C18 Jupiter column (150 × 4.6 mm, 5 μm) and water/acetonitrile/TFA eluent.

4.2. Experimental Procedures: Synthesis and Characterization. 4.2.1. (E)-4-((3-Ethyl-2,4,4-trimethylcyclohex-2-en-1-ylidene)methyl)benzoic Acid (1). To a solution of compound 6 (0.38 mmol, 113 mg) dissolved in 4 mL of methanol was added a solution of NaOH (2 N, 1.14 mmol); the reaction was monitored by thin-layer chromatography (TLC) (eluent EtOAc/light petroleum 0.2/9.8) and ESI MS, and after 16 h, hydrolysis was completed. The reaction was treated with 1 N HCl until pH 1 and extracted with 3 × 15 mL of ethyl acetate. The organic layer was dried with sodium sulfate anhydrous and concentrated in vacuum. The crude acid (1) was crystallized from diethyl ether to afford the pure product in 74% yield.

(1): C19H24O2; mp 150−155 °C. ESI [MH]+ 285.21. ESI-Q-TOF exact mass: [M + H]+ calcd, 285.1849; found, 285.1839. 1H NMR (400 MHz, MeOD): δ 7.84 (d, 2H, J = 7.6 Hz, CHar), 7.20 (d, 2H, J = 7.6 Hz, CHar), 6.41 (s, 1H, CH= Cq), 2.54−2.52 (m, 2H, CH2−CH2−Cq), 2.18 (q, 2H, J = 7.6 Hz, CH2−CH3), 1.85 (s, 3H, CH3−Cq), 1.45−1.42 (m, 2H, CH2−CH2−Cq), 1.03 (s, 6H, CH3−C−CH3), 1.02 (t, 3H, J = 7.6 Hz, CH3−CH). 13C NMR (100 MHz, MeOD): δ 148.59 (CH3−CH2−Cq), 142.91 (CO−CqAr), 142.13 (CH2−Cq−CH), 134.92 (CqAr−CH−Cq), 130.12 (2CHAr), 129.75 (2CHAr), 128.41 (Cq−CH3), 121.17 (Cq−CH= Cq), 40.10 (CH2−CH2−C−), 36.80 (CH3−C−CH3), 28.14 (2CH3), 25.31 (CH2−CH2−C−), 23.73 (CH2−CH3), 15.48 (CH3−C or CH3−CH2), 15.21 (CH3−CH or CH3−C). IR cm−1: 2958.76 C−H stretching, 1669.14 C=C stretching, 1589.06 C=C bending aromatic ring. X-ray: crystal data: C19H24O2; triclinic; space group: P1̅; Z = 2; a = 7.1637(2) Å, b = 7.6937(2) Å, c = 14.8938(4) Å, α = 82.749(1)°; β = 81.158(1)°; γ = 88.023(1)°; V = 804.54(4) Å3; Mo Kα radiation θmax = 27.5°; 3635 unique reflections measured; 2892 observed reflections [I > 2σ(I)]; final R index = 0.0518 (observed reflections), Rw = 0.1518 (all reflections).

4.2.2. (E)-N-Carbamimidoyl-4-((3-ethyl-2,4,4-trimethylcyclohex-2-en-1-ylidene)methyl) Benzamide (2). To a solution of guanidine hydrochloride (2.66 mmol, 254 mg) dissolved in a mixture of dimethylformamide (DMF)/dioxane (1:2), potassium tert-butoxide (2.66 mmol, 298 mg) was added
portion wise. After KCl precipitation, the reaction was filtered and added to a solution of acid 1 (1.33 mmol, 378 mg) dissolved in 10 mL of anhydrous DMF and carbonyl diimidazole (1.33 mmol, 216 mg) over argon atmosphere. After 15 min, the solvent was removed under vacuum, and the crude solid was crystallized by water/methanol 1:1 at 0 °C to give a white solid in 77% yield.

