Chemistry of Heterocyclic Compounds, Vol. 37, No. 7, 2001

REGIOSELECTIVE CYCLOADDITION OF THE DIMETHYL ESTER OF ACETYLENEDICARBOXYLIC ACID TO 2,4,6-TRIAZIDOPYRIDINES

S. V. Chapyshev

2,4,6-Triazido-3,5-dichloropyridine was obtained in the reaction of pentachloropyridine with sodium azide. At room temperature, this azide reacts regioslectively with norbornene at the γ-azide group to give the corresponding 4-(3-azatricyclo[3.2.1.0]octanyl)-2,6-diazidopyridine in 88% yield. The cycloaddition of the dimethyl ester of acetylenedicarboxylic acid to this triazide proceeds at the azide groups at $C_{(2)}$ and $C_{(6)}$ in the pyridine ring to give 4-azido-2,6-di(4',5'-dimethoxycarbonyl)-1H-1,2,3-triazolopyridine. The analogous reaction of 2,4,6-triazido-3,5-dicyanopyridine with the dimethyl ester of acetylenedicarboxylic acid stops at the formation of 2,4-diazido-6-(4',5'-dimethoxycarbonyl)-1H-1,2,3-triazolopyridine. In contrast to reactions with electron-rich dipolarophiles, the cycloaddition of electron-deficient dipolarophiles to 2,4,6-triazidopyridines proceeds with thermodynamic control primarily at the azide groups bearing the highest orbital density in the HOMO.

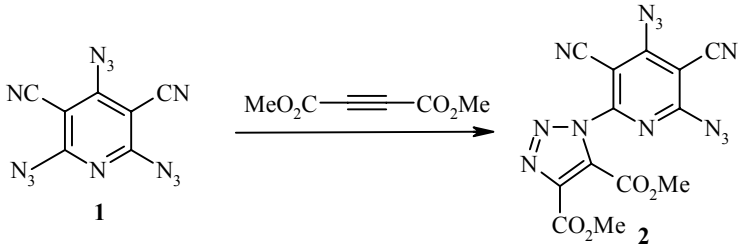
Keywords: azidopyridines, triazoles, cycloaddition, regioselectivity, molecular orbitals, thermodynamic control.

The cycloaddition of electron-rich dipolarophiles to 2,4,6-triazidopyridines proceeds regioselectively at the γ-azide groups due to the lower activation energy for this reaction pathway [1-6]. The activation energy for such reactions is determined by the distribution of bonding orbital density on the azide groups and decreases with decreasing HOMO coefficients for N_α and N_β in these groups [6]. Hence, the kinetically controlled cycloaddition of electron-deficient dipolarophiles to 2,4,6-triazidopyridines should also proceed at the γ-azide groups, which have lower bonding orbital density. However, if the reaction obeys thermodynamic control, the cycloaddition of electron-deficient dipolarophiles to 2,4,6-triazidopyridines would be expected to proceed at the α-azide groups, which bear significantly higher HOMO density [6].

The reactions of azidopyridines **1** and **5** with the dimethyl ester of acetylenedicarboxylic acid (DMAD) were studied to elucidate the direction of the cycloaddition of electron-deficient dipolarophiles to 2,4,6-triazidopyridines. The reaction of triazide **1** with excess of DMAD was carried out in ether solution at room temperature in the dark over six weeks. The isolation and purification of the reaction products gave **2** in 34% yield. Furthermore, 52% starting triazide **1** was recovered.

Institute of Chemical Physics Problems, Russian Academy of Sciences, 142432 Chernogolovka, Moscow Region, Russia; e-mail: chap@icp.ac.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 935-941, July, 2001. Original article submitted November 15, 1999.

