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SHORT COMMUNICATION

Photocatalytic reaction of 4-cyanopyridine with tertiary amines

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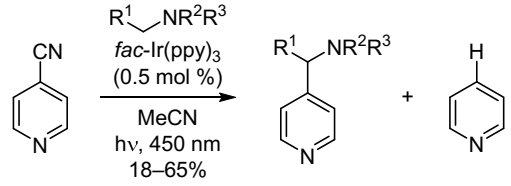


R^1, R^2 = H, Me, Et, *n*-Pr, *i*-Pr; R^3 = Et, *i*-Pr, *n*-Bu, $(CH_2)_2OH$, $(CH_2)_2NMe_2$

The reaction of 4-cyanopyridine with tertiary aliphatic amines photocatalyzed by *fac*-tris[2-phenylpyridinato-C^2,*N*]iridium(III) complex was studied. The reactions led to arylation of the α-C–H bond of the amine to form the corresponding pyridin-4-yl derivatives along with unsubstituted pyridine.

Keywords: 4-cyanopyridine, tertiary amines, arylation, C–H activation, visible-light photocatalysis.

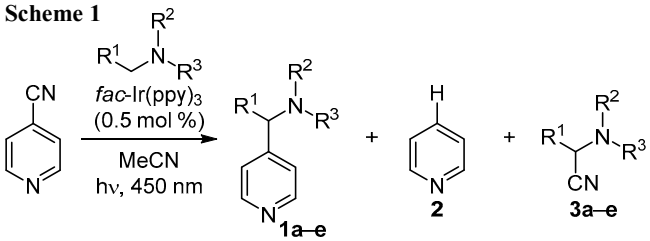
Visible- and UV-light photocatalysis has become a convenient and widely used tool of organic synthesis in recent years.[1,2] One of the uses of photocatalysis is the functionalization of α-C–H bonds in tertiary amines.[3–5] In these reactions, substituted benzylamines and their analogs, for example, tetrahydroisoquinolines, or *N*,*N*-dialkyl-substituted arylamines are the most often used substrates. Photocatalytic activation of aliphatic amines is also possible. For instance, the reaction of tertiary amines with trimethylsilyl cyanide in the presence of the rose bengal dye and air when irradiated with visible light led to α-amino-nitriles.[6] The possibility of α-C–H arylation of aliphatic amines with 2-chloroazoles in the presence of *fac*-tris-[2-phenylpyridinato-C^2,*N*]iridium(III) complex (*fac*-Ir(ppy)$_3$) under blue light irradiation has also been demonstrated.[7] In addition, aromatic nitriles can be used in photocatalytic arylation reactions.[8] Among other things, the photocatalytic benzylation of 4-cyanopyridine and its analogs with 1-benzyl-1,2,3,4-tetrahydroisoquinolines is known.[9] In the present study, the photocatalytic reaction of 4-cyano-pyridine with tertiary aliphatic amines was investigated.

Irradiation of 4-cyanopyridine and Et_3N in MeCN in the presence of *fac*-Ir(ppy)$_3$ with blue light (450 nm) until complete conversion of cyanopyridine results in a mixture of 4-alkylaminopyridine **1a** and unsubstituted pyridine **2** (Scheme 1, Table 1). Aminonitrile **3a** was also detected in the reaction mixture by ^{1}H NMR spectroscopy. In the absence of irradiation or iridium complex, the reaction does not occur. Other widely used photocatalysts, such as tris-(2,2'-bipyridyl)ruthenium dichloride, eosin, rose bengal, and rhodamine 6G, lead to only trace amounts of products. Replacing MeCN with Me_2CO, DMF, THF, or PhH leads to a significant decrease in the reaction rate, and pyridine is found as the only reaction product in DMSO. Reducing catalyst loading to less than 0.5 mol % leads to a signifi-cant decrease in the reaction rate; at the same time, an increase in the loading of *fac*-Ir(ppy)$_3$ does not lead to a noticeable increase in the rate and yield of the reaction (see the Supplementary information file).

