

Synthesis and X-ray Crystal Structure of Hydantoin Derivatives

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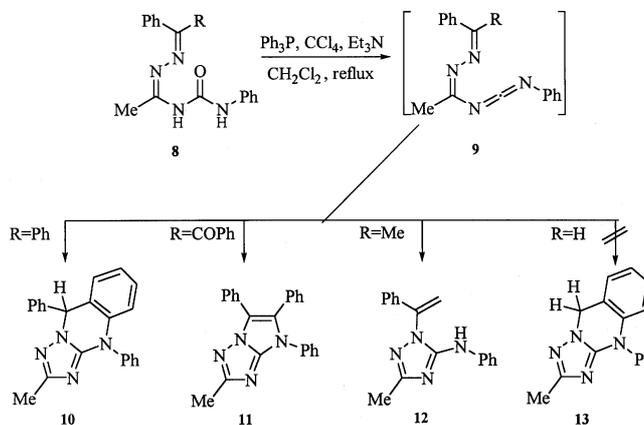
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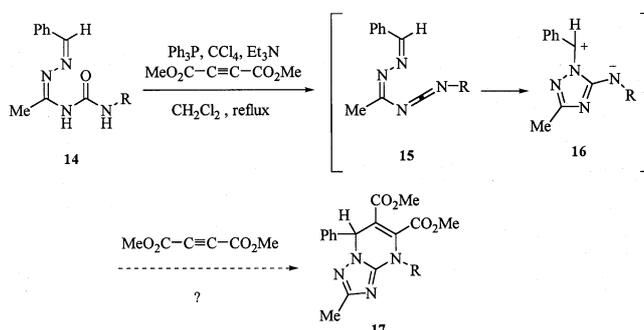
Aldehyde and ketone azines **1** (2,3-diazabutadienes) react with the olefins to yield perhydropyrazolo[1,2-a]pyrazoles **3**, a reaction known as "criss-cross" cycloaddition.¹ Analogous reactivity has been observed with acetylenes,^{2,3} leading to 1,5-dihydropyrazolo[1,2-a]pyrazoles **4**. The intermediacy of azomethinimine 1,3-dipole **2** has been confirmed by the isolation and characterization⁴ in the reaction of hexafluoroacetone azine with isobutylene (Scheme 1).

Also, Schweizer and co-workers reported that the thermal rearrangements of unsaturated azines **5** with cumulated double bonds in conjugation with the azine moiety have been shown⁵⁻¹² to provide excellent syntheses for a variety of pyrazolo fused heterocyclic compounds **7** (Scheme 2). We recently described a new route to 1,2,4-triazolo fused heterocycles such as 5,10-dihydro-1,2,4-triazolo[5,1-*b*]quinazolines **10**,¹³ 7*H*-imidazo[1,2-*b*][1,2,4]triazoles **11**¹⁴ and monocyclic *N*- α -styryl-5-(phenylamino)-1,2,4-triazoles **12**¹⁵ involving thermal rearrangement of azinocarbodiimides **9** obtained from the corresponding ureas **8** using Appel's dehydration method ($\text{Ph}_3\text{P}/\text{CCl}_4/\text{Et}_3\text{N}$)¹⁶ (Scheme 3). However, in the case of the reaction of benzaldehyde 1-ureidoethylidenehydrazone with Appel's reagent was unsuccessful. We presume that although the azinocarbodiimide intermediate was formed, the thermal rearrangement of **9** to give **13** did not occur, but decomposed under the reaction conditions.

It occurred to us that intermolecular cycloaddition reaction might be observed in the reaction of intermediacy azomethinimine **16** with a dipolarophile such as dimethyl acetylene



Scheme 3

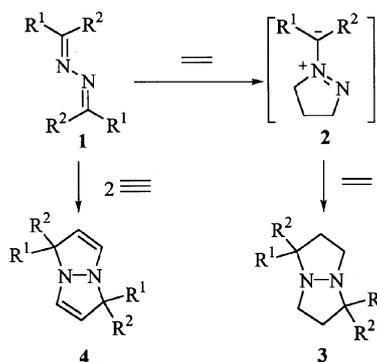


Scheme 4

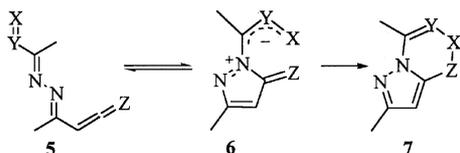
dicarboxylate (DMAD) generating bicyclic heterocycles **17**. To establish the feasibility of this reaction concept, we have chosen to study the thermal reaction of known benzaldehyde 1-ureidoethylidenehydrazones **14**¹⁵ with DMAD under the Appels conditions.

