N,N-Dialkyl-*N′*-(2-pyridyl)formamidines and *N*-(3,5-dichloro-2-pyridyl)formamide. Reactions of azides, tetrazoles and nitrenes with nucleophiles. Part 1

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Abstract
6,8-Dichlorotetrazolo[1,5-*a*]pyridine/2-azido-3,5-dichloropyridine **3** undergoes a slow reaction with dialkylamines (R = ethyl or propyl) in the dark at room temperature to afford 2-pyridylformamidines **8**, which on chromatography on silica gel hydrolyse to afford the formamide **9**.

Keywords: Azides, formamides, formamidines, nitrenes, pyridines, tetrazoles

Introduction

Heterocyclic compounds undergo numerous and sometimes unexpected transformations.[2] The valence tautomeric tetrazolo[1,5-*a*]pyridines/2-azidopyridines **1** are convenient sources of 5*H*- and 1*H*-1,3-diazepines (e.g. **2)** via ring expansion of photochemically (and sometimes thermally) generated 2-pyridylnitrenes to 1,3-diazacyclohepta-1,2,4,6-tetraenes followed by trapping with nucleophiles, most commonly amines.[3,4] However, the chlorine atom in position 8 of tetrazole **3** undergoes substitution by strong nucleophiles (RO^-) in the dark. The resulting 8-alkoxy-6-chlorotetrazolo[1,5-*a*]pyridines **4** undergo photochemical ring expansion to afford 5*H*-1,3-diazepines **5** with amines.[3] Some tetrazolopyridines, e.g. **6**, undergo a rapid, quantitative ring opening reaction with nucleophiles such as sodium hydroxide[5] or dimethylamine[6] in the dark to afford dienyltetrazoles, e.g. **7**.

We now report an unexpected dark reaction of tetrazolopyridine **3** with amines.

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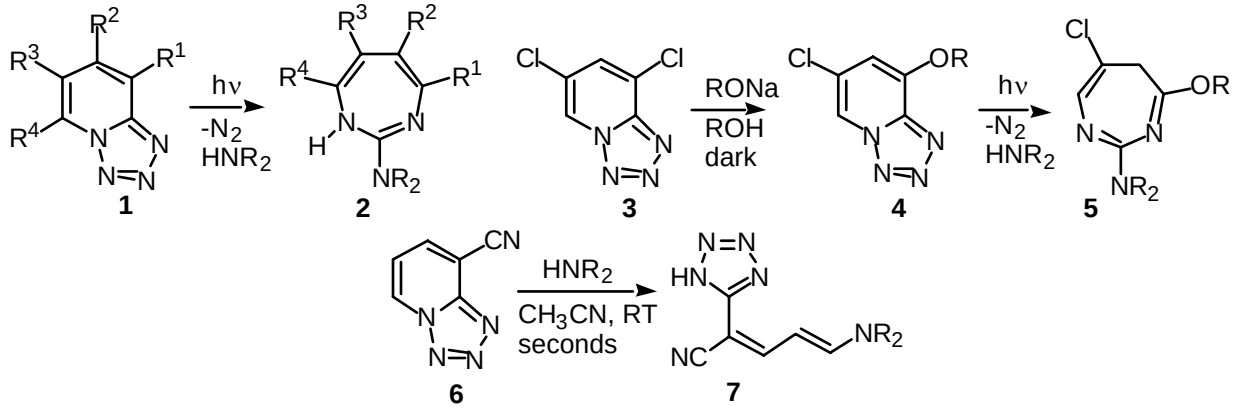
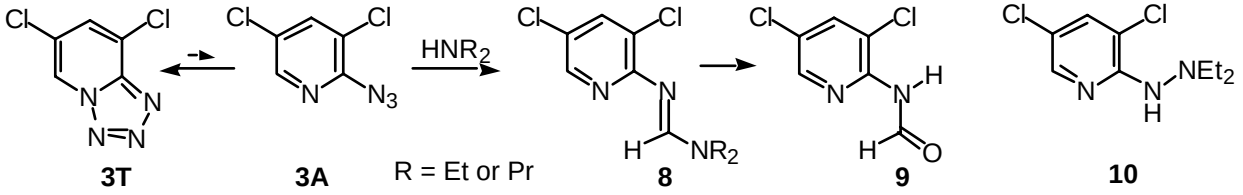


