Chemistry of Heterocyclic Compounds, Vol. 32, No. 1, 1996

EFFECT OF ELECTRONIC FACTORS ON 1,3-DIPOLAR CYCLOADDITION OF 2,4,6-TRIAZIDOPYRIDINES TO *tert*-BUTYLPHOSPHAACETYLENE

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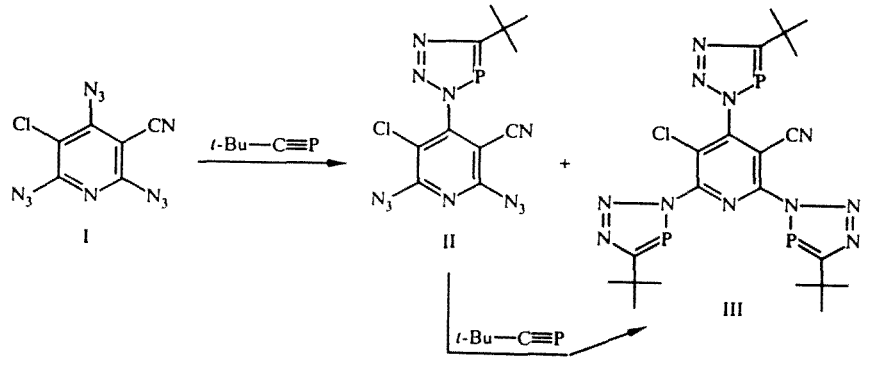
2,4,6-Triazido-3-chloro-5-cyanopyridine and 2,4,6-triazido-3,5-dicyanopyridine react with tert-*butylphosphaacetylene with formation of the corresponding 2,4,6-tris(3H-1,2,3,4-triazaphospholo)pyridines. The first step of both reactions is regioselective cycloaddition of the phosphaalkyne to the azido groups in the 4 position of the pyridine ring. The electronic properties of the substituents on the pyridine ring of the azidopyridines exert a significant effect both on the reactivity of the monoadduct intermediates and on the properties of the end products of 1,3-dipolar* tris-*cycloaddition.*

2,4,6-Triazidopyridines are of both theoretical and synthetic interest, but the chemistry of these compounds has remained practically unstudied. Recently we showed that 1,3-dipolar cycloaddition even of such a highly reactive dipolarophile as norbornene to 2,4,6-triazido-3-chloro-5-cyanopyridine (I) proceeds regioselectively, with formation of the aziridine cycloadduct only at the azido group in the 4 position of the pyridine ring [1,2]. The weakly expressed 1,3-dipolar properties of the α-azido groups of the azide I were explained by the strong conjugation of these groups with the pyridine system, which withdraws negative charge from the α nitrogen atoms of the azido groups [3]. However, the insufficiently high reactivity of norbornene in the reaction with azide I made it impossible to assess the role of electronic factors in reactions of 2,4,6-triazidopyridines with dipolarophiles. Therefore we were very interested in studying the reactions of 2,4,6-triazidopyridines with phosphaalkynes, as dipolarophiles having exceptionally high potential for cycloaddition [4,5].

The goal of this work was to study the reactions of 1,3-dipolar cycloaddition of *tert*-butylphosphaacetylene to 2,4,6-triazidopyridines I and V.

The reactions of triazidopyridines I and V with *tert*-butylphosphaacetylene were carried out in absolute ether under an argon atmosphere at a temperature of 0-25°C, using different ratios of the reactants. The reactions were monitored by ^{31}P NMR spectroscopy from the appearance of characteristic signals of phosphorus atoms in the +160 to 205 ppm region, indicating formation of triazaphosphole rings [4-6].



