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Reaction of *N*-fluoropyridinium fluoride with isonitriles: a convenient route to picolinamides

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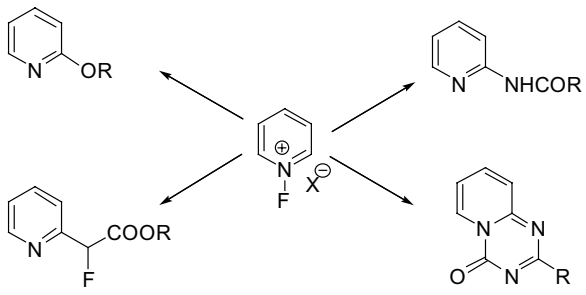
Abstract—Reaction of *N*-fluoropyridinium fluoride generated in situ with a series of isonitriles led to the formation of the corresponding picolinamides in good yields. A similar reaction sequence for quinoline yielded the respective derivatives of 2-quinoline carboxylic acid. The proposed reaction mechanism involves the intermediate formation of a highly reactive carbene species.

2-Substituted pyridines continue to attract considerable interest as ligands for metals,[1] building blocks in organic synthesis,[2] and physiologically active compounds.[3] However, methods for the introduction of a substituent at position 2 of the pyridine ring are quite limited. In addition to the Chichibabin amination methodologies,[4] the more general approaches involve displacement of a nucleophugal group (usually a halogen),[5] diazotation strategies (for example, Ullman reaction),[6] Reissert–Henze and related conversions,[7] Abramovitch and Saha reaction,[8] and transformations of a functionality already present at position 2 of the pyridine.[9] In this respect, we were interested in the synthetic potential of *N*-fluoropyridinium salts conveniently generated from pyridines and elemental fluorine.[10] Reactions of these highly reactive substrates have been used in the synthesis of 2-halogeno pyridines,[11] and for the introduction of hydroxy,[12] amido,[13] phosphonio,[14] heteroaryl, arylthio, and aryloxy groups at position 2 of pyridine ring.[15] Additional examples of the synthetic utility of *N*-fluoropyridinium cation include preparations of pyridine-2-yl acetates[16] and 2-acetamidopyridines.[17] Representative examples of these chemistries are summarized in Scheme 1.[18]

In our attempt to further expand the synthetic potential of these useful substrates, we studied the reaction of *N*-fluoropyridinium fluoride with isonitriles. This one-pot reaction yielded 2-pyridilcarboxamides **3** in good yields



Scheme 1.

(Scheme 2).[19,20] Varying amounts of 2-chloropyridines **4** were also isolated from the reaction mixtures.[11]

In general, the reaction outcome did not depend on the nature of the isonitrile component (Scheme 2, entries **a**–**h**). With the notable exception of benzyl isonitrile and ethyl isocyanoacetate (entries **f** and **g**), yields of the desired compounds **3** exceeded 50%. Furthermore, reactions with cyclohexyl- and *p*-nitrophenyl isocyanides were most practical as they both (i) afforded the highest yields and (ii) allowed for the easy isolation of the desired products **3** via straightforward recrystallization of reaction concentrate from EtOH.[19] We also studied the effect of pyridine substitution on the reaction outcome (entries **i**–**p**). Both weak electron-donating and -withdrawing groups enhanced the overall yields of the desired products **3** (entries **i**–**m**). Strong electron-donating and withdrawing groups (entries **n** and **p**) as well as aromatic substituents (entry **o**) on the pyridine ring led to considerably lower yields of the targeted compounds

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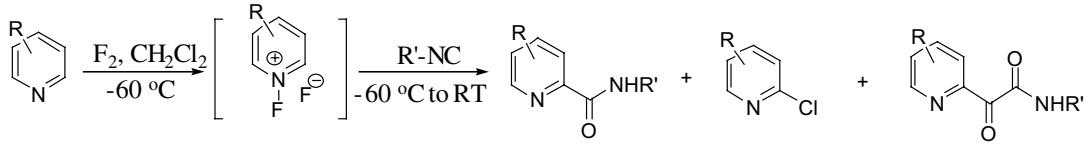