(2): C<sub>29</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub>; mp 125–130 °C. HRMS [MH]<sup>+</sup> 326.22193. HRMS: [MH]<sup>+</sup> calcd, 326.22269. 1H NMR (400 MHz, acetone-d<sub>6</sub>): δ 8.04 (br, 3H, NH), 7.98 (d, 2H, J = 8 Hz, CH<sub>2</sub>), 7.25 (d, 2H, J = 8 Hz, CH<sub>2</sub>), 6.50 (s, 1H, CH=CH=), 3.40 (br, NH), 2.63–2.60 (m, 2H, CH<sub>2</sub>−CH=−C−), 2.25 (q, 2H, J = 7.6 Hz, CH<sub>2</sub>−CH=−), 1.91 (s, 3H, CH−C−C−), 1.49–1.47 (m, 2H, CH<sub>2</sub>−CH=−C−), 1.08 (s, 6H, 2CH<sub>3</sub>), 1.04 (t, 3H, J = 7.6 Hz, CH<sub>2</sub>−CH=−). 13C NMR (100 MHz, acetone-d<sub>6</sub>): δ 173.13 (NH−CO−Ar), 160.62 (NH−C==NH), 147.94 (CH<sub>2</sub>−CH<sub>2</sub>−), 141.41 (2C<sub>q</sub>Ar), 141.14 (CH−C−C≡CH), 130.05 (2CH<sub>2</sub>), 129.32 (3CH<sub>2</sub>), 128.10 (CH−C−C), 122.30 (C<sub>q</sub>−CH≡C−C≡N), 39.68 (CH<sub>2</sub>−CH=−C=−), 36.46 (CH<sub>2</sub>−CH=−C=−), 28.02 (2CH<sub>3</sub>), 24.98 (CH−CH=−C=−), 23.39 (CH<sub>2</sub>−CH<sub>3</sub>), 15.48 (CH−C−C=), 15.17 (CH<sub>2</sub>−CH<sub>2</sub>−).

4.2.3. 1-(2,6,6-Trimethylcyclohex-1-yl) Ethanol (4). To a solution of β-cyclocitral (6.66 mg, 1 g) in 20 mL of anhydrous tetrahydrofuran (THF), methylmagnesium bromide (0.02 mmol, 384 mg) was added. The reaction was mixed overnight, and the reaction was monitored by TLC (eluent: EtOAc/light petroleum 1/6) and was completed, methanol was evaporated under reduced pressure; and the crude yellow solid was puriﬁed by silica gel chromatography (eluent EtOAc/light petroleum 0.2/9.8) to give a white solid in 77% yield.

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evaporated under vacuum, and the crude material was dissolved in 5 mL of water. The aqueous phase was extracted twice with ethyl acetate (20 mL each), dried under sodium sulfate, and concentrated in vacuum. Diene 12 was obtained in 36% yield after flash chromatography purification using EtOAc/light petroleum 0.2/9.8 as the eluent.

\[(\text{12}): \text{C}_{11}\text{H}_{18}. \ ESI \ [\text{MH}]^+ 151.29. \ 1^H \text{NMR (400 MHz, CDCl}_3\text{: }\delta 5.60 \text{ (m, 1H, } \text{CH} \equiv \text{C}_q \text{-CH}_3), 5.53 \text{ (q, 1H, } J = 7.5 \text{ Hz, } \text{CH}_2 \equiv \text{CH}_2), 2.15 \text{ (m, 2H, } \text{CH}_2 \equiv \text{CH}_2), 1.95 \text{ (d, 3H, } J = 7.2 \text{ Hz, } \text{CH} \equiv \text{C}_q \text{-CH}_3), 1.79 \text{ (s, 3H, } \text{CH}_3 \equiv \text{C}_q \text{-CH}, 1.20 \text{ (s, 6H, } 2\text{CH}_3), 2.45 \text{ (t, } 2\text{H, } J = 12.2 \text{ Hz, } \text{CH}_2 \equiv \text{CH}_2), 1.95 \text{ (d, 3H, } J = 7.2 \text{ Hz, } \text{CH} \equiv \text{C}_q \text{-CH}_3), 1.79 \text{ (s, 3H, } \text{CH}_3 \equiv \text{C}_q \text{-CH}), 1.20 \text{ (s, 6H, } 2\text{CH}_3), 2.45 \text{ (t, } 2\text{H, } J = 12.2 \text{ Hz, } \text{CH}_2 \equiv \text{CH}_2)\]

**ASSOCIATED CONTENT**

* Supporting Information
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Representative experimental procedure and monodimensional and bidimensional NMR and HRMS spectra (PDF)

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**Notes**

The authors declare no competing financial interest.

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