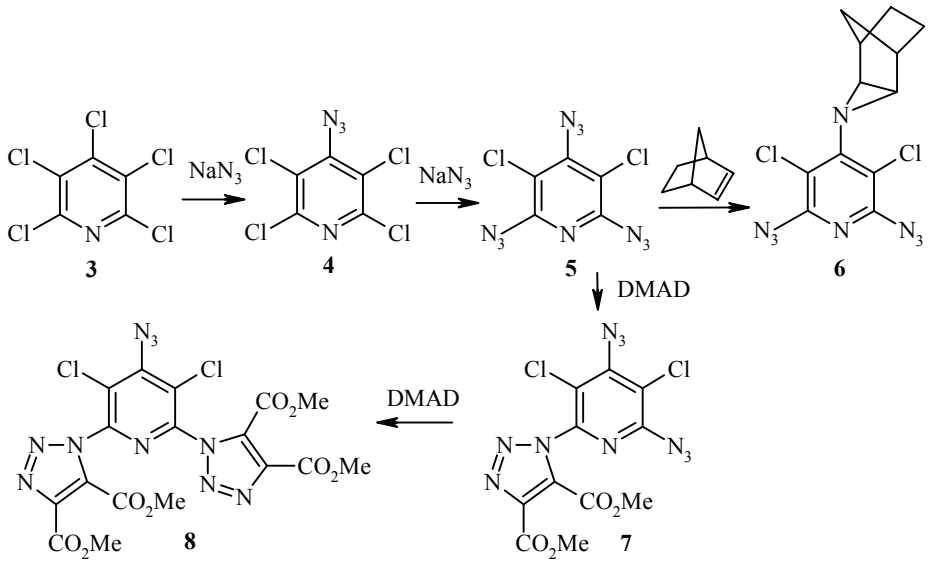
0009-3122/01/3707-0861$25.00



The composition and structure of adduct **2** are in complete accord with the elemental analysis, IR, ^{1}H and ^{13}C NMR spectra, and mass spectrometric data. The presence of five signals for the pyridine ring carbon atoms in the ^{13}C NMR spectrum at 93.1, 93.6, 151.2, 159.8, and 159.3 ppm indicates that the addition of DMAD to triazide **1** proceeds regioselectively at the azide group, specifically at $C_{(2)}$ in the pyridine ring. The positions of the signals for the triazole ring carbon atoms at 131.2 and 140.6 ppm and methoxycarbonyl carbon atoms at 53.4, 54.4, 157.2, and 160.1 ppm in the ^{13}C NMR spectrum of adduct **2** are in good agreement with the analogous data for 4,5-dimethoxycarbonyl-1H-1,2,3-triazoles [7, 8].

The formation of cycloadduct **2** shows that, in contrast to reactions with electron-rich dipolarophiles, the cycloaddition of electron-deficient dipolarophiles to 2,4,6-triazidopyridines obeys thermodynamic control and proceeds primarily at the azide group bearing the higher HOMO density. The low reactivity of **1** relative to DMAD and, as a consequence, low cycloaddition product yield, probably should be attributed to the low energy of the HOMO of the starting triazide. Cycloadduct **2** has still lower HOMO energy (Table 1) and practically does not react with DMAD at room temperature.

A detailed study of the 1,3-dipolar cycloaddition of 2,4,6-triazidopyridines to electron-deficient dipolarophiles became possible with our discovery of a synthesis of triazide **5**, which has relatively weak electron-withdrawing substituents at $C_{(3)}$ and $C_{(5)}$ in the pyridine ring. Various workers have reported that monoazidopyridine **4** is the only product of the reaction of pentachloropyridine **3** with sodium azide in aprotic polar solvents such as DMF and DMSO. The yield of **4** varies from 22 to 69% depending on the reaction conditions [9-12]. Although Pannell also reported a method for obtaining triazidopyridine in his patents, physical characteristics and the method for synthesizing this compound were not given [11, 12]. Our study showed that the yield of azide **4** is raised to 98% when the reaction of **3** with excess sodium azide is carried out in 10% aq. acetone at room temperature. The same reaction but with heating at reflux for 72 h gave triazidopyridine **5** in 84% yield.



