Islamic Azad University
Marvdasht Branch

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

Mohammad Mehdi Ghanbari [a], * and Zahra Sharafi [b]

[a] Department of Chemistry, Sarvestan Branch, Islamic Azad University, Sarvestan, Iran
[b] Department of Chemistry, Marvdasht Branch, Islamic Azad University, Marvdasht, Iran

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-1*H*-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 ($\Delta G^{\#}$) for their interconversion process of rotational isomers equals to (68.2 and 71.7) $\pm$ 2 kJ mol^{-1}.

1. Introduction

Hydantoins and thiohydantoins display a wide range of biological properties, including anticonvulsant [1], antidepressant [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-imidazols **4**. Thus, the reaction of

hydantoins **2** and activated acetylenes **1** in the presence of triphenylphosphine (Ph$_3$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-diarylhiohydantoin

 *Corresponding author
E-mail address: M.Mehdi.Ghanbari@Gmail.com

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. ^{1}H and ^{13}C NMR spectra (CDCl$_3$) 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 cm^3 ethylacetate was added dropwise a solution of 0.524 g triphenylphosphine (2mmol) in 2 cm^3 ethylacetate or ethylacetate at 5^{0}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-(triphenylphosphanylidene)succinate (3a)

Yellow powder; mp: 174-176°C; yield: 1.13 g (86%). IR (KBr) (v_{max}/cm^{-1}): 3425 (NH), 1723 (C=O), 1437 (C=C). EIMS: *m/z* (%). 657 (M$^+$, 2), 405 (32), 251 (16), 262 (100), 166 (75), 77 (23), 59 (8). Major isomer (*Z*)-**3a** (53%); ^{1}H NMR (300 MHz, CDCl$_3$): δ = 3.14 (3 H, s, MeO), 3.83 (3 H, s, MeO), 4.58 (1 H, d, $^3J_{PC}$ = 15.3, CH), 7.28–7.72 (25 H, m, 5 C$_6$H$_5$), 8.45 (1 H, s, NH) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ = 37.1 (d, $^1J_{PC}$ = 130, P=C), 49.5 (MeO), 50.4 (MeO), 57.0 (d, $^2J_{PC}$ = 17, CH), 71.0 (C), 127.3 (d, $^1J_{PC}$ = 91, P–C$_{ipso}$), 127.4 (CH) 128.2 (CH), 128.9 (d, $^3J_{PC}$ =12, C$_{meta}$), 129.4 (CH), 132.1 (d, $^4J_{PC}$ = 2, C$_{para}$), 134.0 (d, $^2J_{PC}$ = 11, C$_{ortho}$), 139.1 (C$_{ipso}$), 168.6 (C=O), 170.1 (d, $^2J_{pc}$ = 14, PC=C), 172.7 (C=O), 178.7 [C=O] ppm; Minor isomer (*E*)-**3a** (47%); ^{1}H NMR (300 MHz, CDCl$_3$): δ = 3.57 (H, s, MeO), 3.77 (H, s, MeO), 4.62 (1 H, d, $^3J_{pc}$ = 16.6, CH), 7.28–7.72 (25 H, m, 5 C$_6$H$_5$), 8.45 (1 H, s, NH) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ = 38.5 (d, $^1J_{PC}$ = 140, P–C),

49.5 (MeO), 53.1 (MeO), 56.5 (d, $^2J_{PC}$ = 17, CH), 71.0 (C), 126.5 (d, $^1J_{PC}$ = 93, P–C$_{ipso}$), 127.4 (CH), 128.3 (CH), 129.2 (d, $^3J_{PC}$ = 12, C$_{meta}$), 129.4 (CH), 132.3 (d, $^4J_{PC}$ = 2, C$_{para}$), 134.1 (d, $^2J_{PC}$ = 11, C$_{ortho}$), 139.2 (C$_{ipso}$), 168.7 (C=O), 170.1 (d, $^2J_{PC}$ = 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 cm^3 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*-tolyl-1*H*-imidazol-4-yl)fumarate (7c)

