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A novel three-component reaction of *N*-fluoropyridinium salts: a facile approach to imidazo[1,2-*a*]pyridines

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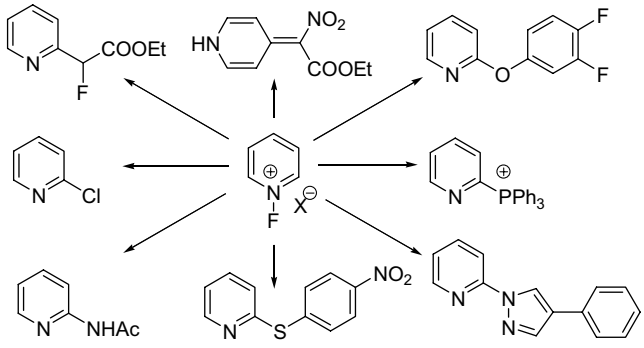
Abstract—The reaction of *N*-fluoropyridinium triflate with isonitriles in acetonitrile and propionitrile in the presence of $NaBH(OAc)_3$ led to the formation of the corresponding imidazo[1,2-*a*]pyridines in 44–73% yields. The proposed reaction mechanism involves the intermediate formation of a highly reactive carbene species and apparent reduction of the pyridinium intermediate with $NaBH(OAc)_3$ to yield the targeted heterocycles.

The synthetic potential of *N*-fluoropyridinium salts conveniently generated from pyridines and elemental fluorine has been the subject of ongoing interest.[1] Reactions of these highly reactive substrates have been used in the synthesis of 2-halogeno pyridines,[2] and for the introduction of hydroxy,[3] amido,[4] phosphonio,[5] heteroaryl, arylthio, and aryloxy groups at position 2 of pyridine rings.[6] Additional examples of the synthetic utility of the *N*-fluoropyridinium cation include the preparations of pyridine-2-yl acetates[7] and 2-acetamidopyridines.[8] Representative examples of these chemistries are summarized in Scheme 1.

In our attempt to further expand the synthetic potential of these useful substrates,[9] we studied the reaction of *N*-fluoropyridinium triflates **1** with isonitriles in acetonitrile and propionitrile in the presence of $NaBH(OAc)_3$.[10] This one-pot reaction yielded imidazo[1,2-*a*]pyridin-3-amines **2a**–**p** in good yields (Table 1).[11,12] Varying amounts of 2-acetylamidopyridines **3** were also isolated from the reaction mixtures.[2,8] Notably, products **2a**–**p** are not accessible by a previously reported three-component condensation of 2-aminopyridines with isonitriles and aldehydes.[13]



Scheme 1.

In general, the reaction outcome did not depend on the nature of the isonitrile component (Table 1, entries **a**–**i**). With the notable exception of benzyl isonitrile (entry **g**), yields of the desired compounds **2** exceeded 50%. We also studied the effect of pyridine substitution on the reaction outcome (entries **f**–**i** and **m**–**p**). Both weak electron donating and withdrawing groups afforded good yields of **2**. The strong electron donating group (MeO, entry **n**) led to a notably lower yield of **2n** (45%) and significant formation of side products, including the respective 2-acetamidopyridine **3n** (26%). Under similar reaction conditions, *N*-fluoropyridinium salts **1** containing strong electron-withdrawing groups (3,5-chloro, 2-carbmethoxy) afforded very low yields of the desired products **2** (10–22%) along with the respective 2-acetamidopyridines **3** (35–40%) and high-molecular weight products (LC–MS analysis).[1–3,8] 3-Substituted

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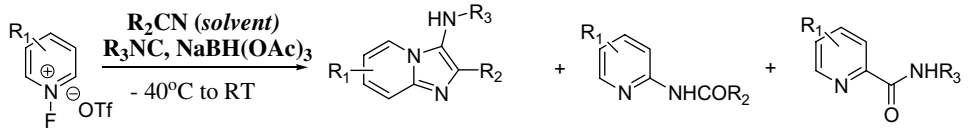
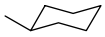
Table 1.



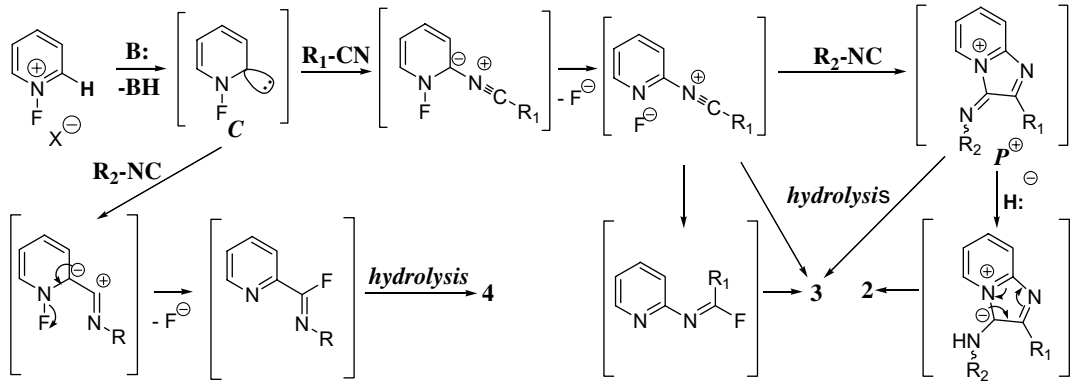
1 **2a-p** **3** **4**[a]