In comparison to cyano-substituted 2,4,6-triazidopyridines studied in our previous work [5, 6], triazide **5** has higher HOMO and LUMO energies (Table 1). This finding suggests that triazide **5** should be more reactive relative to electron-deficient dipolarophiles and less reactive to electron-rich dipolarophiles. Analysis of the HOMO and LUMO frontier orbital density distribution in pyridine **5** shows that the presence of the chlorine atoms on the pyridine ring of the 2,4,6-triazidopyridines enhances the differentiation of the electronic properties of the α- and γ-azide group of these compounds (Fig. 1).

The reaction of **5** with norbornene was studied to evaluate the reactivity of this compound relative to electron-rich dipolarophiles. The reaction was carried out in diethyl ether solution at room temperature in the dark over two weeks using a four-fold excess of the dipolarophile. As in the case of 2,4,6-triazido-3-chloro-5-cyanopyridine [1, 2, 5], the cycloaddition proceeded regioselectively and stereospecifically to give the less sterically hindered *exo* cycloadduct **6** in 88% yield. As a result of the electron-donor nature of the aziridine substituent, the cycloadduct formed has higher HOMO energy by 8.6 kcal/mole relative to the starting triazide (Table 1), which apparently dictates termination of the reaction after the addition of only one norbornene molecule to triazide **5**. The synthesis of **6** shows that, despite the moderate reactivity of triazide **5** toward electron-rich dipolarophiles, this reaction may be used for the mild, selective modification of the γ-azide group in this triazide.

The cycloaddition of electron-rich acetylenes at the γ-azide groups of 2,4,6-triazidopyridines is favored over the analogous reactions at the azide groups of 2,6-diazido-4-1H-1,2,4-triazolopyridines despite the lower LUMO energies of the latter by 5.5-6 kcal/mole [6]. Such effects for the cycloaddition of norbornene to 2,4,6-triazidopyridines have not been reported previously [5]. The reaction of triazide **5** with norbornene studied in this work permits the first analysis of such a case. As already noted, the cycloaddition of norbornene to cyanotriazide **5** at room temperature terminates upon formation of cycloadduct **9**. Furthermore, PM3 calculations showed that the LUMO energy of this cycloadduct is 1.4 kcal/mole less than for triazide **5**. This finding suggests that, as for electron-rich acetylenes, the cycloaddition of norbornene to 2,4,6-triazidopyridines obeys kinetic control and primarily proceeds at those azide groups having lower bonding orbital density.

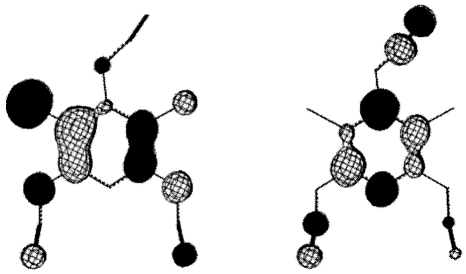
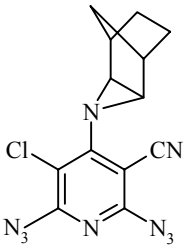


Fig. 1. Orbital density distribution in the HOMO and LUMO of **5**.

TABLE 1. Frontier Orbital Energies for **1, 2, 5-8,** Norbornene and DMAD

Compound	HOMO, eV	LUMO, eV	Compound	HOMO, eV	LUMO, eV
1	-9.661	-1.707	**7**	-9.350	-1.615
2	-10.137	-2.157	**8**	-10.012	-2.098
5	-8.882	-1.176	Norbornene*	-8.97	1.70
6	-8.753	-0.802	DMAD	-12.077	-0.941

* The experimentally determined ionization potentials [13] and electron affinity [14] are given instead of the calculated HOMO and LUMO energies.



HOMO -9.098 eV
LUMO -1.235 eV

9

The reaction of **5** with excess DMAD was carried out in a solution of diethyl ether at room temperature in the dark over two weeks. Bisadduct **8** was obtained as the only product in 75% yield. The composition and structure of **8** are in complete accord with the elemental analysis, IR, ^{1}H NMR, and ^{13}C spectral data. Thus, the ^{13}C NMR spectrum of **8** has only three signals for pyridine carbon atoms (at 114.7, 142.9, and 149.8 ppm), indicating that the triazole substituents in this molecule are found at $C_{(2)}$ and $C_{(6)}$ in the pyridine ring. The signals for the triazole carbon atoms on the pyridine ring of bisadduct **8** are virtually identical to those for monoadduct **2**.