Colorless crystals; mp:151-153°C; yield: 0.36 g (71%). IR (KBr) (v_{max}/cm^{-1}): 3468 (NH), 1765 and 1703 (C=O). ^{1}H NMR (300 MHz, CDCl$_3$): 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). ^{13}C NMR (75 MHz, CDCl$_3$): 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. ^{1}H and ^{13}C 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, ^{1}H and ^{13}C NMR spectra. The mass spectra of these stable ylides
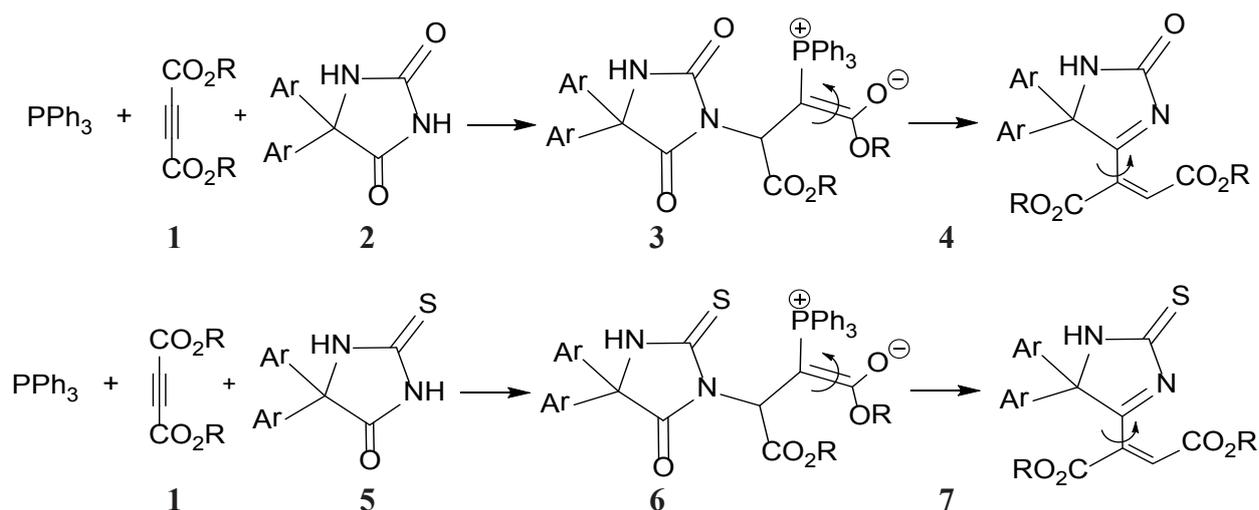
Scheme 1. Synthesis of compounds **3**, **4**, **6** and **7** involving two possible dynamic ¹H NMR effects around carbon–carbon double bonds and carbon–carbon single bonds.

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 consisted 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 dialkyl 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=C*H* 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 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.

Tc (K)	Resonance (P–C–CO$_2$CH$_3$) ppm	Δv (Hz)	$\Delta G\#$ (kJ/mol)	k_c (s^{-1})
343	3.14	3.57	129	68.2±2	286
	3.36			

$$\Delta G^{\mp} = 4.57\,T_C\left[9.97 + \log\frac{T_C}{\Delta v}\right] \qquad K_C = \frac{\pi\Delta v}{\sqrt{2}}$$

The Ar-CH$_3$ region of the ^{1}H NMR spectrum of **7d** in CDCl$_3$ at ambient temperature (25°C) exhibits two sharp singlets for the Ar-CH$_3$ groups. The ^{1}H NMR of **7c** in 1,2-dichlorobenzene at 25°C is similar to that measured in CDCl$_3$. Increasing the temperature results in coalescence of the Ar-CH$_3$ 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 = $\pi\Delta v$/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 ($\Delta G^{\neq}$) of 71.7 ± 2 kJ mol^{-1} 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 CDCl$_3$, for rotation around the carbon–carbon single bond

Tc (K)	δ (ppm)	Δv (Hz)	$\Delta G^{\#}$ (kJ/mol)	k_c (s^{-1})
363	3.98, 4.12	20	71.7±2	44.43

References

[1] N. Mehta, C.A. Risiger, F.E. Soroko, *J. Med. Chem.*, 24 (1981) 465.

[2] F.L. Wessels, T.J. Schwan, S.F. Pong, *J. Pharm. Sci.*, 69, (1980) 1109.

[3] B.M. Nilsson, H.M. Vargas, U. Hacksell, *J. Med. Chem.*, 25 (1992) 3270.

[4] A.A. El-Barbary, A.I. Khodair, E.B. Pedersen, C. Nielsen, *J. Med. Chem.*, 37(1994) 73.

[5] A.M. Al-Obaid, H.I. El-Subagh, A.I. Khodair, M.M.A. Elmazar, *Anti-Cancer Drugs.*, **7** (1980) 873.

[6] A.G. Caldwell, C.J. Harris, R. Stepney, N. Wittaker, *J. Chem. Soc. Perkin Trans.*, 1 (1980) 495.

[7] A.I. Khodair, P. Bertrand, Tetrahedron, 54 (1998) 4859.

[8] I. Yavari, N. Zabarjad-Shiraz, *Monats. Chem.*, 134, (2003) 445.

[9] I. Yavari, M.M. Ghanbari, J. Azizian, F. Sheikholeslami, *J. Chem. Res.*, (2011) 87.

[10] I.Yavari, M.M. Ghanbari, A.S. Shahvelayati and M. Ghazvini, *Phosphorus, Sulfur, Silicon, Relat. Elem.* 185 (2010) 2551.

[11] E. Zbiral, *Synthesis,* (1974) 775.

[12] K.C. Nicolaou, M.W. Harter, J.L Gunzner, A. Nadin Liebigs Ann.*, (1997) 1283.

[13] K.B. Becker, *Tetrahedron,* 36 (1980) 1717.

[14] E.L Eliel, S.H Wilen, Stereochemistry of Organic Compounds., Wiley, New York, 1994, pp 569–573.

[15] J. Safari, H. Naeimi, M.M Ghanbari, O. Sabzi-Fini, *Russ. J. Org. Chem.*, 45 (2009) 477.

[16] A.R. Butler, J. Broan, *J. C. S. Perkin II.* (1989) 731.