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Short communication

Di- and triazidation of 3-chlorotetrafluoropyridine

Sergei V. Chapyshev *

Institute of Problems of Chemical Physics, Russian Academy of Sciences, 142432 Chernogolovka, Moscow Region, Russian Federation

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ABSTRACT

3-Chlorotetrafluoropyridine and pentafluoropyridine readily react with an excess of sodium azide in dimethylsulfoxide at room temperature to give corresponding 2,4,6-triazido-3-chloro-5-fluoropyridine and 2,4,6-triazido-3,5-difluoropyridine in high yields. The reaction of asymmetric 3-chlorotetrafluoropyridine with two equimolar amounts of sodium azide under similar reaction conditions occurs regioselectively to give 2,4-diazido-5-chloro-3,6-difluoropyridine as a sole product. ^{19}F, ^{13}C and ^{15}N NMR spectral characteristics of the triazides suggest that these compounds can be of interest as cross-linking reagents for polymer chemistry and as starting materials for organic synthesis.

1. Introduction

Fluorine-containing aromatic azides are widely used as photoaffinity labeling reagent in molecular biology and as photoactive cross-linking additives in polymer chemistry [1]. A typical representative of such compounds is 4-azidotetrafluoropyridine obtained by the reaction of pentafluoropyridine with equimolar amounts of sodium azide in various organic solvents at room temperature [2]. Upon UV irradiation, this azide produces the photochemically very stable tetrafluoropyridyl-4-nitrene that efficiently reacts with biomacromolecules to form new C–N or S–N bonds [1–3]. The position of such new bonds in modified biomacromolecules can readily be established by ^{19}F NMR spectroscopy.

Until now, there is known only one fluorinated aromatic triazide, namely, 2,4,6-triazido-3,5-difluoropyridine (**2**), obtained by the reaction of pentafluoropyridine (**1**) with an excess of sodium azide in boiling aqueous acetone (Scheme 1) [4]. The photolysis of this triazide in argon at 4 K has been used for photochemical generation of septet 3,5-difluoropyridyl-2,4,6-trinitrene (**3**) as a model of super high-spin organic molecular systems [5]. Extensive EPR studies have shown that trinitrene **3**, due to the presence of two fluorine atoms on the pyridine ring, exhibited stronger magnetic properties on comparison with septet 3,5-dichloropyridyl-2,4,6-trinitrene and 3,5-dicyanopyridyl-2,4,6-trinitrene [6].

The commercially available 3-chlorotetrafluoropyridine (**4**) is yet another promising precursor of fluorine-containing aromatic triazides. Previous studies have shown that this pyridine readily reacts with an equimolar amount of sodium azide in dry acetonitrile at room temperature to give 4-azido-3-chlorotrifluoropyridine (**5**) in 76% yield [2]. The further azidation of pyridine **5** can, theoretically, lead to the formation of isomeric 2,4-diazido-5-chloro-3,6-difluoropyridine (**6**) and 2,4-diazido-3-chloro-5,6-difluoropyridine (**7**), which should then interact with an excess of sodium azide to yield 2,4,6-triazido-3-chloro-5-fluoropyridine (**8**) (Scheme 2). Thus, recent studies have shown that *tris*-defluorination of pyridine **4** with liquid ammonia occurred step-wise to give, at the first stage, 4-amino-3-chlorotrifluoropyridine, then a mixture of isomeric 2,4-diamino-5-chloro-3,6-difluoropyridine and 2,4-diamino-3-chloro-5,6-difluoropyridine in the 3:1 ratio, and, finally, 2,4,6-triamino-3-chloro-5-fluoropyridine [7]. The latter could be obtained only under severe reaction conditions (160 °C, high pressure, 20 h) and in only 65% yield. Unlike triamination, triazidation of polyhalopyridines does not require, as a rule, the use of high temperature and can be considered as a useful alternative approach to the synthesis of fluorinated polyfunctional pyridines [8].

In this work we report on a highly regioselective diazidation and a remarkably mild triazidation of pyridine **4** in the reaction with two and three equimolar amounts of sodium azide, respectively. The reaction conditions developed for the synthesis of triazide **8** allowed us also to considerably simplify the synthesis of triazide **2**.

* Fax: +7 496 5349676.
E-mail address: chap@icp.ac.ru.