Figure 2 gives a diagram for the relative position of the HOMO energy levels of azidopyridines **1, 2, 5, 7,** and **8** constructed using the data from Table 1, which permits us to compare the reactivity of these compounds relative to electron-deficient dipolarophiles. Triazidopyridine **1** has lower HOMO energy by 17.96 kcal/mole relative to its dichloro-substituted analog **5** and, thus, should be less reactive than the latter relative to DMAD.

The addition of one DMAD molecule to triazides **1** and **5** reduces the HOMO energy of both azidopyridines by almost the same magnitude, namely, about 11 kcal/mole. Monoadduct **7** has higher HOMO energy by 7.16 kcal/mole in comparison with triazide **1** and should be more reactive than the latter toward DMAD. It is apparently precisely this factor, which accounts for the rapid conversion of monoadduct **7** to bisadduct **8**. The addition of a DMAD molecule at the α-azide group of monoadduct **7** obeys thermodynamic control and occurs due to the higher HOMO density precisely at this group in **7** (Fig. 3). It is interesting to note that even greater HOMO density is concentrated on the α-azide group of monoadduct **2** (Fig. 3), which, nevertheless, does not react with DMAD as the result of the low HOMO energy of this azide. Bisadduct **8** has about the same HOMO energy and also does not react with DMAD at room temperature.

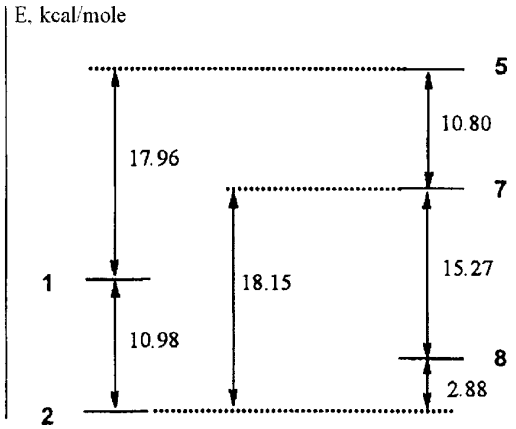
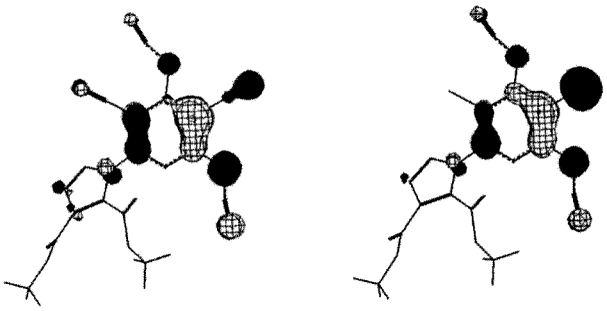


Fig. 2. Diagram of the HOMO energy levels of azidopyridines **1, 2, 5, 7,** and **8**.



HOMO **2** HOMO **7**

Fig. 3. Orbital density distribution in the HOMO in **2** and **7**.

Our study has shown that, in contrast to reaction with electron-rich dipolarophiles, the cycloaddition of electron-deficient dipolarophiles to 2,4,6-triazidopyridines obeys thermodynamic control and proceeds selectively at the α-azide groups, which have higher HOMO density.

EXPERIMENTAL

The IR spectra were taken on a Specord M-80 spectrometer. The ^{1}H NMR spectra were registered on a Bruker AMX-400 spectrometer at 400 MHz using TMS as the internal standard. The ^{13}C NMR spectra were registered on a Bruker AM-400 spectrometer at 100.6 MHz. The mass spectra were taken on a Finnigan MAT-90 mass spectrometer at 70 eV ionizing radiation. The reaction course was monitored by thin-layer chromatography on Silufol UV-254 plates. The geometry and electronic properties of **2** and **5-8** were calculated using the semiempirical PM3 method [15] in the Spartan program package [16]. The molecular structures were calculated with complete optimization of the geometrical parameters.