Previously, compound **1a** was obtained by irradiating a mixture of pyridine and Et_3N (in a 1:1 ratio by volume) with shortwave UV radiation (253 nm).[10] However, the yield of the target compound was extremely low — ~ 0.4% mixed with other products, and its isolation necessitated the use of preparative GLC. In this regard, the technique using a photocatalyst, despite the low yield of the product, is more preferable.

Other tertiary aliphatic amines also form α-C–H-arylation products (Scheme 1, Table 1). In sterically hindered diisopropylethylamine, arylation occurs solely at

Scheme 1



a R^1 = Me, R^2 = R^3 = Et; **b** R^1 = Me, R^2 = R^3 = *i*-Pr;
c R^1 = H, R^2 = Me, R^3 = $(CH_2)_2OH$;
d R^1 = H, R^2 = Me, R^3 = $(CH_2)_2NMe_2$; **e** R^1 = *n*-Pr, R^2 = R^3 = *n*-Bu

Table 1. Yields of compounds **1a–d** and ratios of products **1a–d**:**2** in reaction mixtures according to NMR spectroscopy data

Compound	Yield, %	Ratio **1a–d**:**2**
1a	25	1:2.4
1b	18	1:3.6
1c	65	2.8:1
1d	14 (54)*	5.5:1
1e	–** (8)	1:4.8

* Yield determined by NMR spectroscopy of the reaction mixture is given in parentheses.
** Compound was not isolated.

the ethyl group to form product **1b**. However, the main product of the reaction is unsubstituted pyridine. Methyl-substituted amines form arylation products with significantly higher yields. Thus, *N*,*N*-dimethylethanolamine reacts selectively with the 4-pyridyl fragment addition at the methyl group. Along with product **1c**, aminonitrile **3c** was isolated. Arylation of only the methyl group also occurs in the case of tetramethylethylenediamine (TMEDA). However, analysis of the reaction mixture by GC-MS showed that, along with the monoarylated product, a set of isomeric TMEDA diarylation products was obtained, which was not observed in the previous cases. Tributylamine forms product **1e** in admixture with a number of other substances, among which, according to GC-MS, predominates aminonitrile **3e**; it was not possible to isolate pyridine **1e** in pure form. The low reactivity of tributylamine in regards to the α-C–H arylation appears to be related to its poor solubility in MeCN — the reaction actually takes place in a two-phase system.

The structure of the obtained compounds was confirmed by NMR spectroscopy data. In the ^{1}H NMR spectra of compounds **1a–e**, the characteristic signals of the 4-substituted pyridyl ring are observed at 8.42–8.49 ppm (signals of protons H-2,6) and in the 7.17–7.35 ppm range (signals of protons H-3,5). Also, the carbon atoms of the 4-substituted pyridyl ring appear in the ^{13}C NMR spectrum in the intervals of 123.0–123.9 and 148.1–156.9 ppm. For all compounds, the peaks of the corresponding molecular ions are observed in the high-resolution mass spectra.

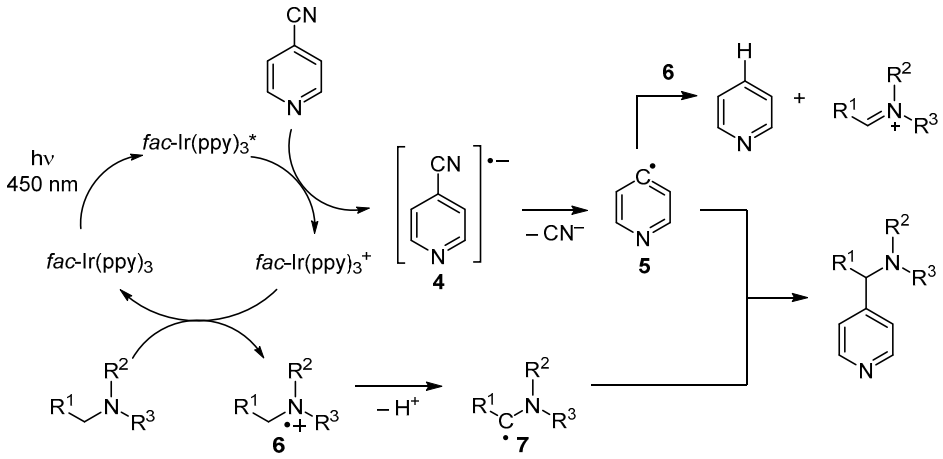
The proposed mechanism for the formation of compounds **1a–e** (Scheme 2) is similar to that previously described[8] and consists of photoexcitation of the sensitizer *fac*-Ir(ppy)$_3$ followed by electron transfer to 4-cyanopyridine with the formation of the corresponding anion radical **4** and *fac*-Ir(ppy)$_3^+$. Further, anion radical **4** undergoes fragmentation with the formation of pyridyl radical **5**. In turn, the *fac*-Ir(ppy)$_3^+$ ion oxidizes the tertiary amine to cation radical **6**, which, when deprotonated, forms aminoalkyl radical **7**. Recombination of radicals **5** and **7** leads to products **1a–e**. The formation of unsubstituted pyridine apparently occurs by the abstraction of a hydrogen atom from radical cation **6** by radical **5**, due to the significantly lower energy of the homolytic cleavage of the α-C–H bond as compared to that in the original amine.[4] The mechanism for the formation of aminonitriles is apparently the same as for photocatalytic cyanation of amines.[6]