Experimental Section

All reagents and solvents were reagent grade or were purified by standard methods before use and the reactions were routinely carried out under an inert atmosphere. Silica gel 60 (70-230 mesh ASTM) used for column chromatography was supplied by E. Merck. Analytical thin layer chromatography (tlc) was performed on silica gel with fluorescent indicator coated on aluminium sheets. Melting points were taken using an Electrothermal melting point apparatus and are uncorrected. The ^1H NMR spectra were measured on a Gemini 300 spectrometer. All chemical shifts are reported in parts per million (δ) relative to tetramethylsilane. The benzaldehyde 1-ureidoethylidenehydrazones (**14**) were prepared following the literature.¹⁵



Scheme 1



Scheme 2

Table 1. Hydantoin Derivatives **20** Prepared

Compound	R	Yield ^a (%)	Mp (°C)	¹ H NMR (CDCl ₃) δ, J _{PH} (Hz)				
				CH ₃ ^b	CH ^c	Aromatic+N=CH ^d	others	Ratio ^e
20a	C ₆ H ₅	26	199-201	2.78, 3.59	4.76 (J=21.6)	7.27-7.86		1/0.9
20a'				2.74, 3.05	4.72 (J=20.6)			
20b	4-ClC ₆ H ₄	30	194-196	2.72, 3.56	4.76 (J=20.9)	7.31-7.84		1/1.4
20b'				2.76, 3.04	4.71 (J=20.0)			
20c	4-CF ₃ C ₆ H ₄	36	198-200	2.73, 3.57	4.79 (J=20.9)	7.32-7.85		1/1.5
20c'				2.77, 3.05	4.75 (J=19.8)			
20d	CH ₃	16	200-202	2.70, 3.49	4.60 (J=21.6)	7.27-7.84	3.10 (NCH ₃)	1/1.6
20d'				2.75, 3.03	4.55 (J=20.7)		3.13 (NCH ₃)	

^a Yield of pure isolated product. ^b All singlets. ^c Doublets and values may be reversed. ^d Values are both isomers. CH proton was not resolved separately. ^e Ratios based on 300 MHz ¹H NMR of methoxy proton.

Synthesis of Hydantoin Derivatives 20; General Procedure. To a stirred suspension of the urea **14** (3.0 mmol) in dichloromethane (50 mL) was added triphenylphosphine (1.18 g, 4.5 mmol), carbon tetrachloride (1.16 mL, 12 mmol), triethylamine (0.63 mL, 4.5 mmol), and DMAD (0.43 g, 3.0 mmol) and the mixture was heated to reflux temperature for 24 h. After cooling to room temperature the reaction mixture was partitioned between water and dichloromethane (20 mL × 2), and combined each other, and the solvent was removed after drying over magnesium sulfate. The residue was chromatographed on silica gel column and eluted with hexane - ethyl acetate 3 : 1 to give **20** as a white solid after crystallization from ether (Table 1).

X-ray Structure Analysis of 20b. A white crystal of C₃₉H₃₂ClN₄O₄P is monoclinic, space group P2₁/n with a = 12.699 (2) Å, b = 14.204 (1) Å, c = 19.676 (2) Å, β = 100.660 (10), and Z = 4. Single X-ray diffraction data was collected on Bruker P4 four-circle diffractometer using Mo-Kα radiation. The solution of structure was carried out by a combination of heavy atom Patterson techniques, direct methods, and Fourier techniques. The refinement of the structure by full matrix least squares methods was based on 4549 unique reflections (2θ = 45, I > 2σ). Anisotropic temperature factors were used for all non-hydrogen atoms. At the current stage of refinement on 498 parameters with all atoms present in the asymmetric units, R = 0.0389, wR = 0.0950. The data processing and refinement parameters are listed in Table 2. Bond distances and angles are presented in Table 3.

Results and Discussion

The starting compounds, benzaldehyde 1-ureidoethylidenehydrazones **14** were obtained by the reaction of acetamidrazone hydrochloride with benzaldehyde, followed by the treatment with isocyanates.¹⁵ When the reaction of ureas **14** with triphenylphosphine, carbon tetrachloride, triethylamine, and DMAD in dichloromethane was heated at reflux temperature for 24 h, the reaction mixture turned brown solution and thin layer chromatography showed the disappearance of **14** and the formation of a number of very small products. Attempts to separate these complex mixtures resulted only in the isolation of unexpected hydantoin derivatives **20**¹⁷ and