Results and Discussion

6,8-Dichlorotetrazolo[1,5-*a*]pyridine/2-azido-3,5-dichloropyridine **3** exists as the tetrazole **3T** in the solid state, but as an equilibrium mixture of tetrazole and azide (**3T/3A**) in solution.[3] Compound **3** undergoes a slow reaction with dialkylamines (R = ethyl or propyl) in the dark at room temperature to afford 2-pyridylformamidines **8**. The same product **8** is obtained whether the solvent is degassed or not, or whether the neat dialkylamine is used as a solvent.

The formamidine **8** (R = ethyl) was fully characterized spectroscopically, but chromatography on silica gel resulted in complete hydrolysis to afford the formamide **9**. The same formamide was also obtained from **8** (R = propyl).



This formal 'carbon acquisition' belongs to a rare type of reaction first observed by Stanovnik, Tisler and their coworkers on both thermolysis (reflux) and photolysis of azidoazines (particularly azidoazolopyridazines) in secondary amines $(RCH_2)_2NH$.[7] These workers postulated a reaction sequence involving dehydrogenation of the dialkylamine by the (triplet) nitrene to form imines and/or vinyl(alkyl)amines, RCH=N-CH_2R and R'CH=CH-NH-CH_2R. 1,3-Dipolar cycloaddition of the azide to the vinylamines followed by decomposition of the triazolines so formed would give rise to heteroarylformamidines. Amidine formation has also been observed in photolyses of pentafluorophenyl azide (up to 50 %)[8] and *o*-azidobenzonitrile (10 %)[9] in diethylamine. Thus, this type of reaction always involves electron deficient aryl- or heteroaryl azides and/or nitrenes.

The formation of hydrazines Ar-NH-NR_2 from the reactions of aryl azides and secondary amines is also a reaction typical of electron deficient nitrenes.[7a,8,9,10] It has not been observed with phenyl azide itself or electropositively substituted aryl azides. Schuster reasoned that it is

the electrophilic singlet nitrene that gives hydrazine, whereas the triplet nitrenes are thought to be responsible for amine formation by hydrogen abstraction.[11] However, Schuster asserted that this is not the only pathway to aniline in the case of photolysis of 4-nitrophenyl azide in alkylamines, and that product-determining electron transfer from the alkylamine to form the nitrene radical anion Ar-$N^{\bullet-}$ and the amine radical cation $R_3N^{\bullet+}$ is also involved. The nitrene radical anion leads to aniline via H abstraction from the amine radical cation, which thereby affords an immonium ion $R_2N(^+)=CH_2R'$.[11] This immonium ion can be the source of dealkylation of tertiary amines. It may also be the source of Stanovnik's vinylamines mentioned above, which are required for amidine formation via the 1,3-dipolar cycloaddition reaction. In our reaction of tetrazole/azide **3** in diethylamine we also observed the intermittent formation of hydrazine **10** when the reaction was carried out with microwave heating (80 ^oC) for 10 min. Only a very small amount of amidine **8** was formed under these conditions. Hydrazine **10** was observed by GCMS but disappeared again in the course of further reaction, when the **3** was converted to amidine **8** (6 weeks at RT; unreacted tetrazole/azide **3** still present; no other product detected by GCMS). Therefore, **10** has not been isolated and characterized. Thus, tetrazole/azide **3** reacts as an electron deficient azide or nitrene. The amazing fact is that this takes place thermally, at room temperature. There is no evidence for nitrene formation in the amidine-forming reaction, since the typical nitrene product, 2-amino-3,5-dichloropyridine, is missing. The room temperature electron transfer reaction between the amine and the azide/tetrazole itself (rather than the nitrene) is an attractive possibility, and further mechanistic investigation is planned. The formation of the hydrazine **10** would be a separate pathway, taking place via the electrophilic singlet nitrene, which is formed only on heating.