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0009-3122/96/3201-0059$15.00

TABLE 1. Some Characteristics of Compounds II, III, V-VII

Compound	Empirical formula	mp, °C	IR spectrum, ν, cm^{-1}		^{1}H NMR spectrum, $CDCl_3$, δ, ppm (J, Hz), $C(CH_3)_3$	^{31}P NMR spectrum, $CDCl_3$, δ, ppm	Yield, %
			N_3	C = N			
II	$C_{11}H_9ClN_{11}P$	182...182	2150	2230	1,47 d. ($^4J_{PH}$ = 1,4)	180, 32 (P(γ))	36
III	$C_{21}H_{27}ClN_{11}P_3$	118...119	—	2225	1,47 d. ($^4J_{PH}$ = 0,7), 1,45 d. ($^4J_{PH}$ = 1,4), 1,43 d. ($^4J_{PH}$ = 1,4)	181,15 (P(α)), 177,89 (P(α))	80
V	C_7N_{12}	120...121	2160, 2130, 2090	2230		—	90
						181,03 (P(γ))	75
VI	$C_{12}H_9N_{12}P$	176...177	2150	2225	1,59 d. ($^4J_{PH}$ = 1,6)	182,35 (P(γ)), 181,82 (P(α))	80
VII†	$C_{22}H_{27}N_{12}P_3$	202...203	—	2225	1,59 d. ($^4J_{PH}$ = 1,7), 1,57 d. ($^4J_{PH}$ = 1,7), 1,56 d. ($^4J_{PH}$ = 1,6)	179,74 (P(α)), 179,20 (P(α)), 177,60 (P(γ)), 176,95 (P(γ))	—

*Decomposition temperature.

†H NMR spectrum of compound VII at 60°C.

Addition of one equivalent of *tert*-butylphosphaacetylene to an ether solution of triazidopyridine I at 0°C led to formation of two compounds which, according to PMR, ^{13}C and ^{31}P NMR, IR, and elemental analysis, corresponded to the monoadduct II and the *tris*-adduct III. Analysis of the reaction mixture by PMR showed that the ratio of these compounds was 3:1.

The characteristic position of the signals from phosphorus atoms in the ^{31}P NMR spectra (Table 1) of compounds II (+180.32 ppm) and III (+181.15 and +177.89 ppm) is convincing evidence that 1,3-dipolar cycloaddition of *tert*-butylphosphaacetylene to all three azido groups of compound I proceeds regioselectively with formation of bonds between the phosphorus atoms and the α-nitrogen atoms of the azido groups, which leads to formation of 3H-1,2,3,4-triazaphosphole rings [4-6]. An interesting feature in the ^{31}P NMR spectrum of compound III is the equivalence of the phosphorus atoms of the two triazaphosphole rings in the α-positions of the pyridine ring, appearing as a single signal at 181.15 ppm whose intensity is four times greater than the intensity of the signal from the phosphorus atom of the γ-triazaphosphole ring at 177.89 ppm. At the same time, in the ^{13}C NMR spectrum of compound III (Table 2), the ring carbon atoms of the two α-triazaphosphole rings prove to be nonequivalent, as a result of which the spectrum contains three signals from the $C_{(5)}$ atoms of the three triazaphosphole rings at 200.57, 200.07, and 199.56 ppm with characteristic spin–spin coupling constants for these rings of $^1J_{PC}$ = 57.6, 59.3, and 57.7 Hz respectively. The three *tert*-butyl groups of compound III give two sets of signals in the ^{13}C NMR spectrum: three signals at 35.71, 35.65, and 35.56 ppm with $^2J_{PC}$ = 11.7-15.3 Hz correspond to quaternary carbon atoms, and the other three signals at 31.30, 31.16, and 31.08 ppm with $^3J_{PC}$ = 7.6-9.3 Hz belong to the carbon atoms of the methyl groups of the three different *tert*-butyl moieties. Similarly, in the ^{1}H NMR spectrum of compound III (Table 1), the protons of the three different *tert*-butyl groups appear as three doublets of identical intensity at 1.47, 1.45, and 1.43 ppm with $^4J_{PH}$ = 0.7, 1.4, and 1.4 Hz respectively.