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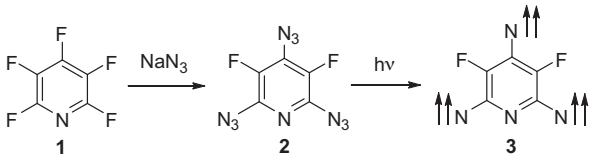
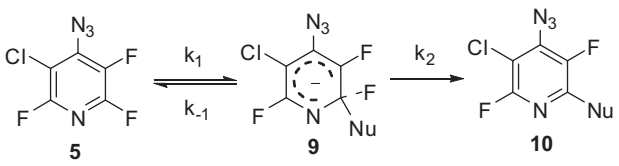


Scheme 1.



Scheme 3.

2. Results and discussion

In the search of optimum conditions for triazidation of pyridine **4**, aqueous acetone and dimethylsulfoxide were tested as solvents. According to previous studies, aqueous acetone was the most optimum solvent for triazidation of pentachloropyridine [8a]. On the other hand, this solvent was not the best for triazidation of pyridine **1**, from which the final triazide **2** was obtained in only 62% yield [4]. These effects are explained by two factors: (i) electronic effects of ring halogens and (ii) different electron-withdrawing abilities of chlorine and fluorine atoms [7]. While the replacement of α-chlorine atoms in pentachloropyridine is activated by both *ortho*- and *para*-chlorine effects from atoms in β-positions, the replacement of α-fluorine atoms in fluoropyridine **1** is activated only by *ortho*-fluorine effect, but deactivated by *para*-fluorine effect. In addition, the azido group is a weaker electron-withdrawing substituent on comparison with fluorine atom and a stronger electron-withdrawing substituent on comparison with chlorine atom, therefore partly azidated chloropyridines are more reactive and partly azidated fluoropyridines are less reactive than their non-azidated precursors in the reactions of triazidation.

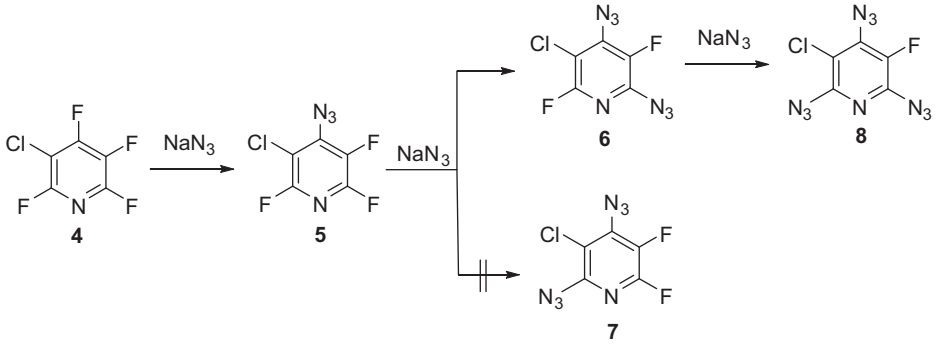
The reaction of fluoropyridine **4** with two equimolar amounts of sodium azide in aqueous acetone at room temperature yielded only monoazide **5**, according to TLC analysis (Scheme 2). However, on boiling the reaction mixture at 77 °C for 12 h, diazide **6** was isolated in 92% yield. The same diazide was also obtained in 96% yield from the reaction of fluoropyridine **4** with two equimolar amounts of sodium azide in dimethylsulfoxide at room temperature. Moreover, fluoropyridine **4** readily reacted with three equimolar amounts of sodium azide in dimethylsulfoxide at room temperature to give triazide **8** in 95% yield (Scheme 2).

The structures of new azides **6** and **8** are confirmed by analytical and spectroscopic data. Thus, for instance, the splitting of the signal of C–Cl atom at δ 103.4 with $^{2}J_{C,F}$ = 38 Hz and $^{3}J_{C,F}$ = 1 Hz in the ^{13}C NMR spectrum of diazide **6** unambiguously indicates that α-fluorine atom of this compound is located in the position 2. The formation of diazide **6** results from selective nucleophilic substitution of fluorine atom for azide group in the position 6 of intermediate monoazide **5**. This reaction is activated by both *para*-effect of β-chlorine atom and by *ortho*-effect of β-fluorine atom. Since an alternative replacement of fluorine atom for azide group in the position 2 of monoazide **5** is activated by only *ortho*-effect of β-chlorine atom and deactivated by *para*-effect of β-fluorine atom, this reaction pathway appears to be much less favorable.

The facile triazidation of fluoropyridine **4** in dimethylsulfoxide at room temperature has prompted us to investigate triazidation of fluoropyridine **1** under similar conditions. Previous studies have shown that the reaction of pyridine **1** with an excess of sodium azide on boiling in aqueous acetone for 48 h affords just a mixture of 2,4-diazido-3,5,6-trifluoropyridine and triazide **2** in the 1:3 ratio, respectively [4]. Unlike the reaction in aqueous acetone, fluoropyridine **1** readily reacted with three equivalences of sodium azide in dimethylsulfoxide at room temperature to give very pure (>99%) triazide **2** in 96% yield (Scheme 1).