To conclude, we have discovered the possibility of photocatalytic arylation of tertiary aliphatic amines at the α-C–H bond with 4-cyanopyridine with the formation of the corresponding pyridin-4-yl derivatives. The reaction is accompanied by hydrodecyanation of 4-cyanopyridine, and the ratio of products highly depends on the structure of the amine. The highest yields are achieved in the case of methyl-substituted amines.

Experimental

^{1}H NMR spectra were acquired on a Bruker AV-400 (400 MHz) spectrometer and ^{13}C NMR spectra were

Scheme 2



acquired on a Bruker AV-300 (300 MHz) spectrometer. Chemical shifts were assigned relative to the signal of the solvent (7.26 ppm for ^{1}H nuclei and 77.2 ppm for ^{13}C nuclei). High-resolution mass spectra were recorded on a DFS Thermo Electron mass spectrometer, EI ionization (70 eV). Mass spectra were recorded on an Agilent 5973 MSD-N mass spectrometer with an Agilent 6890N gas chromatograph, EI ionization (70 eV). Neutral alumina was used for column chromatography. Monitoring of the reaction progress was done by TLC on Sorbfil plates (silica gel), visualization by UV light.

4-Cyanopyridine, amines, and *fac*-Ir(ppy)$_3$ were purchased from commercial sources and used without additional purification. MeCN was distilled from P_2O_5 and kept over 4 Å molecular sieves. An LED strip with a total power of LEDs of 5 W was used for irradiation, the maximum emission wavelength was 450 nm.

Synthesis of substituted (pyridin-4-yl)amines 1a–e (General method). A solution of 4-cyanopyridine (100 mg, 0.96 mmol), tertiary amine (1.92 mmol), and *fac*-Ir(ppy)$_3$ (1.3 mg) in MeCN (5 ml) was irradiated with blue light until the disappearance of 4-cyanopyridine by TLC. MeCN was then removed under reduced pressure, and the residue was purified by column chromatography on neutral Al_2O_3 to afford *fac*-Ir(ppy)$_3$ and the respective target amine **1a–d**.

[1-(Pyridin-4-yl)ethyl]diethylamine (1a).[10] Yield 42 mg (25%), colorless oil, R_f 0.31 (EtOAc–hexane, 1:1). ^{1}H NMR spectrum (CCl_4–$CDCl_3$), δ, ppm (*J*, Hz): 0.92 (6H, t, *J* = 7.0, $2CH_2C\underline{H}_3$); 1.21 (3H, d, *J* = 6.8, $CHC\underline{H}_3$); 2.39–2.45 (4H, m, $2C\underline{H}_2CH_3$); 3.70 (1H, q, *J* = 6.8, $C\underline{H}CH_3$); 7.22–7.24 (2H, m, H-3,5 Py); 8.41–8.43 (2H, m, H-2,6 Py). Found, *m*/*z*: 178.1473 $[M]^+$. $C_{11}H_{18}N_2$. Calculated, *m*/*z*: 178.1470.