In the case of formation of compound II, support for the idea that 1,3-dipolar cycloaddition of *tert*-butylphosphaacetylene occurs at the azido group in the 4 position of the pyridine ring of the starting triazidopyridine I is found in the ^{31}C NMR spectrum of compound II, from the characteristic splitting of the signal from the $C_{(4)}$ atom of the pyridine ring at 149.81 ppm with $^2J_{PC}$ = 7.9 Hz, due to spin–spin coupling of this atom with the phosphorus atom of the triazaphosphole ring. Similar spin–spin coupling between the phosphorus atoms of the triazaphosphole rings and the carbon atoms in the 2, 4, and 6 positions of the pyridine ring is observed in the ^{13}C NMR spectrum of the *tris*-adduct III (Table 2). We also must note that the positions of the signals from the rest of the carbon atoms of the pyridine ring of the monoadduct II are quite consistent with the ^{13}C NMR data for other previously studied 2,6-diazidopyridines [1-3].

TABLE 2. Parameters of ^{13}C NMR Spectra, $CDCl_3$, δ, ppm (J, Hz) of Compounds II, III, and V-VII

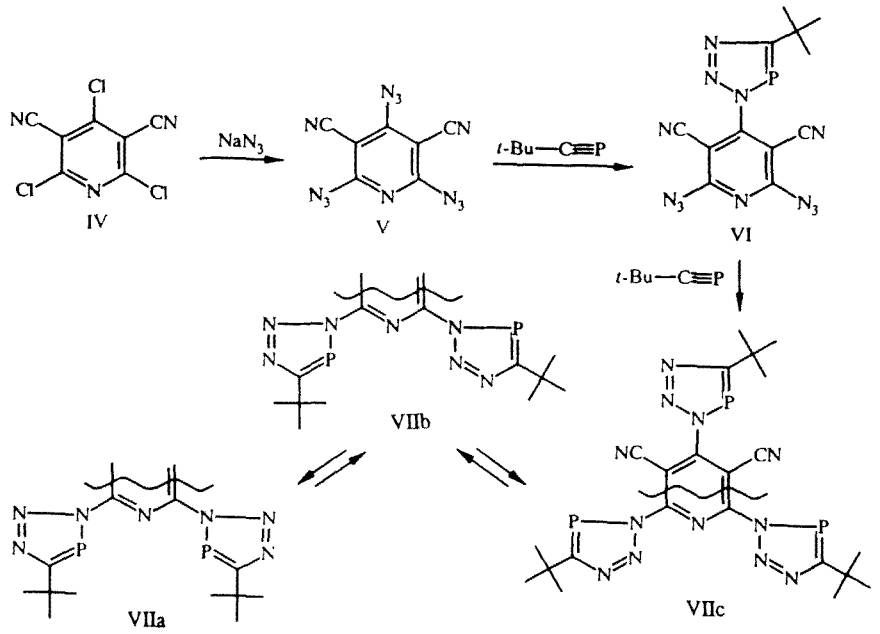
Compound	$C_{(5')}$	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	C ≡ N	$C(CH_3)_3$	$C(CH_3)_3$
II	199,57 d $^1J_{PC}$ = 59,2	154,96 s	112,63 s	149,81 d $^2J_{PC}$ = 7.9	94,12 s	154,65 s	110,25 s	35,51 d $^2J_{PC}$ = 15,0	31,15 d $^3J_{PC}$ = 8,2
III	200,57 d $^1J_{PC}$ = 57,6, 200,07 d $^1J_{PC}$ = 59,3, 199,56 d $^1J_{PC}$ = 57,7	153,74 d ^2J = 7,6	122,37 s	149,90 d $^2J_{PC}$ = 9,3	101,49 s	150,90 d $^2J_{PC}$ = 9,3	110,47 s	35,71 d $^2J_{PC}$ = 15,3, 35,65 d $^2J_{PC}$ = 14,4 35,56 d $^2J_{PC}$ = 11,7	31,30 d $^3J_{PC}$ = 7,6, 31,16 d $^3J_{PC}$ = 8,5, 31,08 d $^3J_{PC}$ = 9,3
V	–	159,97	86,92	155,17	86,92	159,97	109,67	–	–
VI	200,28 d $^1J_{PC}$ = 59,3	160,00 s	91,96 s	154,84 d $^2J_{PC}$ = 8,2	91,96 s	160,00 s	110,25 s	35,69 d $^2J_{PC}$ = 14,7	31,45 d $^3J_{PC}$ = 8,2
VII*	202...198 broad s	161...159 broad s	115...107 broad s	155...153 broad s	115...107 broad s	161...159 broad s	115...107 broad s	36,00...35,50 broad s	31,30...30,75 broad s

*Spectrum of compound VII at +25°C, pulse delay time 5 sec.

