Dynamic $^1$H NMR Study Around the Carbon–Carbon Double Bonds and Carbon–Carbon Single Bonds in a Particular Phosphorous Ylide and 2,5-Dihydro-5,5-Diaryl-2-Thio-1H-Imidazoles

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Abstract

Stable crystalline phosphorus ylides are obtained in excellent yields from the 1:1:1 addition reaction between hydantoins or thiohydantoins and dialkyl acetylenedicarboxylates in the presence of triphenylphosphine. These phosphoranes undergo smooth intramolecular Wittig reaction followed by an electrocyclic ring opening to produce dialkyl (E)-2-(2,5-dihydro-5,5-diaryl-2-thioxo-1H-imidazol-4-yl)fumarates and 2,5-Dihydro-5,5-diaryl-2-thio-1H-imidazoles in good yields. Dynamic effects were observed in the $^1$H NMR spectra of these compounds and were attributed to restricted rotation around the Carbon–Carbon single bonds. Rotational energy barrier (ΔG°) for their interconversion process of rotational isomers equals to (68.2 and 71.7) ± 2 kJ mol$^{-1}$.

Keywords: Dynamic $^1$H NMR; Acetylenic ester; Restricted rotation; Triphenylphosphine

1. Introduction

Hydantoins and thiohydantoins display a wide range of biological properties, including anticonvulsant [1], antidepressent [2], anti-inflammatory [3], antiviral [4], antitumor [5], and platelet-inhibitory activities [6], and are a conspicuous structural feature of several inhibitors of reductase [7]. As part of our study on the development of new routes to heterocyclic and carbocyclic systems [8-10], we now report on the chemoselective synthesis of functionalized 2,5-dihydro-2-oxo-5,5-diaryl-1H-imidazoles 4. Thus, the reaction of hydantoins 2 and activated acetylenes 1 in the presence of triphenylphosphine $(\text{Ph}_3\text{P})$ leads to phosphoranes 3, which undergo intramolecular Wittig reaction in boiling toluene to produce 4 in good yields. Synthesis of 6 and 7 has been reported previously [10]. Some of these compounds exhibited dynamic $^1$H NMR effect that affords good information regarding the interchangeable process of rotational isomers that provide important kinetic data (Scheme 1).

2. Experimental

Acetylenic esters and triphenylphosphine were obtained from Fluka and were used without further purification. 5,5-diarylthiohydantoin
was prepared by known methods [15-16]. Melting points (uncorrected) were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, N and S were performed using a Heraeus CHN-O-Rapid analyzer. The experimental data were in good agreement with the calculated values. 1H and 13C NMR spectra (CDCl3) were measured with a Bruker DRX-500 Avance spectrometer. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Chromatography columns were prepared from Aldrich silica gel 70-230 mesh.

General procedure for the preparation of phosphorus ylides 3
To a magnetically stirred solution of 0.504 g 1 (2mmol) and 0.284 g dimethyl acetylene dicarboxylate (2mmol) in 5 cm3 ethyl acetate was added dropwise a solution of 0.524 g triphenylphosphine (2mmol) in 2 cm3 ethylacetate or ethylacetate at 5°C over 10min. After 6 h stirring at room temperature, the product was filtered and washed with cold ethyl acetate.

Dimethyl-2-(5,5-diphenylimidazolidine-2,4-dione)-3-(triphenylphosphanylidenesuccinate (3a)
Yellow powder; mp: 174-176°C; yield: 1.13 g (86%). IR (KBr) (ν max/cm−1): 3425 (NH), 1765 and 1703 (C=O). 1H NMR (300 MHz, CDCl3): δ = 3.14 (3 H, s, MeO), 3.85 (3 H, s, MeO), 4.58 (1 H, d, 3JPC = 15.3, CH), 7.28–7.72 (25 H, m, 5 C6H5), 8.45 (1 H, s, NH) ppm; 13C NMR (75 MHz, CDCl3): δ = 37.1 (d, 1JPC = 130, P=C), 49.5 (MeO), 53.1 (MeO), 56.5 (d, 2JPC = 17, CH), 71.0 (C), 126.5 (d, 1JPC = 93, P–Cipso), 127.4 (CH), 128.3 (CH), 129.2 (d, 1JPC = 12, Cmeta), 129.4 (CH), 132.3 (d, 1JPC = 2, Cpara), 134.1 (d, 2JPC = 11, Cortho), 139.2 (Cipso), 168.7 (C=O), 170.1 (d, 2JPC = 14.8, PC=C), 172.7 (C=O), 178.7 (C=O) ppm.

