SYNTHESIS OF HIGHLY SUBSTITUTED PYRIDINES THROUGH NUCLEOPHILIC SUBSTITUTION OF TETRACHLORO-3-CYANOPYRIDINE

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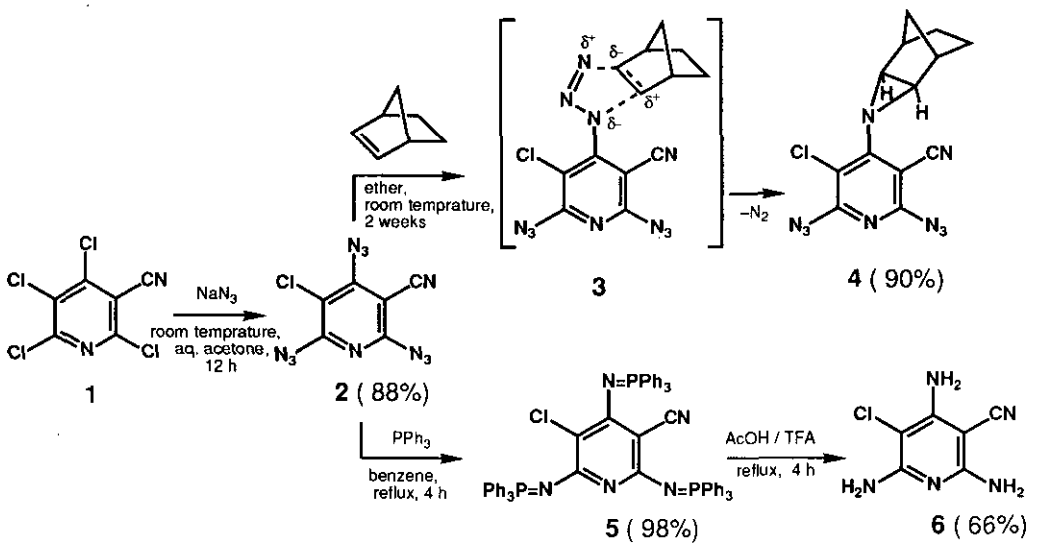
Abstract—Tetrachloro-3-cyanopyridine reacts with anilines and/or sodium azide through replacement of three chlorine atoms at the 2-, 4-, and 6-positions, whereas with difunctional nucleophiles by replacement of chlorines at the 5- and 6-positions. Using these reactions synthesis of highly substituted pyridines has been developed.

Nucleophilic substitution of polychloropyridines by various nucleophiles is of considerable interest and has been extensively studied actually for all known polychloropyridines.[1] It is surprising that so little has been published[2-4] concerning the chemistry of tetrachloro-3-cyanopyridine (**1**) which could be a good starting material in the synthesis of various pyridine derivatives. In our previous paper[5] we have shown that the reaction of **1** with anilines led only to monoamination of **1** at the 4- and 6-positions to give corresponding 4- and 6-arylamino substituted pyridines. At the same time it was considered important to develope the method of the replacement of several chlorine atoms in **1**. In this paper we wish to report the synthesis of highly substituted pyridines through nucleophilic substitution of chlorine atoms at different positions of **1**.

As has been reported by Pannell,[4] some of polychlorinated pyridines can give in the reactions with sodium azide corresponding triazidopyridines. Nevertheless, their

attempt to obtain triazidopyridine in the reaction of **1** with sodium azide in refluxing DMF gave only 6-azidotrichloro-3-cyanopyridine. We have found that when the reaction is carried out in aqueous acetone, the replacement of three chlorine atoms at the 2-, 4-, and 6-positions of **1** takes place even under remarkably mild conditions (0 °C) to give triazidopyridine (**2**) in high yield.



Taking into account the fact that azido group can be easily modified in numerous fashions into other *N*-containing functions[6] and there were no any literature regarding the reactivity of triazidopyridines, it was of interest to apply some of the most known transformations of azido group of **2**. It was found that the reaction of **2** with such reactive dipolarophile as norbornene[7] proceeds regioselectively only on azido group at the 4-position to give cycloadduct (**4**) as the sole product in high yield. As expected, adduct (**4**) proved to have the less hindered exo-configuration what follows from the absence of coupling between the C_2 and C_3 endo-protons at δ 2.90 and the bridgehead protons at δ 2.73 ppm.[8] The regioselectivity found in the cycloaddition reactions of **2** may be the useful method of selective modification of azido group in this compound. As can be seen from the Table 1, after replacement of chlorine atoms at the 2-, 4-, and 6-positions of **1** by electron-

withdrawing azido group the less increase of electrophilicity is observed for the 4-position (downfield shift of C_4 signal from δ 148.1 *in* **1** *only to* δ 148.9 *ppm in* **2**)

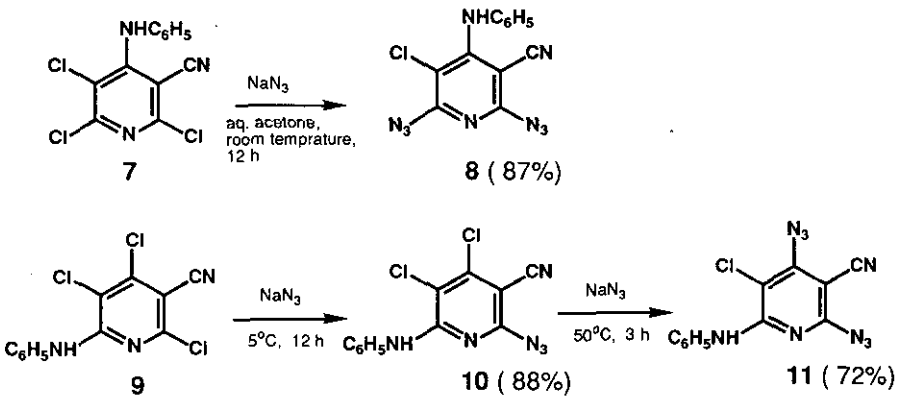
Table 1. ^{13}C nmr chemical shifts (δ/ppm) for the pyridine ring of compounds (**1, 2, 4, 7-10**).