Addition of 0.5 equivalents of *tert*-butylphosphaacetylene to the azide I and carrying out the reaction at −20°C resulted in practically no change in the ratio of the cycloadducts II and III formed, and led only to an increase in the fraction of the starting azidopyridine I in the mixture of reaction products. On the other hand, carrying out the reaction of triazidopyridine I with excess (4 equivalents) *tert*-butylphosphaacetylene made it possible to isolate the *tris*-adduct III as the only reaction product.

The data obtained show that, as in the norbornene case [1, 2], the reaction of the azidopyridine I with *tert*-butylphosphaacetylene also proceeds regioselectively via initial cycloaddition of the dipolarophile at the azido group in the 4 position of the pyridine ring. The monoadduct II formed in the first stage of the reaction in turn easily reacts with the exceptionally reactive *tert*-butylphosphaacetylene, which leads to simultaneous formation in the reaction of the *tris*-adduct III. The higher reactivity of the α-azido groups in the monoadduct II compared with the α-azido groups of the starting azide I is probably due to the effect of the electron-donor triazaphosphole ring in the molecule of compound II, which promotes an increase in the negative charge on the $N_{(\alpha)}$ atoms of its azido groups. Thus we were unable to observe intermediate *bis*-adducts in appreciable concentration when monitoring the reaction of azide I with *tert*-butylphosphaacetylene by ^{31}P NMR spectroscopy, which indicates significantly higher reactivity of the α-azido groups in pyridines having two electron-donor triazaphosphole substituents. Considering these data, we were very interested in studying the reaction of addition of *tert*-butylphosophaacetylene to 2,4,6-triazidopyridine, which would have stronger electron-acceptor β-substituents on the pyridine ring compared with azide I. As the model compound for such an investigation, we synthesized 2,4,6-triazido-3,5-dicyanopyridine (V).

The reaction of 2,4,6-trichloro-3,5-dicyanopyridine (IV) with excess sodium azide was carried out at room temperature in an aqueous acetone medium, in analogy with the previously described method for synthesis of triazidopyridine I [2]. The triazidopyridine V was obtained as the only product in 90% yield. We found that in contrast to the reaction of azide I, addition of one equivalent of *tert*-butylphosphaacetylene to triazidopyridine V led to formation of only one product, which according to ^1H NMR, ^{13}C, and ^{31}P NMR, IR, and elemental analysis corresponded to the monoadduct VI. As in the case of compounds II and III, the presence of a signal from the phosphorus atom at 181.03 ppm in the ^{31}P NMR spectrum of compound VI (Table 1) shows that cycloaddition of the azidopyridine V also occurs regioselectively with formation of the 3H-1,2,3,4-triazaphosphole ring. The simultaneous presence in the ^{13}C NMR spectrum of compound VI of only three signals from the carbon atoms of the pyridine ring at 160.66, 155.17, and 91.92 ppm, one of which ($C_{(4)}$ at 155.17 ppm) appears as a doublet with characteristic $^2J_{PC}$ = 8.2 Hz, is convincing evidence that the reaction proceeds regioselectively at the azido group in the 4 position of the pyridine ring of triazidopyridine V.



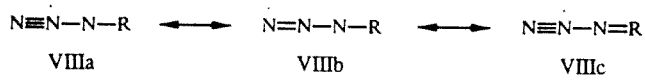
Formation of the monoadduct V as the only product of reaction of azide V with one equivalent of *tert*-butylphosphaacetylene suggests that enhancement of the electron-acceptor properties of the substituents on the pyridine ring of azidopyridines in fact is accompanied by significant decrease in the reactivity of the α-azido groups of these compounds.