General procedure for conversion of 3 to 4
A mixture of 0.788 g 3a (1.2mmol) in 30 cm3 toluene was refluxed for 48 h. The solvent was removed under reduced pressure and the yellowish oil was separated from triphenylphosphine oxide using cold ethylacetate. The solvent was removed and the product residue was separated by silica column chromatography (Merck 230 - 400 mesh) using hexane-ethyl acetate as eluent.

Dimethyl (E)-2-(2,5-dihydro-2-thioxo-5,5-di-p-toly-1H-imidazol-4-yl)fumarate (7c)
Colorless crystals; mp:151-153°C; yield: 0.36 g (71%). IR (KBr) (ν max/cm−1): 3468 (NH), 1765 and 1703 (C=O). 1H NMR (300 MHz, CDCl3): δ = 2.38 (3 H, s, Me), 2.39 (3 H, s, Me), 3.54 (3 H, s, MeO), 3.85 (3 H, s, MeO), 7.21 (1 H, s, CH), 7.15-7.41 (8 H, m, CH), 7.83 (1 H, s, NH). 13C NMR (75 MHz, CDCl3): δ = 21.5 (Me), 21.6 (Me), 52.7 (MeO), 53.9 (MeO), 74.0 (C), 127.1 (2 CH), 127.7 (2 CH), 130.0 (2 CH), 130.1 (2 CH), 130.9(CH), 132.5 (C), 134.5(C), 135.7(C), 137.7(C), 137.8(C), 162.3 (OC=O), 162.9 (OC=O), 171.8 (C=N), 180.3 (C=S).

3.Results and Discussion
The reaction of hydantoin 1 or thiohydantoin 5 with dialkyl acetylenedicarboxylates 1 in the presence of triphenylphosphine proceeded at room temperature in ethylacetate, and was complete within a few hours. 1H and 13C NMR spectra of the crude products clearly indicated the formation of stable phosphorus ylides 3 and 6 (Scheme 1). No other products than 3 and 6 could be detected. The structures of compounds 3 and 6 were deduced from their elemental analyses and IR, 1H and 13C NMR spectra. The mass spectra of these stable ylides
displayed molecular ion peaks at appropriate m/z values. Any initial fragmentation involves loss from, or complete loss of the side chains and scission of the heterocyclic ring system.

On the basis of the well established chemistry of trivalent phosphorus nucleophiles [11–13], it is reasonable to assume that phosphorus ylides 3 and 6 result from the initial addition of triphenylphosphine to the acetylenic ester and subsequent protonation of the 1:1 adduct followed by attack of the nitrogen atom of the anion of the NH-acid to the vinylphosphonium cations to generate ylides 3 and 6. 1H and 13C NMR spectra of the ylides 3 and 6 are consistent with the presence of two diastereoisomers (Scheme 2). Phosphorus ylides 3 and 6 undergo a smooth reaction in boiling toluene to produce triphenylphosphine oxide and di-alkyl 2-(2,5-dihydro-2-oxo-5,5-diaryl-1H-imidazol-4-yl)fumarate 4 and 2,5-Dihydro-5,5-diaryl-2-thio-1H-imidazoles 7 (Scheme 1).

Structure 4 was assigned to the isolated products on the basis of their elemental analyses and IR, 1H, and 13C NMR and mass spectral data. Thus, the 1H NMR spectrum of each of the isolated products exhibited a C=CH proton signal at about 7.1–7.3 ppm, which is in agreement with the (E) configuration [14] for the vinyl moiety in 4 and 7. Further evidence was obtained from the 13C NMR spectra, which displayed C=CH carbon resonances at about 129–131 ppm. The mechanism of formation of 4 and 7 has been reported previously [10].