The effect of dimethylsulfoxide on azidation of fluoropyridines can be rationalized from mechanistic considerations. According to theory, the rate-determining stage in S_NAr reactions of fluoroaromatics with hard nucleophiles ($AlkO^-$, NH_3, $AlkNH_2$, etc.) is the formation of σ-complex **9** (Scheme 3) [9]. In such reactions, the reactivity of aryl halides decreases in the order of fluoride > chloride > bromide > iodide. However, in reactions with soft nucleophiles ($AlkS^-$), the opposite order of reactivity for aryl halides is observed [9]. The rate-determining stage in such reactions is the bond breaking between carbon and halogen atoms in σ-complex **9**. The rate of this stage can dramatically be increased (by five–six orders of magnitude) if the reaction is carried out in aprotic dipolar solvents with large dielectric constant ε [9]. On comparison with fluoropyridines **1** and **4**, pentachloropyridine much easier undergoes triazidation [8a]. This fact suggests that N_3^- anion acts in these reactions as a soft nucleophile, and the rate-determining stage in azidation of fluoropyridines is the elimination of F^- anion from σ-complex **9**. Therefore, the use of dimethylsulfoxide (ε = 49) as a solvent considerably facilitates the azidation of fluoropyridines.

Triazides **2** and **8** represent white solid materials that are almost insensitive toward impact and friction. Thus, for instance, they do not explode on intense grinding in a mortar or strong hammering. As usual, aromatic polyazides are sensitive toward impact and friction if their molecules contain nitrogen more than 70% of the molecular weight [10]. After melting, triazides **2** and **8** transform into transparent, colorless liquids that do not decompose on heating until 155 °C. In ^{19}F NMR spectra, these triazides



Scheme 2.

display signals at δ −146.4 and −148.6 ppm that are shifted by ~30 ppm to the lower field on comparison with signals of fluorine atoms in the corresponding 2,4,6-triamino-substituted derivatives [7]. These spectral differences between azido- and amino-substituted fluoropyridines allow one to conduct a ^{19}F NMR spectroscopic monitoring of cross-linking processes in polymers, on using triazides **2** and **8** as photoactive cross-linking reagents. Owing to a simple method of preparation, low impact sensitivity and useful spectroscopic characteristics, triazides **2** and **8** can be promising cross-linking reagents for molecular biology and polymer chemistry.

Due to the presence of nonequivalent azido groups, triazides **2** and **8** can also be of interest as starting materials for organic synthesis. Previous studies have shown that electron-deficient γ-azido groups of 2,4,6-triazidopyridines selectively reacted with electron-rich dipolarophiles (RC≡CH, *t*-BuC≡P, norbornene), selectively added triphenylphosphine and underwent selective reduction till amines [11]. By contrast, electron-rich α-azido groups of such triazides selectively reacted with electron-poor dipolarophiles and selectively underwent photolysis and γ-radiolysis to form nitrenes [11]. According to ^{15}N NMR spectroscopy, similar selective reactions can also be expected for nonequivalent azido groups of triazides **2** and **8**. A relatively simple ^{15}N NMR spectrum was recorded for C_{2V} symmetric triazide **2**. In this spectrum, nitrogen atom of the pyridine ring is manifested as a triplet with $^3J_{N,F}$ = 5 Hz at δ 131.6 ppm. Much more intense signals of nitrogen atoms of two α-azido groups are manifested at δ −139.7 (N_β), −141.8 (N_γ) and −277.7 (N_α) ppm, while nitrogen atoms of the γ-azido group display signals at δ −137.5 (N_β), −141.5 (N_γ) and −294.1 (N_α) ppm. The assignment of signals to the central N_β and the terminal N_γ atoms of azido groups was based on a large difference in intensities of such signals in ^{15}N NMR spectra of azides with natural isotopic abundance [12]. According to theory, electron-deficient azido groups show signals of the N_α atoms at very high magnetic field [13]. Therefore, the γ-azido group of triazide **2** can be classified as much more electron-deficient group on comparison with α-azido groups. In ^{15}N NMR spectrum of asymmetric triazide **8**, nitrogen atom of the pyridine ring is manifested already as a doublet with $^3J_{N,F}$ = 4.7 Hz at δ 131.6 ppm. A signal at δ −287.2 ppm can safely be assigned to the N_α atom of the γ-azido group. This group is less electron-deficient in respect with the γ-azido group of difluorinated triazide **2**. Other eight signals of nitrogen atoms of three nonequivalent azido groups can be assigned only conventionally. Thus, for instance, if to suppose that α-azido groups of triazide **8** display nearly the same spectral characteristics, the following assignment can be suggested: δ −136.6 (N_β), −140.5 (N_γ) and −270.9 (N_α) ppm for the azido group in the position 2; δ −136.5 (N_β), −140.4 (N_γ) and −276.7 (N_α) ppm for the azido group in the position 6, and δ −139.5 (N_β) and −142.4 (N_γ) ppm for the azido group in the position 4. In this case, the azido group in the position 2 of triazide **8** is the least electron-deficient azido group and should be decomposed first upon the action of short-wavelength UV and γ-irradiation.