Entry, 1	R	R'	Yields, % 3	4	Entry, 1	R	R'	Yields, % 3	4
a	H	n-Bu	64	12	**i**	2-Me	*p*-NO_2-C_6H_4-	68	10
b	H	t-Bu	60	11	**j**	3-Me	*p*-NO_2-C_6H_4-	69[b]	12[c]
c	H		62	15	**k**	4-Me	*p*-NO_2-C_6H_4-	71	15
d	H	Ph	55	24	**l**	2-Cl	*p*-NO_2-C_6H_4-	68	22
e	H	*m*-CF_3-C_6H_4-	61	21	**m**	4-Cl	*p*-NO_2-C_6H_4-	66	25
f	H	CH_2COOEt	46	15	**n**	2-OMe	*p*-NO_2-C_6H_4-	52	26
g	H	CH_2Ph	39	20	**o**	2-Ph	*p*-NO_2-C_6H_4-	33[d]	11
h	**H**	***p*-NO_2-C_6H_4-**	**69**	**11**	**p**	2-COOMe	*p*-NO_2-C_6H_4-	31	40

[a]Yields of **5** did not exceed 5-8% (isolated yields, 7-10% LC MS yields), small amounts of 2-fluoropyridines (2-5%, LC MS yields) were also detected in reaction mixtures; [b]Mixture of 2- and 6-substituted derivatives, *ca.*1.5:1 isolated ratio, respectively; [c]Mixture of 2- and 6-substituted derivatives, *ca.* 1.5:1 isolated ratio, respectively; [d]Mixture contained products of fluorination of the Ph ring (*ca.* 25%, LC MS)

Scheme 2.

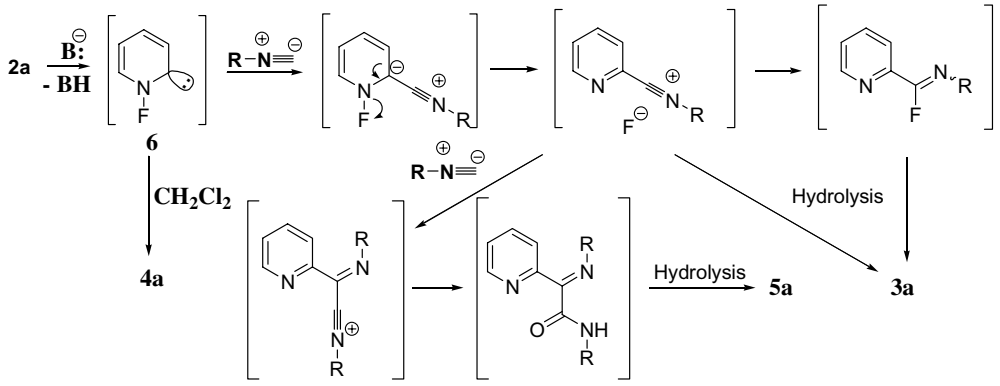
3 and significant formation of side products, including the respective 2-chloropyridines **4**. Possible reasons for this outcome are (a) partial fluorination of pyridine ring for **1n** or phenyl ring for **1o** under the reaction conditions and (b) relative instability of the intermediate *N*-fluoropyridinium fluoride species for **2p**.[10–13] 3-Substituted pyridine yielded mixture of the respective 2- and 6-regioisomers in ca. 1.5:1 ratio and 69% overall isolated yield (Scheme 2, **1j**). Similar regioselectivity was observed by us earlier.[18] Ratio 1:2, pyridine to isonitrile, was found to furnish the best yields of the desired products **3**, larger molar excess of pyridines afforded increased amounts of the respective 2-chloro derivatives **4**. Dichloromethane was found to be the optimal solvent for this reaction, similar procedures conducted in $CHCl_3$, dichloroethane or CH_3CN resulted in considerably lower yields of the desired materials and significant formation of side products.[18] Thorough temperature control was found to be critical for securing good yields of the desired materials. Specifically, both the generation of **2** as well as the addition of isonitriles to the reaction mixtures have to be conducted at temperatures less than −50 °C.[18]