In contrast to monoadduct II, the electron-acceptor effect of the two cyano groups in the molecule of compound VI completely compensates the electron-donor effect of its triazaphosphole ring. As a result, the reactivity of the α-azido groups of compound VI remains significantly lower than for the γ-azido group of the starting azide V, which allows the reaction to occur exclusively at this group. Nevertheless, the reaction of the monoadduct VI with excess *tert*-butylphosphaacetylene led to formation of the *tris*-adduct VII, suggesting rather high reactivity of the α-azido groups in the monoadduct VI with respect to this exceptionally highly reactive dipolarophile. We also could not observe intermediate *bis*-adducts in appreciable concentration when monitoring this reaction by ^{31}P NMR spectroscopy, despite the stronger electron-acceptor properties of the substituents on the pyridine ring of such intermediates.

A very interesting property of the *tris*-adduct VII is its ability to exist in $CDCl_3$ solution as three rotational isomers VIIa-c. Thus, in the ^{31}P NMR spectrum of compound VII (Table 1), we observe the presence of six well resolved signals from the phosphorus atoms of the 3H-1,2,3,4-triazaphosphole rings, three of which at 181.82, 179.74, and 179.20 ppm are distinguished by high intensity and, in analogy with the ^{31}P NMR spectrum of the *tris*-adduct III (Table 1), correspond to the phosphorus atoms of the α-triazaphosphole rings of the three rotamers VIIa-c. The intensity of the remaining three signals at 182.35, 177.60, and 176.95 ppm is 3.5 to 4 times lower, which makes it possible to assign these signals to the phosphorus atoms of the γ-triazaphosphole rings of rotamers VIIa-c. In the PMR spectrum of compound VII at 25°C, the three *tert*-butyl groups appear as a large group of broadened signals of different intensities in the 1.60-1.45 ppm region, which suggests the presence of a dynamic equilibrium between the different rotameric forms of this compound. Lowering the temperature down to −40°C proved to be insufficient for good resolution of the signals from the *tert*-butyl groups of the three isomers VIIa-c. On the other hand, as we might expect, in the PMR spectrum at 60°C (Table 1) there are three rather well resolved doublets of about equal intensity at 1.59, 1.57, and 1.56 ppm with $^4J_{PH}$ = 1.7-1.6 Hz, due to averaging of the spectrum of compound VII with an increase in temperature. In the ^{13}C NMR spectrum at 25°C (Table 2) with standard pulse delay time 5 sec, we observed only strongly broadened signals from all the carbon atoms of the *tris*-adduct VII, which also is characteristic for compounds participating in dynamic isomerization processes [7].

The presence of rotational isomerism for compound VII is the first example of such isomerism observed for aromatic derivatives of 3H-1,2,3,4-triazaphospholes. The major factors promoting the appearance of such isomerism are probably the absence of significant steric hindrances for maximum conjugation of the pyridine ring with the triazaphosphole rings in the molecule of the *tris*-adduct VII, and the rather strong electron-acceptor effect of the pyridine ring on the $N_{(3)}$ atom of the triazaphosphole rings. Thus the presence of a chlorine atom (less of an electron acceptor and more bulky than the cyano group) in the 3 position of the pyridine ring of the *tris*-adduct III no longer makes it possible to observe equilibrium coexistence of rotational isomers for this compound at room temperature.

The results of the investigation of the reactions of triazidopyridines I and V with *tert*-butylphosphaacetylene completely support the hypothesis we discussed earlier [3] that the reason for the low reactivity of the α-azidopyridines in 1,3-dipolar cycloaddition reactions is the strong conjugation of the α-azido groups with the electron-acceptor pyridine ring. The stronger the electron-acceptor effect of the pyridine system, the stronger the conjugation of the α-azido groups with this system and the lower the reactivity of the azido groups in reactions with dipolarophiles. An interesting feature of the observed effect is the fact that, according to literature data [8], enhancement of the electron-acceptor properties of substituents on the aromatic ring of azides should facilitate addition of electron-rich dipolarophiles to the azides (dipole−LUMO controlled reactions). Based on these data, addition of norbornene to azide I should primarily occur specifically at the α-azido group of this compound. Therefore we may hypothesize that the exceptionally low reactivity of the α-azido groups in azides I and V with respect to dipolarophiles is due to the appreciable contribution of the resonant structure VIIIc, in which the azido groups are significantly deprived of their 1,3-dipolar properties.