The method for preparing triazide **1** was described in our previous work [3]. A sample of pentachloropyridine **3** supplied by Aldrich was used in this work.

2,4-Diazido-3,5-dicyano-6-(4',5'-dimethoxycarbonyl)-1H-1,2,3-triazolopyridine (2). A sample of dimethyl ester of acetylenedicarboxylic acid (0.568 g, 4 mmol) was added dropwise to a stirred solution of **1** (0.252 g, 1 mmol) in dry diethyl ether (100 ml) and the reaction mixture was left in the dark at room temperature for two weeks. The solvent was distilled off in vacuum. The residue was washed with pentane and subjected to chromatography on a silica gel column using 4:1 benzene–ethyl acetate as the eluent. The product was recrystallized from hexane–benzene and dried to give 0.134 g (34%) **2**; mp 95-96°C. IR spectrum (vaseline), cm^{-1}: 2225, 2200 (C=N), 2160, 2140 (N_3), 1734 (CO_2CH_3), 1586, 1546 (C=N, C=C). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.96 (3H, s, OCH_3); 4.01 (3H, s, OCH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 53.4 and 54.4 (OCH_3), 93.1 ($C_{(5)}$), 93.6 ($C_{(3)}$), 109.1 and 111.0 (C=N), 131.2 ($C_{(5')}$), 140.6 ($C_{(4')}$), 151.2 ($C_{(4)}$), 157.2 (C=O), 159.3 ($C_{(6)}$), 159.8 ($C_{(2)}$), 160.1 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 394 (M^+, 25). Found, %: C 39.71; H 1.77; N 42.51. $C_{13}H_6N_{12}O_4$. Calculated, %: C 39.59; H 1.52; N 42.64. Furthermore, 0.131 g (52%) starting **1** was recovered.

2,4,6-Triazido-3,5-dichloropyridine (5). A sample of sodium azide (2.6 g, 40 mmol) was added to a stirred solution of **3** (2.51 g, 10 mmol) in 10% aq. acetone (300 ml) and heated at reflux at 70°C for 72 h. Acetone was distilled off in vacuum and water (200 ml) was added to the residue. The crystalline product was filtered off, dried in the air, and recrystallized from hexane–benzene. Drying gave 2.28 g (84%) **5**; mp 78-79°C. IR spectrum (KBr), cm^{-1}: 2148, 2131, 1099 (N_3), 1576, 1555, 1541 (C=N, C=C), 1427, 1413, 1387, 1258, 1169,

1111, 936, 832, 778. ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 109.1 ($C_{(3)}$, $C_{(5)}$), 144.6 ($C_{(4)}$), 148.7 ($C_{(2)}$, $C_{(6)}$). Mass spectrum, *m/z* (I_{rel}, %): 270 (M^+, 43). Found, %: C 22.26; N 51.57. $C_5Cl_2N_{10}$. Calculated, %: C 22.16; N 51.68.

4-(3,3-Azatricyclo[3.2.1.0]octyl)-2,6-diazido-3,5-dicyanopyridine (6). A solution of norbornene (0.376 g, 4 mmol) in dry diethyl ether (30 ml) was added dropwise to a stirred solution of **5** (0.271 g, 1 mmol) in dry diethyl ether (100 ml) and left in the dark at room temperature for six weeks. The solvent was distilled off in vacuum. The residue was washed with pentane and recrystallized from hexane–benzene. Drying gave 0.297 g (88%) **6**; mp 144-145°C. IR spectrum (KBr), cm^{-1}: 2970, 2935, 2884 (CH), 2148 (N_3), 1612, 1572 (C=N, C=C). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 0.81 (1H, d, *J* = 10.2, 8-H_{syn}); 1.21 (2H, d, *J* = 7.5, 6- and 7-H_{ax}); 1.35 (1H, d, *J* = 10.2, 8-H_{anti}); 1.48 (2H, d, *J* = 7.5, 6- and 7-H_{eq}); 2.59 (2H, s, H_{bridge}); 2.71 (2H, s, NCH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 26.5 (CH_2–CH_2), 29.1 (CH–CH_2), 37.3 (CH), 45.0 (NCH), 107.8 ($C_{(3)}$, $C_{(5)}$), 148.5 ($C_{(2)}$, $C_{(6)}$), 155.2 ($C_{(4)}$). Mass spectrum, *m/z* (I_{rel}, %): 336 (M^+, 55). Found, %: C 42.86; H 3.12; N 33.11. $C_{12}H_{10}Cl_2N_8$. Calculated, %: C 42.75; H 2.99; N 33.24.