Compd	Solvent	C-2	C-3	C-4	C-5	C-6
1[a)]	$CDCl_3$	148.9	111.7	148.1	129.2	151.6
2	$CDCl_3$	154.0	87.9	148.9	107.9	154.5
4	$CDCl_3$	152.9	86.6	159.6	105.7	154.7
7	$CDCl_3$	151.4	94.5	152.7	116.4	153.5
8	DMSO-d_6	151.6	83.5	155.4	103.8	152.3
9	$CDCl_3$	151.9	101.6	145.4	113.8	152.9
10	$CDCl_3$	152.7	94.3	147.3	108.0	153.2

a) B. Iddon, A. G. Mack, H. Suschitzky, J. A. Taylor, and B. J. Wakefield, J. Chem. Soc., Perkin Trans. 1, 1980, 1370.

than other protons. This can be explained by the steric hindrance caused by the ortho-substituents Cl and CN which reduces the conjugation between azido group and pyridine ring. Because the activation energe for the cycloaddition reactions of aromatic azides is attributed to the decrease of the resonance energy between azido group and aromatic ring[9] the higher reactivity of azido group at the 4-position of **2** may be explained by the lowest energy of activation for the cycloaddition on the azido group at C_4 in three azido groups. While the cycloaddition reactions of azides can be considered as electrophilic attack by dipolarophile at the α-N atom of azido group,[9] the reactions of azides with triphenylphosphine represent the case of nucleophilic attack by PPh_3 at the azide terminus.[10] It was found that all three azido groups of **2** readily react with PPh_3 to give triiminophosphorane (**5**) in high yield. The hydrolysis of iminophosphoryl groups of **5** in the mixture of acetic and

trifluoroacetic acids[6] gave triaminopyridine (**6**) which may be useful starting material in the synthesis of various pyridine derivatives.

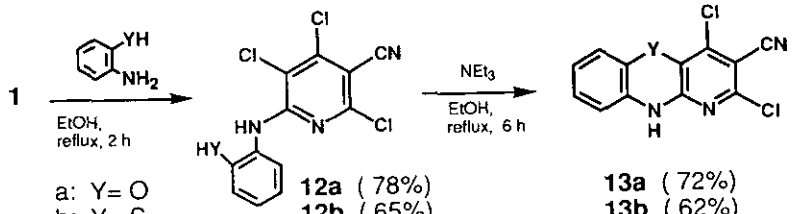


Another way of the synthesis of highly substituted pyridines on the basis of **1** can be reactions of **1** with nucleophiles such as anilines[5] followed by the replacement of remaining chlorine atoms at the electrophilic positions of monoaminated products by sodium azide. Thus, by analogy with **1**, the reaction of 4-phenylaminopyridine (**7**) with sodium azide took place readily at room temperature to give diazidopyridine (**8**) in high yield. It is interesting to note that diazidopyridine (**8**) was also unreactive toward cycloaddition reaction with norbornene similar to the related diazidopyridine (**4**) (close similarity in the ^{13}C nmr spectra of **4** and **8** is shown in Table 1).

In contrast to **7**, the reaction of **9** with sodium azide at room temperature gave mainly monoazidopyridine (**10**) reacting at the 2-position. The low reactivity of the 4-position in **9** is in good agreement with ^{13}C nmr spectrum of this compound. As can be seen from the Table 1, the replacement of chlorine at the 2-position in **9** by azido group results in an increase of the electrophilicity of the 4-position of **10** (downfield shift of C-4 from δ 145.4 in **9** to δ 147.3 ppm in **10**) and, as a result, at an elevated temperature (50 °C) diazidopyridine (**11**) was obtained in good yield.

The replacement of chlorine atoms in **1** is possible not only at the electrophilic 2-, 4-, and 6-positions but also at the 5-position as well. Thus, the reaction of **1** with

difunctional nucleophiles such as *o*-aminophenol, *o*-aminothiophenol, and *o*-phenylenediamine gave 6-arylaminopyridines (**12a-c**) which, by the action of triethylamine in boiling ethanol, readily underwent intramolecular cyclization to give corresponding pyrido[2,3-*b*]benzoxazine (**13a**), benzthiazine (**13b**), and quinoxaline (**13c**).



It is interesting to note that in electron impact mass spectra of **12a-c**, one of the main fragmentation process was the formation of intensive (90-100%) fragment ions corresponding to m/z of molecular ions of **13a-c**.

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8. **4**: ^{1}H Nmr (200 MHz, $CDCl_3$) δ 0.94 (1H, d, J=10.7 Hz, 8-H_{syn}), 1.32 (3H, m, 8-H_{anti}, 6,7-H_{exo}), 1.58 (2H, m, 6,7-H_{endo}), 2.73 (2H, s, bridgehead-H), 2.90 (2H, s, CHNCH); Signals of substituents on pyridine ring in ^{13}C nmr (50 MHz, $CDCl_3$) δ 25.6, 28.7, 36.8, 43.8, 112.7.

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