3. Conclusion

3-Chlorotetrafluoropyridine and pentafluoropyridine readily undergo triazidation with sodium azide in dimethylsulfoxide at room temperature to give triazides **2** and **8** in high yields. Diazidation of asymmetric 3-chlorotetrafluoropyridine with sodium azide under similar reaction conditions occurs regioselectively to give diazide **6** as a sole product. ^{19}F, ^{13}C and ^{15}N NMR spectral characteristics of triazides **2** and **8** suggest that these compounds can be of interest as cross-linking reagents for polymer chemistry and as starting materials for organic synthesis.

4. Experimental

4.1. Materials and instruments

Melting points were obtained with Shimadzu DSC-50 thermal analyzer. ^{13}C and ^{19}F NMR spectra were recorded on Bruker DPX-250 spectrometer (62.90 and 233.36 MHz for ^{13}C and ^{19}F correspondingly) using residual signals of the deuterated solvent and C_6F_6 (δ = −163.0 ppm from CCl_3F) as internal standards; δ are given in ppm relative to TMS and CCl_3F, *J* are given in Hz. ^{15}N NMR spectra were recorded on Bruker Avance III-500 spectrometer (50.68 MHz) using residual signal of CD_3NO_2 (δ = 0 ppm) as internal standard; δ are given in ppm relative to CD_3NO_2. IR spectra were recorded on Bruker Equinox 55 FTIR instrument. UV spectra were recorded on Varian Cary 1 UV–Vis spectrometer. Elemental analyses were performed on LECO-CHNS-932 analyzer. Plates Kieselgel 60 F_{254} (Merk) were used for analysis of the reaction mixtures. Sodium azide, acetone, ethanol, dimethylsulfoxide, 3-chlorotetrafluoropyridine and pentafluoropyridine were obtained from commercial sources and used without further purification.

4.2. Safety precautions

Triazides **2** and **8** are typical representatives of high-energy materials that can show unpredictable behavior. For example, they can explode on pyrolitic combustion with MgO during the elemental analysis for fluorine atoms.

4.3. Synthetic procedures

4.3.1. 2,4-Diazido-5-chloro-3,6-difluoropyridine (6)

Method A. A solution of 3-chlorotetrafluoropyridine (**4**) (1.86 g, 10 mmol) and NaN_3 (1.36 g, 22 mmol) in 100 mL of aq acetone (10% of water) was boiled for 12 h, then the solvent was removed under vacuum, and a solid residue was washed with water, dried on air and crystallized from ethanol. Diazide **6** (2.13 g, 92%) was obtained as colorless crystals (mp 28 °C).

UV (MeOH): λ_{max} (log ε) 213 (4.21), 242 (4.34), 307 (3.90) nm.

IR (microcrystalline film): ν 2152vs and 2111vs (N_3); 1608s, 1594s, 1574m, 1462s, 1431s, 1398s, 1347w, 1258s, 1231s, 1204m, 1167m, 1048w, 956m, 899s, 807w, 794w, 735w, 593w, 536w cm^{-1}.

^{13}C NMR ($CDCl_3$): δ 103.4 (dd, $^2J_{C,F}$ = 38, $^3J_{C,F}$ = 1, C-5), 138.6 (d, $^2J_{C,F}$ = 9, C-4), 138.7 (d, $^2J_{C,F}$ = 11, C-2), 140.4 (dd, $^1J_{C,F}$ = 259, $^4J_{C,F}$ = 5, C-3), 153.3 (dd, $^1J_{C,F}$ = 240, $^4J_{C,F}$ = 3, C-6).

^{19}F NMR ($CDCl_3$): δ −71.6 (d, 1F, $J_{F,F}$ = 26, F-6), −146.9 (d, 1F, $J_{F,F}$ = 26, F-3).

Anal. Calcd. for $C_5ClF_2N_7$: C, 25.94; N, 42.34. Found: C, 26.19; N, 42.12.