Mechanistically, the outcome of this reaction could be explained by an initial formation of *N*-fluoropyridinium species **2** followed by proton abstraction from the strongly activated position 2 of the *N*-fluoropyridinium cation by fluoride to yield the highly reactive carbene **6** (Scheme 3).[10–15] We suggest that this resulting carbene undergoes a subsequent reaction with isonitrile to afford the respective isonitrilium ylide, the postulated precursor to 2-carboxamidopyridines **3**. Product **5** is likely to originate from the addition of 2 equiv of isonitrile to the carbene species as shown below. In addition, the strong electron-deficient nature of **6** allows for its reaction with CH_2Cl_2 and formation of **4**, as described earlier.[11]

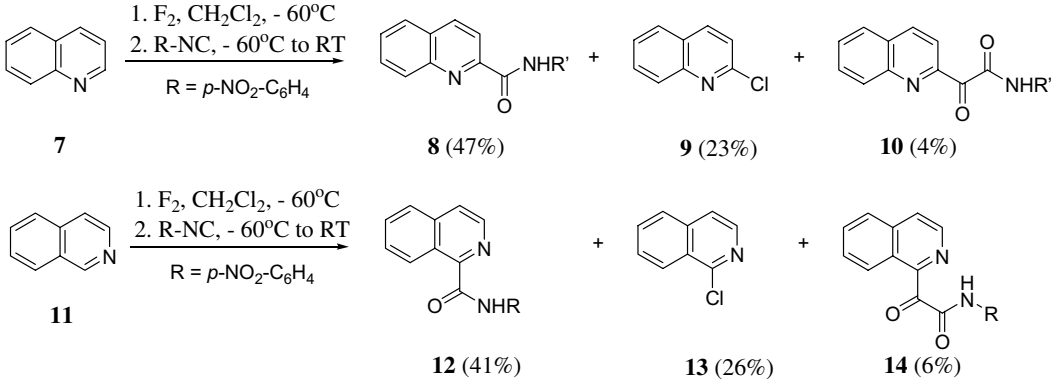
The postulated intermediacy of the carbene **6** in the amidation reactions of pyridine is in agreement with the lack of formation of the respective acetamido derivative in an attempted reaction of 2,6-dimethylpyridine under the described conditions.

Consistent with this reactivity pattern is the formation of the respective 2-quinoline and 1-isoquinoline derivatives upon treatment of quinoline and isoquinoline with fluorine and isonitrile as described above (**8**, **12**; 47% and 41% yields, respectively, Scheme 4).[19] Yields of the desired materials were lower than observed for the similar reaction protocols with pyridines **1**. In addition, significant amounts of high molecular weight products were detected in the reaction mixtures (LC–MS).

In summary, we described the reaction of in situ generated *N*-fluoropyridinium fluorides with isonitriles to yield the respective picolinamides in good yields. A



Scheme 3.



Scheme 4.

similar reaction was observed for both quinoline and isoquinoline (isoquinoline was functionalized at position 1). Intermediate formation of a highly reactive carbene intermediate is proposed to explain the outcome of this reaction.