***N*-Isopropyl-*N*-[1-(pyridin-4-yl)ethyl]propan-2-amine (1b)**. Yield 36 mg (18%), colorless oil, R_f 0.35 (EtOAc–hexane, 1:1). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.97 (6H, d, *J* = 6.7, $2CH(C\underline{H}_3)_2$); 1.06 (6H, d, *J* = 6.7, $2CH(C\underline{H}_3)_2$); 1.42 (3H, d, *J* = 6.9, $CHC\underline{H}_3$); 3.03 (2H, sept, *J* = 6.7, $2C\underline{H}(CH_3)_2$); 4.04 (1H, q, *J* = 6.9, $C\underline{H}CH_3$); 7.33–7.35 (2H, m, H-3,5 Py); 8.45–8.47 (2H, m, H-2,6 Py). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 18.8; 22.6; 23.5; 45.5; 51.4; 123.0; 149.4; 156.9. Found, *m*/*z*: 206.1780 $[M]^+$. $C_{13}H_{22}N_2$. Calculated, *m*/*z*: 206.1783.

2-[Methyl(pyridin-4-ylmethyl)amino]ethanol (1c). Yield 104 mg (65%), colorless oil, R_f 0.26 (EtOAc). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.18 (3H, s, NCH_3); 2.55 (2H, t, *J* = 5.5, $NCH_2C\underline{H}_2OH$); 3.18 (1H, br. s, OH); 3.51 (2H, s, $NC\underline{H}_2Py$); 3.60 (2H, t, *J* = 5.5, $NC\underline{H}_2CH_2OH$); 7.18–7.20 (2H, m, H-3,5 Py); 8.45–8.47 (2H, m, H-2,6 Py). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 41.9; 58.7; 58.9; 61.2; 123.8; 148.1; 149.7. Found, *m*/*z*: 166.1103 $[M]^+$. $C_9H_{14}ON_2$. Calculated, *m*/*z*: 166.1101.

***N*,*N*,*N*'-Trimethyl-*N*'-(pyridin-4-ylmethyl)ethane-1,2-diamine (1d)**. Yield 26 mg (14%), yellowish oil, R_f 0.18 (EtOAc). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.17 (6H, s, $N(C\underline{H}_3)_2$); 2.19 (3H, s, $NC\underline{H}_3$); 2.38–2.40 (2H, m, $C\underline{H}_2$); 2.42–2.44 (2H, m, $C\underline{H}_2$); 3.47 (2H, s, $NC\underline{H}_2Py$); 7.21–7.24 (2H, m, H-3,5 Py); 8.46–8.48 (2H, m, H-2,6 Py). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 42.7; 45.9; 55.5; 57.4; 61.8; 123.9; 148.5; 149.8. Found, *m*/*z*: 193.1581 $[M]^+$. $C_{11}H_{19}N_3$. Calculated, *m*/*z*: 193.1579.

Dibutyl[1-(pyridin-4-yl)butan]amine (1e) and 2-(dibutylamino)pentanenitrile (3e), a mixture containing 60% compound **1e** and 31% compound **3e** according to GC-MS, yellow oil, R_f 0.30 (EtOAc–hexane, 1:1). Mass spectrum of compound **1e**, *m*/*z* (I_{rel}, %): 262 $[M]^+$ (2), 219 $[M–C_3H_7]^+$ (100), 134 $[M–N(C_4H_{10})_2]^+$ (60), 119 (12), 92 (16), 41 (14), 29 (14). Mass spectrum of compound **3e**, *m*/*z* (I_{rel}, %): 210 $[M]^+$ (2), 183 $[M–HCN]^+$ (9), 167 $[M–C_3H_7]^+$ (100), 140 (28), 125 (61), 98 (23), 84 (44), 57 (32), 41 (37), 29 (32).

Supplementary information file containing ^{1}H and ^{13}C NMR spectra of all synthesized compounds and mass spectra of compounds **1d**, **3d**, as well as data on the optimization of the reaction conditions of α-C–H arylation of triethylamine with 4-cyanopyridine is available at the journal website at http://link.springer.com/journal/10593.

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