Method B. A solution of 3-chlorotetrafluoropyridine (**4**) (1.86 g, 10 mmol) and NaN_3 (1.36 g, 22 mmol) in 10 mL of DMSO was stirred at room temperature for 10 h, then the reaction mixture was poured into ice water, the solid product was filtered off, washed with water, dried and crystallized from ethanol. Yield 2.22 g (96%).

4.3.2. 2,4,6-Triazido-3-chloro-5-fluoropyridine (8)

A solution of 3-chlorotetrafluoropyridine (**4**) (1.86 g, 10 mmol) and NaN_3 (2.08 g, 32 mmol) in 10 mL of Me_2SO was stirred at room temperature for 10 h, then the reaction mixture was poured into ice water, the solid product was filtered off, washed with water, dried on air and crystallized from ethanol. Triazide **8** (2.42 g, 95%) was obtained as colorless crystals (mp 65–66 °C).

UV (MeOH): λ_{max} (log ε) 202 (4.30), 250 (4.55), 309 (3.89) nm.

IR (microcrystalline film): ν 2150s, 2130vs, 2110w (N_3); 1597w, 1560w, 1453vs, 1413vs, 1396s, 1376s, 1263m, 1229w, 1195w, 1152w, 948w, 900m, 789w, 735w, 605w, 537w cm^{-1}.

^{13}C NMR ($CDCl_3$): δ 107.0 (d, $^3J_{C,F}$ = 2, C-3), 137.2 (d, $^2J_{C,F}$ = 9, C-4), 139.7 (d, $^2J_{C,F}$ = 11, C-6), 140.0 (d, $^1J_{C,F}$ = 260, C-5), 145.9 (d, $^4J_{C,F}$ = 4, C-2).

^{19}F NMR ($CDCl_3$): δ −148.6 (s, 1F, F-5).

^{15}N NMR ($CDCl_3$): δ −131.6 (d, 1 N, $^3J_{N,F}$ = 4.7, N_{Py}), −136.5 (s, 1 N, N_β of 6-N_3), −136.6 (s, 1 N, N_β of 2-N_3), −139.5 (s, 1 N, N_β of 4-N_3), −140.4 (s, 1 N, N_γ of 6-N_3), −140.5 (s, 1 N, N_γ of 2-N_3), −142.4 (s, 1 N, N_γ of 4-N_3), −270.9 (s, 1 N, N_α of 2-N_3), −276.7 (s, 1 N, N_α of 6-N_3), −287.2 (s, 1 N, N_α of 4-N_3).

Anal. Calcd. for C_5ClFN_{10}: C, 23.59; N, 55.02. Found: C, 23.71; N, 54.92.

*4.3.3. 2,4,6-Triazido-3,5-difluoropyridine (**2**)*

A solution of pentafluoropyridine (**1**) (1.69 g, 10 mmol) and NaN_3 (2.08 g, 32 mmol) in 10 mL of Me_2SO was stirred at room temperature for 10 h, then the reaction mixture was poured into ice water, the solid product was filtered off, washed with water, dried on air and crystallized from ethanol. Triazide **2** (2.29 g, 96%) was obtained as colorless crystals (mp 75–76 °C).

UV (MeCN): λ_{max} (log ε) 238 (4.60), 302 (3.84) nm.

IR (microcrystalline film): ν 2168vs, 2140m, 2108m (N_3); 1628w, 1615w, 1485m, 1432vs, 1400w, 1380w, 1340vs, 1280w, 1238w, 964w, 938w, 812w, 664w, 535w cm^{-1}.

^{13}C NMR ($CDCl_3$): δ 129.6 (t, $^2J_{C,F}$ = 10, C-4), 136.3 (dd, $^2J_{C,F}$ = 11, $^4J_{C,F}$ = 5, C-2, C-6), 138.7 (d, $^1J_{C,F}$ = 260, C-3, C-5).

^{19}F NMR ($CDCl_3$): δ −146.4 (s, 2F, F-3, F-5).

^{15}N NMR ($CDCl_3$): δ −131.6 (t, 1 N, $^3J_{N,F}$ = 5, N_{Py}), −137.5 (s, 1 N, N_β of γ-N_3), −139.7 (s, 2 N, N_β of α-N_3), −141.5 (s, 1 N, N_γ of γ-N_3), −141.8 (s, 2 N, N_γ of α-N_3), −277.7 (s, 2 N, N_α of α-N_3), −294.1 (s, 1 N, N_α of γ-N_3).

Anal Calcd. for $C_5F_2N_{10}$: C, 25.22; N 58.82. Found: C, 25.48; N, 58.74.

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