VIIIa VIIIb VIIIc

EXPERIMENTAL

The IR spectra were obtained on a Specord M-80; the ^1H NMR spectra were obtained on a Bruker AMX-400 (400 MHz) using TMS as the internal standard. The ^{13}C NMR spectra were recorded on a Bruker AMX-400 (100 MHz); the ^{31}P

NMR spectra were recorded on a Bruker AC-200 (80.82 MHz); the mass spectra were recorded on a Finnigan MAT-90 with ionization energy 70 eV.

The method for obtaining *tert*-butylphosphaacetylene and the starting compounds I and IV is described in [6, 2, and 9] respectively.

The elemental analysis data for C, H, and N in compounds II, III, and V-VII correspond to the calculated values.

4-(3H-1,2,3,4-Triazaphospholo)-2,6-diazido-3-chloro-5-cyanopyridine (II). A solution of 0.1 g (1 mmole) *tert*-butylphosphaacetylene in 10 ml absolute diethyl ether was added dropwise to a stirred solution of 0.262 g (1 mmole) of compound I in 20 ml absolute diethyl ether at 0°C under an argon atmosphere. Then the reaction mixture was stirred at room temperature for 2 h. The solvent was driven off under high vacuum, and the residue was twice recrystallized from diethyl ether, removing the *tris*-adduct III which is slightly soluble in ether. The ether was driven off from the mother liquor obtained after the last recrystallization, and the yellow crystalline residue obtained was washed twice with hot pentane and recrystallized from a hexane–ethylacetate mixture.

2,4,6-Tris(3H-1,2,3,4-triazaphospholo)-3-chloro-5-cyanopyridine (III). A solution of 0.4 g (4 mmole) *tert*-butylphosphaacetylene in 10 ml absolute diethyl ether was added dropwise to a stirred solution of 0.262 g (1 mmole) compound I in 20 ml absolute diethyl ether at 0°C under an argon atmosphere. Then the reaction mixture was allowed to stand at room temperature for three days. The yellow crystalline precipitate isolated from the reaction mixture was filtered, washed on the filter with three portions of cold ether, and recrystallized from a hexane–ethylacetate mixture.

2,4,6-Triazido-3,5-dicyanopyridine (V). A solution of 2.6 g (40 mmole) sodium azide in 20 ml water was added to a stirred solution of 2.32 g (10 mmole) compound IV in 200 ml aqueous acetone (20% water) at room temperature. The reaction mixture was stirred at room temperature for 5 h, then the acetone was driven off at reduced pressure and 200 ml ice water was added to the residue. The white crystalline precipitate obtained was filtered, dried on the filter, and recrystallized from a benzene–hexane mixture.

4-(3H-1,2,3,4-Triazaphospholo)-2,6-diazido-3,5-dicyanopyridine (VI). A solution of 0.1 g (1 mmole) *tert*-butylphosphaacetylene in 10 ml absolute diethyl ether was added dropwise to a stirred solution of 0.252 g (1 mmole) compound V in 40 ml absolute diethyl ether at 0°C under an argon atmosphere. Then the reaction mixture was stirred at room temperature for 4 h. The solvent was driven off under high vacuum, and the yellow crystalline residue was recrystallized from a hexane–ethylacetate mixture.

2,4,6-Tris(3H-1,2,3,4-triazaphospholo)-3,5-dicyanopyridine (VII). A solution of 0.4 g (4 mmole) *tert*-butylphosphaacetylene in 10 ml absolute diethyl ether was added dropwise to a stirred solution of 0.252 g (1 mmole) compound V in 40 ml absolute diethyl ether at 0°C under an argon atmosphere. Then the reaction was stirred at room temperature for three days. The solvent was driven off under high vacuum, and the yellow crystalline residue was recrystallized from a hexane–ethylacetate mixture.

The characteristics of the synthesized compounds II, III, V-VII are presented in Tables 1 and 2.

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