Table 2. Crystal Data and Structure Refinement for Hydantoin Derivatives **20b**

Empirical formula	C ₃₉ H ₃₂ ClN ₄ O ₄ P
Formula weight	687.13
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal System	monoclinic
Space group	P2 ₁ /n (No.14)
Unit cell dimensions	a = 12.699(2) Å b = 14.204(1) Å c = 19.676(2) Å β = 100.66(1)°
Volume	3487.8(7) Å ³
Z	4
Density (calculated)	1.309 Mg / m ³
Absorption coefficient	0.202 mm ⁻¹
F(000)	1432
Theta range for data collection	1.77 to 22.51 deg.
Index ranges	-1 ≤ h ≤ 13, -1 ≤ k ≤ 15, -21 ≤ l ≤ 21
Refinement method	Full-matrix least-squares on F ²
Data / parameters	4549/498
Goodness-of-fit on F ²	1.038
Final R indices [I > 2σ (I)]	R = 0.0389, wR = 0.0950
Largest diff. peak and hole	0.234 and 0.266 e / Å ³

$R = \sum |F_o| - |F_c| / \sum |F_o|$, $wR = [\sum w(|F_o| - |F_c|)^2 / \sum w(F_o)^2]^{1/2}$, where $w = 1 / \sigma^2(F_o)$.

confirmed by an X-ray analysis of a single crystal of **20b**. An ORTEP diagram is shown in Figure 1.

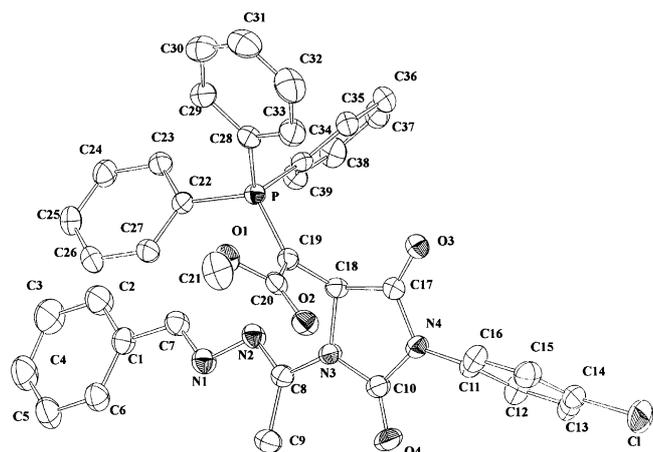
Interestingly, the ¹H NMR spectra showed a characteristic peak at δ = 2.70-2.74, δ = 2.75-2.78, δ = 3.03-3.05, and δ = 3.49-3.59 for the four kinds of methyl protons, and the C5-proton resonated in the δ = 4.55 to 4.75 region and δ = 4.60 to 4.76 region as two doublets (J_{PH} = 19.8-21.6 Hz). This fact suggests that the hydantoinylphosphoranones exist as keto (**20**) enol (**20'**) equilibrium mixture in CDCl₃ solution.

X-ray single crystal diffraction analysis also strongly suggests that the molecule has a keto-enol resonance in solid state structure. The O2-C20 and C19-C20 bond distances are 1.224 Å and 1.411 Å, respectively, which are the intermediate value between those of the single (1.43 Å for C-O and 1.54 Å for C-C) and double bond (1.20 Å for C=O and 1.34

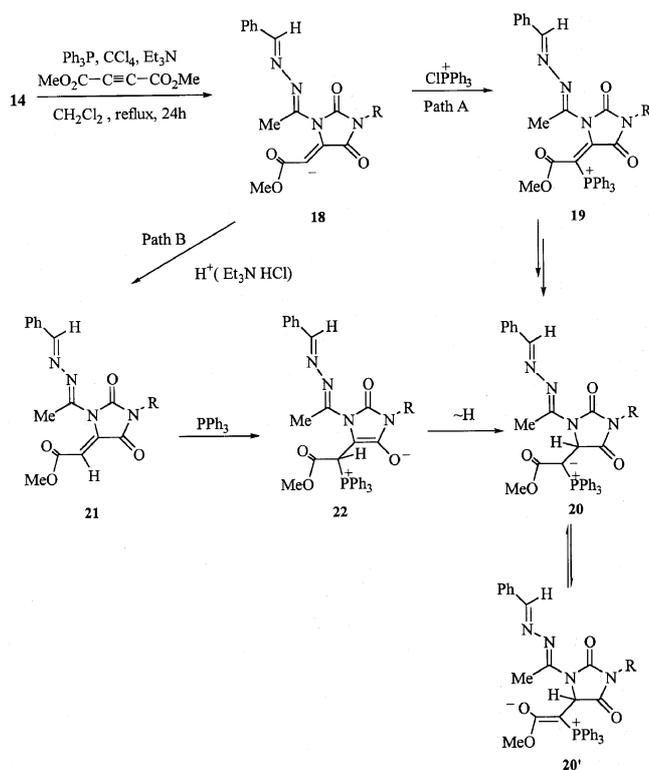
Table 3. Selected Bond lengths [Å] and angles [deg] for Hydantoin Derivatives **20b**

