Synthesis and regioselective cycloaddition reactions of 2,4,6-triazido-3,5-dichloropyridine

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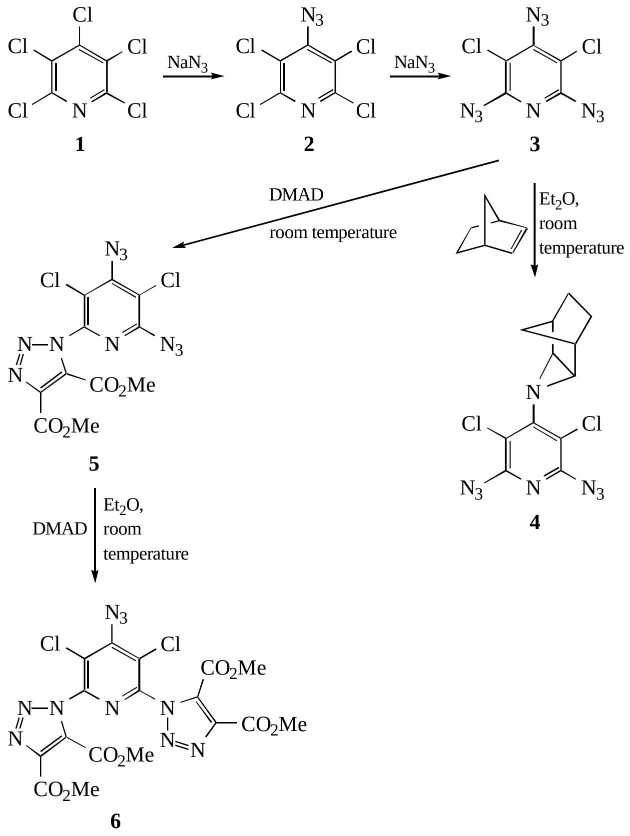
2,4,6-Triazido-3,5-dichloropyridine, obtained by the reaction of pentachloropyridine with sodium azide, readily adds two molecules of dimethyl acetylenedicarboxylate to the azide groups at the 2- and 6-positions, whereas, in the reaction with norbornene, it forms a cycloadduct only at the azido group in the 4-position.

Selective derivatization of azide groups in polyazides is of considerable interest from both theoretical and practical points of view. Recently we have shown[1(a)–(e)] that cycloaddition of electron-rich dipolarophiles such as norbornene, $Bu^tC\equiv CH$ and $Bu^tC\equiv P$ to 2,4,6-triazidocyanopyridines proceeds regioselectively at the azido group in the 4-position of the pyridine ring to give the corresponding monoadducts as intermediates. However, because of the very low reactivity of these triazides toward electron-deficient dipolarophiles, the cycloadditions of this type have not been studied. To perform these experiments under mild conditions, it was tempting to have a model triazide containing no cyano group at the pyridine ring. Here, the synthesis of 2,4,6-triazido-3,5-dichloropyridine **3** and its reactions with norbornene and dimethyl acetylenedicarboxylate (DMAD) are considered.

The reaction of pentachloropyridine **1** with sodium azide was studied earlier.[2(a)–(d)] The reaction was carried out in aprotic polar solvents such as DMSO or DMF which allowed the authors to obtain only monoazide **2** in 22–62% yield. Although Pannell in his patents[2(a),(b)] also claimed the preparation of triazide **3**, no detail concerning the synthesis and physical characteristics of this compound were reported. Our investigation showed that when pyridine **1** is allowed to react with an excess (molar ratio 1:4) of sodium azide in aqueous acetone (1:10) at room temperature the yield of **2** is increased to 98%. Furthermore, the same reaction at 70 °C for 72 h gave triazide **3**[†] in 84% yield.

Figure 1 shows the distribution of the orbital density in the HOMO and the LUMO of triazide **3** computed by the PM3 method.[3] The high orbital density on the α-azido groups and almost the lack of it on the γ-azido group in the HOMO of **3** indicate[4–6] that cycloaddition of electron-deficient dipolarophiles to this triazide occurs at the α-azido groups. By contrast, the higher orbital density on the γ-azido group in the LUMO of **3** suggests that this group should be most reactive toward electron-rich dipolarophiles.