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19. *In a typical reaction sequence*, an excess of fluorine gas (15–20 mmol) was bubbled through a solution of pyridine (0.79 g, 10 mmol) in CH_2Cl_2 (50 mL) at such a rate that the initial temperature of −78 °C (acetone/dry ice bath) did not raise above −50 °C (critical!). The resultant white suspension of **2** was thoroughly flushed with nitrogen to remove molecular fluorine and then treated dropwise (−50 °C) with a solution of isonitrile (20 mmol in 50 mL of CH_2Cl_2). The resultant pale yellow mixture was stirred at −50 °C for 1 h, allowed to reach 0 °C within the next 1 h, and finally stirred for additional 2 h at 0 °C, after which time the KI/starch test showed the absence of **2**. The mixture was concentrated (efficient N_2 trap to contain excess of isonitrile!), passed through a thin layer of silica gel, and the gel was washed with CH_2Cl_2. The solutions were combined, washed with water, dried ($MgSO_4$), and concentrated. Silica gel chromatography (hexanes) afforded 2-chloropyridines **4**. Subsequent elution with hexanes/ether (1:2) furnished 2-pyridylcarboxamides **3** as main products along with varying quantities of **5** (5–7% isolated yields). Alternatively, for *p*-nitrophenyl isocyanide reaction mixtures, the resulting concentrate was washed with ether, the resultant solid residue was recrystallized from EtOH to afford analytically pure **3i**–**p**. Small amounts of side products (**5**, 5–8% isolated yields) along with additional quantities of **3** (10–15%) were isolated from the resulting mother liquors by column chromatography on silica gel as described above.
20. *Representative examples: 6-methoxy-N-(4-nitrophenyl)picolinamide* (**3n**): mp 235–237 °C, 52% yield, ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.75 (s, 3H, Me), 7.14 (d, J = 7.6 Hz, 1H), 7.45 (m, 1H), 7.93 (d, J = 9.2 Hz, 2H), 8.22 (d, J = 9.2 Hz, 2H), 8.28 (d, J = 7.6 Hz, 1H), 8.64 (br s, 1H, exch. D_2O, NH); ^{13}C NMR (DMSO-d_6): δ 56.6, 109.5, 113.0, 121.3, 122.3, 139.4, 142.3, 144.3, 149.0, 162.4, 163.8. ESI MS: (M+1) 274, (M−1) 272; HR ESI MS: exact mass calcd for $C_{13}H_{11}N_3O_4$: 273.0750, found: 273.0746. Elemental analysis, calcd for $C_{13}H_{11}N_3O_4$: C, 57.14; H, 4.06; N, 15.38. Found: C, 57.03; H, 4.08; N, 15.22. *N-(4-Nitrophenyl)-6-phenylpicolinamide* (**3o**): mp >250 °C, 33% yield, ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.28 (m, 1H), 7.35 (m, 2H), 7.88 (m, 2H), 7.98 (m, 3H), 8.05 (d, J = 7.6 Hz, 1H), 7.92 (m, 1H), 8.20 (d, J = 9.2 Hz, 2H), 8.48 (br s, 1H, exch. D_2O, NH); ^{13}C NMR (DMSO-d_6): δ 119.2, 121.5, 122.3, 127.0, 127.5, 127.7, 129.5, 136.5, 138.8, 142.2, 144.0, 151.4, 153.5, 162.5; ESI MS: (M+1) 320, (M−1) 318; HR ESI MS: exact mass calcd for $C_{18}H_{13}N_3O_3$: 319.0957, found: 319.0952. Elemental analysis, calcd for $C_{18}H_{13}N_3O_3$: C, 61.71; H, 4.10; N, 13.16. Found: C, 61.54; H, 4.18; N, 13.02. *Methyl 6-((4-nitrophenyl)carbamoyl)picolinate* (**3p**): mp 212–214 °C, 31% yield, ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.86 (s, 3H, Me), 7.92 (d, J = 9.2 Hz, 2H), 8.20 (d, J = 9.2 Hz, 2H), 8.55 (br s, 1H, exch. D_2O, NH), 8.67 (m, 1H), 8.78 (d, J = 7.6 Hz, 1H), 8.92 (d, J = 7.6 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 51.8, 121.4, 122.5, 125.8, 127.5, 139.8, 142.2, 144.8, 147.1, 150.2, 162.9, 168.0. ESI MS: (M+1) 302, (M−1) 300; HR ESI MS: exact mass calcd for $C_{14}H_{11}N_3O_5$: 301.0700, found: 301.0693. Elemental analysis, calcd for $C_{14}H_{11}N_3O_5$: C, 55.82; H, 3.68; N, 13.95. Found: C, 55.70; H, 3.81; N, 13.81.