The 1H NMR spectra of 3 and 6 are consistent with the presence of two isomers. The methoxy region of 3a and 6a in CDCl3 at ambient temperature (25°C) exhibits two sharp singlets for the CO2CH3 groups of (E) and (Z) isomers and two fairly broad singlets for the OCH3 groups. Near 10°C the broad lines become sharper. The 1H NMR of 3a in 1,2-dichlorobenzene at 10°C is similar to that measured in CDCl3 (Table 2). Increasing the temperature, results in coalescence of the OCH3 resonances. At 90°C, a relatively broad singlet was observed for the OCH3 group, while the CO2CH3 protons appear as a sharp single resonance.

The 1H and 13C NMR spectra of compounds 7 show two different aryl groups, and the 1H NMR spectra of compounds 7b and 7d exhibit characteristic (AB)X3 patterns for the diastereotopic methylene protons (Scheme 1).

Scheme 1. Synthesis of compounds 3, 4, 6 and 7 involving two possible dynamic 1H NMR effects around carbon–carbon double bonds and carbon–carbon single bonds.

Scheme 2. Two rotational interchangeable processes of two isomers (Z and E) for ylide 3 involving a hydantoin.
Table 1. Selected proton chemical shifts (at 300.1 MHz, TMS) and activation parameters of 3a in 1,2-dichlorobenzene, for rotation around the carbon–carbon double bond.

<table>
<thead>
<tr>
<th>Tc (K)</th>
<th>Resonance (P-C=CH2) δ (ppm)</th>
<th>Δν (Hz)</th>
<th>ΔG# (kJ/mol)</th>
<th>k_c (s⁻¹)</th>
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<tr>
<td>343</td>
<td>3.14</td>
<td>3.57</td>
<td>129</td>
<td>68.2±2</td>
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<td>3.36</td>
<td></td>
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\[ \Delta G^\ddagger = 4.57 T_c \left[ 9.97 + \log \frac{T_c}{\Delta v} \right] \]

\[ K_c = \frac{\pi \Delta v}{\sqrt{2}} \]

The Ar-CH₃ region of the ¹H NMR spectrum of 7d in CDCl₃, at ambient temperature (25°C) exhibits two sharp singlets for the Ar-CH₃ groups. The ¹H NMR of 7c in 1,2-dichlorobenzene at 25°C is similar to that measured in CDCl₃. Increasing the temperature results in coalescence of the Ar-CH₃ resonances. At 90°C, a relatively broad singlet was observed for the Ar-CH₃ groups. This dynamic NMR effect is attributed to restricted rotation around the single bond attaching the vinyl substituent to the 2-thio-1H-imidazole ring.

The variable temperature spectra are sufficient to calculate the free energy barrier as well as enthalpy and entropy of activation for the restricted C–C bond rotation. From the coalescence of the methine protons and using the expression \( k = \frac{\pi \Delta v}{1.42} \), the first-order rate constants (k) were calculated. Application of the absolute rate theory with a transmission coefficient of 7c gives a free energy of activation \( \Delta G^\ddagger \) of 71.7±2 kJ mol⁻¹ for 7c, where all known sources of errors are estimated and included [1-5].

In conclusion, the present method features the advantages that the reaction can be performed under neutral conditions and the starting materials and reagents can be mixed without any activation or modification. Phosphorus ylides 3a–3d can be considered as potentially useful synthetic intermediates. It is reasonable to assume that intermediates 3 result from the initial addition of triphenylphosphine to the acetylenic esters and subsequent protonation of the 1:1 adduct followed by attack of the nitrogen atom of the anion of the NH-acidic compound to the vinylphosphonium cation to produce phosphorane 3.

Table 2. Selected proton chemical shifts (at 300.1 MHz, TMS) and activation parameters of 4c, in CDCl₃, for rotation around the carbon–carbon single bond

<table>
<thead>
<tr>
<th>Tc (K)</th>
<th>δ (ppm)</th>
<th>Δν (Hz)</th>
<th>ΔG# (kJ/mol)</th>
<th>k_c (s⁻¹)</th>
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<td>363</td>
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<td>44.43</td>
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References