The reaction of **3** with an excess (1:4) of norbornene was carried out in diethyl ether in the dark at room temperature for two weeks. In contrast to 2,4,6-triazido-3,5-dicyanopyridine, which readily added three molecules of norbornene under similar conditions,[1(e)] triazide **3** reacted only with one molecule of this dipolarophile to give cycloadduct **4**[‡] in 88% yield. The presence of only three signals at δ 107.7, 148.2 and 155.2 ppm for the carbon atoms of the pyridine ring in the ^{13}C NMR spectrum of **4** proves that the cycloaddition of norbornene to triazide **3** occurs regioselectively at the γ-azido group. Apart from that, the absence of coupling between the *endo*-protons at δ 2.71 and the bridgehead protons at δ 2.59 ppm in the ^{1}H NMR spectrum of **4** indicates[1(e)] stereospecificity of the reaction, which yields only the less hindered *exo*-adduct. The high orbital density on the azido groups in the LUMO of **4** (Figure 2) testifies that reactions of these groups with electron-rich dipolarophiles are not forbidden by the orbital selection rules.[4–6] An explanation of the very low reactivity of this compound toward norbornene comes from an analysis of the frontier orbital energies of

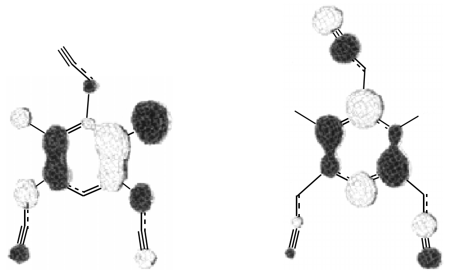
Table 1 The HOMO and LUMO energies of azides **3**–**6**, norbornene and DMAD.

Compound	HOMO/eV	LUMO/eV
3	–8.882	–1.176
4	–8.753	–0.802
5	–9.350	–1.615
6	–10.012	–2.098
Norbornene	–8.97[a]	1.70[b]
DMAD	–12.077	–0.941

[a] Experimental ionization potential (IP) from ref. 9. [b] Experimental electron affinity (EA) from ref. 10.

[†] *Characteristic data for compound* **3**: mp 78–79 °C (decomp.). ^{13}C NMR (CDCl$_3$) δ: 109.1 (C-3, C-5), 144.6 (C-4), 148.7 (C-2, C-6). IR (KBr, ν/cm^{-1}): 2148, 2131, 2099, 1576, 1559, 1555, 1544, 1541, 1427, 1413, 1387, 1258, 1169, 1111, 936, 832, 778. MS (70 eV), *m/z*: 270 (M$^+$, 43%). Found (%): C, 22.26; N, 51.57. Calc. for $C_5Cl_2N_{10}$ (%): C, 22.16; N 51.68.

[‡] *Characteristic data for compound* **4**: mp 144–145 °C (decomp.). ^{1}H NMR (CDCl$_3$) δ: 0.81 (d, 1H, 8-H$_{syn}$, J 10.2 Hz), 1.21 (d, 2H, 6- and 7-H$_a$, J 7.5 Hz), 1.35 (d, 1H, 8-H$_{anti}$, J 10.2 Hz), 1.48 (d, 2H, 6- and 7-H$_e$, J 7.5 Hz), 2.59 (s, 2H, bridgehead-H), 2.71 (s, 2H, NCH). ^{13}C NMR (CDCl$_3$) δ: 26.5 (CH$_2$CH$_2$), 29.1 (CH$_2$), 37.3 (CH), 45.0 (NCH), 107.8 (C-3, C-5), 148.5 (C-2, C-6), 155.2 (C-4). IR (KBr, ν/cm^{-1}): 2970, 2935, 2884, 2148, 1612, 1572, 1418, 1390, 1371, 1286, 1226, 1109, 1066, 975, 827. MS (70 eV), *m/z*: 336 (M$^+$, 55%). Found (%): C, 42.86; H, 3.12; N, 33.11. Calc. for $C_{12}H_{10}Cl_2N_8$ (%): C, 42.75; H, 2.99; N 33.24.