4-Azido-3,5-dichloro-2,6-di(4',5'-dimethoxycarbonyl)-1H-1,2,3-triazolopyridine (8). A sample of dimethyl ester of acetylenedicarboxylic acid (0.568 g, 4 mmol) was added dropwise to a stirred solution of **5** (0.271 g, 1 mmol) in dry diethyl ether (100 ml) and maintained in the dark at room temperature for two weeks. The solvent was distilled off in vacuum. The residue was washed with pentane and recrystallized from hexane–benzene. Drying gave 0.416 g (75%) **8**; mp 139-140°C. IR spectrum (KBr), cm^{-1}: 2956 (CH), 2144 (N_3), 1736 (CO_2CH_3), 1560 (C=N, C=C). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.83 (3H, s, OCH_3); 3.95 (3H, s, OCH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 53.6 and 54.5 (OCH_3), 114.7 ($C_{(3)}$, $C_{(5)}$), 131.7 ($C_{(5')}$), 140.2 ($C_{(4')}$), 142.9 ($C_{(4)}$), 157.4 (C=O), 149.8 ($C_{(2)}$, $C_{(6)}$), 160.1 (C=O). Found, %: C 36.89; H 2.32; N 25.07. $C_{17}H_{12}Cl_2N_{10}O_8$. Calculated, %: C 36.77; H 2.18; N 25.23.

REFERENCES

1. S. V. Chapyshev and T. Ibata, *Heterocycles*, **36**, 2185 (1993).
2. S. V. Chapyshev, *Khim. Geterotsikl. Soedin.*, 1578 (1993).
3. S. V. Chapyshev, U. Bergstrasser,and M. Regitz, *Khim. Geterotsikl. Soedin.*, 67 (1996).
4. S. V. Chapyshev and V. M. Anisimov, *Khim. Geterotsikl. Soedin.*, 676 (1997).
5. S. V. Chapyshev and V. M. Anisimov, *Khim. Geterotsikl. Soedin.*, 1521 (1997).
6. S. V. Chapyshev, *Khim. Geterotsikl. Soedin.*, 1497 (2000).
7. T. Sasaki, S. Eguchi, M. Yamaguchi, and T. Esaki, *J. Org. Chem.*, **46**, 1800 (1981).
8. O. A. Radchenko, E. V. Proshakova, A. N. Kotlinskaya, and A. Ya. Il'chenko, *Zh. Org. Khim.*, **27**, 1463 (1991).
9. I. R. A. Bernard, G. E. Chivers, R. J. W. Cremlyn, and K. G. Mootoosamy, *Aust. J. Chem.*, **27**, 171 (1974).
10. R. A. Abramovitch, S. R. Challand, and Y. Yamada, *J. Org. Chem.*, **40**, 1541 (1975).
11. C. E. Pannell, US Patent 3,773,774 (1973); *Chem. Abstr.*, **80**, 59869 (1974).
12. C. E. Pannell, US Patent 3,883,542 (9175); *Chem. Abstr.,* **83**, 58670 (1975).
13. P. Bischof, *Helv. Chim. Acta*, **53**, 1677 (1970).
14. H. Morrison, T. Singh, L. de Cardenas, and S. Severance, *J. Am. Chem. Soc.*, **108**, 3862 (1986).
15. J. J. P. Stewart, *J. Comput. Chem.*, **10**, 209 (1989).
16. *SPARTAN Version 4.0*, Wavefunction Inc., 18401 Von Karman Ave., #370 Irvine; *Chem. Abstr.*, 92715 (1995).