P-C(19)	1.720(2)	N(4)-C(10)	1.401(3)
P-C(22)	1.808(2)	N(4)-C(11)	1.428(3)
P-C(34)	1.809(2)	O(1)-C(20)	1.375(3)
P-C(28)	1.809(3)	O(1)-C(21)	1.426(4)
Cl-C(14)	1.733(3)	O(2)-C(20)	1.224(3)
N(1)-C(7)	1.258(3)	O(3)-C(17)	1.205(3)
N(1)-N(2)	1.413(3)	O(4)-C(10)	1.207(3)
N(2)-C(8)	1.281(3)	C(1)-C(7)	1.464(4)
N(3)-C(10)	1.367(3)	C(8)-C(9)	1.493(4)
N(3)-C(8)	1.396(3)	C(17)-C(18)	1.504(4)
N(3)-C(18)	1.490(3)	C(18)-C(19)	1.488(3)
N(4)-C(17)	1.383(3)	C(19)-C(20)	1.411(3)
C(19)-P-C(22)	116.25(11)	N(2)-C(8)-C(9)	126.8(3)
C(19)-P-C(34)	107.95(11)	N(3)-C(8)-C(9)	117.6(3)
C(22)-P-C(34)	107.43(11)	O(4)-C(10)-N(3)	129.0(2)
C(19)-P-C(28)	112.16(12)	O(4)-C(10)-N(4)	124.1(2)
C(22)-P-C(28)	106.64(11)	N(3)-C(10)-N(4)	107.0(2)
C(34)-P-C(28)	105.84(11)	O(3)-C(17)-N(4)	125.0(2)
C(7)-N(1)-N(2)	113.1(2)	O(3)-C(17)-C(18)	127.4(2)
C(8)-N(2)-N(1)	112.3(2)	N(4)-C(17)-C(18)	107.6(2)
C(10)-N(3)-C(8)	125.4(2)	C(19)-C(18)-N(3)	116.7(2)
C(10)-N(3)-C(18)	111.9(2)	C(19)-C(18)-C(17)	113.1(2)
C(8)-N(3)-C(18)	122.5(2)	N(3)-C(18)-C(17)	101.3(2)
C(17)-N(4)-C(10)	111.8(2)	C(20)-C(19)-C(18)	116.6(2)
C(17)-N(4)-C(11)	124.1(2)	C(20)-C(19)-P	122.4(2)
C(10)-N(4)-C(11)	123.5(2)	C(18)-C(19)-P	120.5(2)
C(20)-O(1)-C(21)	116.9(3)	O(2)-C(20)-O(1)	121.4(2)
N(1)-C(7)-C(1)	121.3(3)	O(2)-C(20)-C(19)	126.0(2)
N(2)-C(8)-N(3)	115.4(2)	O(1)-C(20)-C(19)	112.6(2)

Symmetry transformations used to generate equivalent atoms.

**Figure 1.** ORTEP diagram of hydantoin derivatives **20b**. Hydrogen atoms are omitted for clarity.

Å for C=C).¹⁸ The sum of bond angles around C20 (\angle O1-C20-C19 + \angle O2-C20-O1 + \angle O2-C20-C19) and C19 (\angle C18-C19-P + \angle C20-C19-P + \angle C20-C19-C18) are approximately 360° and the torsional angle between two planes composed of O1-C20-O2 and P-C19-C18 is 11.86°, which shows that two planes are nearly parallel. These indicate that

**Scheme 5**

the bonds between O2-C20 and C19-C20 have a partial sp^2 hybridization character, which, in turn, is an indication of keto-enol type resonance in the molecule.

The proposed mechanism for formation of **20** is shown in Scheme 5. Instead of the dehydration of ureas **14** under the Appel's conditions takes place, one of the NH bonds condenses with an ester group and the other adds to the triple bond of DMAD by Michael reaction. This can lead to carbanion **18**, then reacts with chlorotriphenylphosphonium ion to give phosphonium salt **19** which is converted to the phosphorane **20**. However, the transformation of **19** to **20** is uncertain. Another possible pathway is that carbanion **18** is converted to the 5-carbomethoxymethylidenehydantoin **21** and subsequent Michael reaction of triphenylphosphine gave **22**, followed by protonation, tautomerization, and deprotonation afford **20**.¹⁹

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