Experimental Section

***N'*-(3,5-Dichloro-2-pyridyl)-*N,N*-diethylformamidine (8).** 3,5-Dichlorotetrazolo[1,5-*a*]pyridine **3T** (0.5g, 2.6 mmol) was dissolved in 50 ml of dry and degassed dioxane, and freshly distilled diethylamine (5 mL) was added. The reaction mixture was protected from light and stirred at room temperature under N_2. The progress of the reaction was followed by TLC and GCMS analysis. The time necessary to complete the reaction varied from 12 to 15 weeks. The solution was concentrated under reduced pressure, and the red oily residue was purified by flash chromatography (hexanes-EtOAc, 7:3) to give **8** as a pale yellow oil (0.306g, 47%); ^1H NMR (300 MHz, acetone-d_6) δ 8.49 (s, 1H), 8.08 (d, 1H, 6-H, $J_{4,6}$ = 1.7 Hz), 7.71 (d, 1H, 4-H, $J_{4,6}$ = 1.7 Hz), 3.61 (q, 2H, NEt_2), 3.46 (q, 2H, NEt_2), 1.22 (t, 6H, NEt_2); ^{13}C NMR (75 MHz, acetone-d_6) δ 158.8 (2-C), 156.0 (amidine-C), 145.6 (6-C), 137.8 (4-C), 125.7 (5-C), 124.2 (3-C), 47.3 (NEt_2), 41.2 (NEt_2), 15.7 (NEt_2), 13.0 (NEt_2); IR (neat) 2973 w, 2932 w, 1607 s, 1556 s, 1461 w, 1411 s, 1382 m, 1359 m, 1307 w, 1262 m, 1222 m, 1202 m, 1122 m, 1108 m, 1081 w, 1052 m, 982 w, 890 w, 836 m, 784 w, 751 m, 753 m, 654 w cm-1. MS (EI) *m/z* 245 (M^+, 52 %), 247 ((M+2), 34), 247, ((M+4), 5). 216 (29), 210 (100), 188 (18), 162 (69), 146 (40), 110 (24), 72 (33), 58 (22). HRMS calcd. For $C_{10}H_{13}N_3Cl_2$ 245.0484. Found 245.0488.

The reaction is fully reproducible. Degassing the solution, or saturating it with CO_2, makes no difference. The same product was obtained by using cyclohaxane/diethylamine or diethylamine only as solvent. When dipropylamine was used in place of diethylamine, the product was *N*′-(3,5-dichloropyridin-2-yl)-*N*,*N*-dipropylformamidine, ^{13}C NMR (75 MHz, acetone-d_6) δ 157.2, 155.2, 144.4, 136.9, 124.9, 123.7, 53.7, 47.4, 22.3, 20.2, 11.5, 11.1); GCMS (EI) *m/z* 273 (M^+).

***N*-(3,5-Dichloro-2-pyridyl)formamide (9).** Column chromatography of **8** (R = ethyl) on silica gel using chloroform as the eluting solvent caused complete hydrolysis to give **9**, mp 185-186 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.41 (d, 1H, CHO, J = 10.1 Hz), 8.14 (d, 1H, 6-H, $J_{4,6}$ = 2.2 Hz), 8.11 (br, 1H, NH, vanishes upon addition of D_2O; the doublet at 9.41 ppm then collapses to a singlet), 7.70 (d, 1H, 4-H, $J_{4,6}$ = 2.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 161.7 (CHO), 145.7 (2-C), 145.1 (6-C), 137.6 (4-C), 126.9 (5-C), 117.3 (3-C); IR (KBr) 3203 br, 1710 vs, 1584 w, 1565 w, 1483 s, 1431 s, 1389 m, 1361 w, 1273 m, 1225 m, 1200 m, 1126 w, 1110 w, 1058 m, 915 w, 892 m, 808 w, 774 w; MS (EI) *m/z* 190 (M^+, 20 %), 192 ((M+2), 12), 194 ((M+4), 2), 162 (100), 164 (70), 166 (11), 137 (20), 135 (39), 127 (54), 100 (22), 102 (8), 92 (18), 75 (20), 73 (24), 64 (20). The same product **9** was obtained by chromatography of **8** (R = propyl). An X-ray crystal structure of **9** will be published.[12]

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