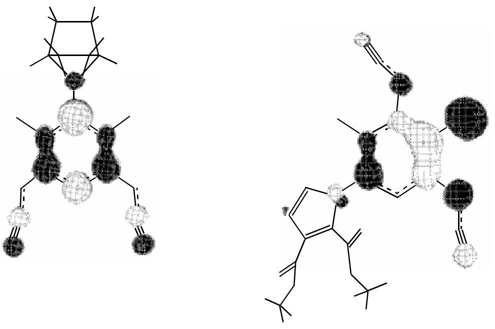


HOMO of **3** LUMO of **3**

Figure 1 The orbital density distribution in the HOMO and the LUMO of **3**.

reactants. This analysis shows that, due to the presence of an electron-donating aziridine substituent at the pyridine ring, the LUMO energy of **4** is higher by 8.6 kcal mol^{-1} than that for **3** (Table 1) and by 16.0 kcal mol^{-1} than the LUMO energy for the 3,5-dicyano derivative of **4**.[1(e)] No surprise that the latter readily reacts with norbornene at room temperature to give the corresponding *tris*-adduct. The synthesis of **4** demonstrates that despite the moderate reactivity of **3** toward electron-rich dipolarophiles the cycloadditions of this type can be successfully used for mild and selective derivatization of the γ-azido group of this triazide.

The reaction of **3** with an excess (molar ratio 1:4) of DMAD was carried out in diethyl ether in the dark at room temperature for two weeks. Compound **6**[§] was obtained as a single product in 75% yield. The presence of only three signals at δ 114.7, 142.9 and 149.8 ppm for the carbon atoms of the pyridine ring in the ^{13}C NMR spectrum of **6** testifies that triazole substituents are placed at the 2- and 6-positions of this compound. The spectral characteristics of triazole fragments in **6** are in good agreement with published data.[7,8] The formation of bis-adduct **6** shows that in full accord with theoretical predictions the cycloaddition of DMAD to triazide **3**, indeed, proceeds at one of the α-azido groups. Intermediate monoadduct **5**, in turn, adds another molecule of DMAD to the α-azido group, which also has the highest HOMO orbital density (Figure 2). By comparison of the HOMO energies of **3**, **5** and **6** (Table 1) one can find that the addition of one molecule of DMAD to **3** decreases the HOMO energy of azide by 10.8 kcal mol^{-1} while the addition of two molecules of DMAD, by 25.1 kcal mol^{-1}. It is obvious that the very low reactivity of **6** toward DMAD is explained by the low HOMO energy of this azide. At the same time, straight conversion of **5** into **6** demonstrates that in comparison with reactions of electron-rich dipolarophiles the cycloadditions of electron-deficient dipolarophiles to azides are less sensitive to changes in the frontier orbital energy of azides and can proceed efficiently at considerably larger energy gaps between the frontier orbitals of addends.



LUMO of **4** HOMO of **5**

Figure 2 The orbital density distribution in the LUMO of **4** and the HOMO of **5**.

Successive selective cycloaddition of electron-rich and/or electron-deficient dipolarophiles to 2,4,6-triazidopyridines provides ample opportunities to synthesise a great variety of novel compounds.

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[§] *Characteristic data for compound* **6**: mp 139–140 °C (decomp.). ^{1}H NMR ($CDCl_3$) δ: 3.83 (s, 3H, CO_2Me), 3.95 (s, 3H, CO_2Me). ^{13}C NMR ($CDCl_3$) δ: 53.6 and 54.5 (OMe), 114.7 (C-3, C-5), 131.7 (C-5′), 140.2 (C-4′), 142.9 (C-4), 149.8 (C-2, C-6), 157.4 and 160.1 (C=O). IR (KBr, ν/cm^{-1}): 2956, 2144, 1736, 1560. Found (%): C, 36.89; H, 2.32; N, 25.07. Calc. for $C_{17}H_{12}Cl_2N_{10}O_8$ (%): C, 36.77; H, 2.18; N 25.23.