Entry **1**	R_1	R_2	R_3	Yields (%)	
				2	**3**
a	H	Me	*i*-Pr	57	18
b	H	Me	*t*-Bu	62	14
c	H	Me	Ph	67	11
d	H	Me	CH_2COOEt	58	16
e	H	Me	*m*-CH_3–C_6H_4–	68	12
f	2-Me	Me	Ph	61	15
g	4-Me	Me	CH_2Ph	44	21
h	4-*i*-Pr	Me	*p*-NO_2–C_6H_4–	65	12
i	2-Ph	Me		55	18
j	H	Et	Ph	69	12
k	H	Et	*m*-Me–C_6H_4–	72	9
l	H	Et	*p*-Me–C_6H_4–	67	12
m	2-Me	Et	*p*-NO_2–C_6H_4–	73	11
n	2-OMe	Et	*p*-NO_2–C_6H_4–	45	26
o	3-Cl	Me	Ph	57[b]	21[c]
p	3-Me	Me	Ph	69[b]	15[c]

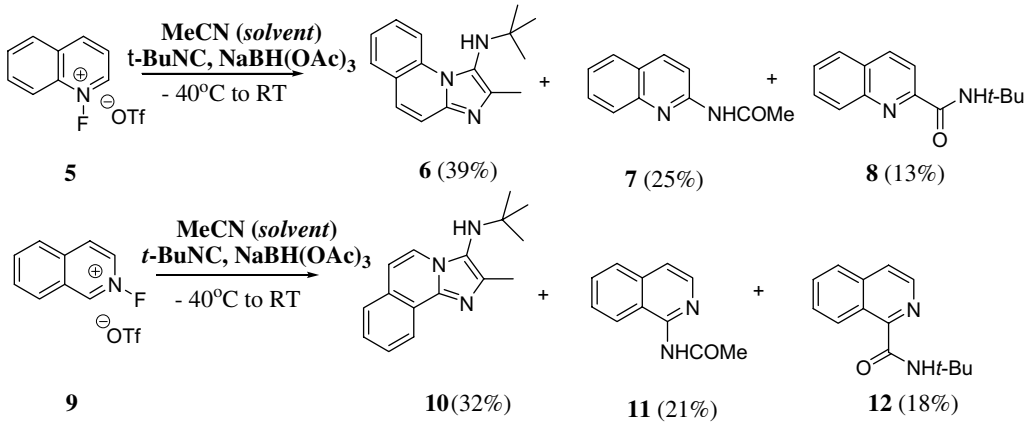
[a]Yields of **4** did not exceed 5–8% (isolated yields, 7–10% LC–MS yields).
[b] Mixture of 2- and 6-substituted derivatives, ca. 2:1 isolated ratio, respectively.
[c] Mixture of 2- and 6-substituted derivatives, ca. 2:1 isolated ratio, respectively.

pyridinium salts **1o**,**p** yielded a mixture of the expected 2- and 6-regioisomers in ca. 2:1 ratio, respectively, and 57% (3-Cl, **1o**) and 69% (3Me, **1p**) overall isolated yields (Table 1). A similar regioselectivity was observed by us earlier.[8] A ratio of 1:2, *N*-fluoropyridinium salt **1** to isonitrile, was found to furnish the best yields of **2**. A larger molar excess of **1** afforded increased amounts of **3**. Precise temperature control, as well as reagent addition order was found to be critical for securing good yields of the desired materials. For example, addition of $NaBH(OAc)_3$ (suspension in MeCN) to the mixture of **1** and isonitrile resulted in higher yields of the respective 2-acetamidopyridines **3** (35–40%, LC–MS analysis). At the same time, mixing **1** and $NaBH(OAc)_3$ resulted in the extensive formation of 2-fluoropyridines along with a number of unidentified products.[2] Addition of **1** to a vigorously stirred mixture of reagents at temperatures not exceeding −35 °C was found to be optimal for the yields of **2**.[11]

Mechanistically, the outcome of this reaction could be explained by proton abstraction from the strongly activated position 2 of the *N*-fluoropyridinium cation **1** by the base ($NaBH(OAc)_3$) to yield the highly reactive carbene ***C*** (Scheme 2).[1–5] We suggest that this resulting carbene undergoes a subsequent reaction with nitrile (solvent) to afford the respective nitrilium ylid, the postulated precursor to **2**.[8] This intermediate undergoes addition of isonitrile followed by a subsequent cyclization of the resulting cation into a respective bicyclic



Scheme 2.



Scheme 3.

pyridinium species P^+. Reduction of this reactive intermediate with $NaBH(OAc)_3$ followed by aromatization of the resultant zwitterion yields the observed imidazo[1,2-*a*]pyridines **2**. Product **3** is likely to originate from the hydrolysis of the intermediate nitrilium ylid. Product **4** probably results from the direct reaction of ***C*** with isonitriles followed by hydrolysis of the intermediate isonitrilium ylid. Consistent with the proposed mechanism, presence of the reducing agent ($NaBH(OAc)_3$) was found to be critical for the preparation of **2**. Specifically, borohydride is likely to serve as a base to yield the ylid ***C***. In addition, it reduces the reactive intermediate P^+ into stable aromatic species **2**. Application of other bases, including diisopropyl ethyl amine (Hunig's base) or Bu_4NF, yielded complex mixture of products, major components (ca. 35–40% by LC–MS analysis) were found to be **3**, **4** in addition to various amounts of the respective 2-chloro- and 2-fluoropyridines.[2] We believe that the species P^+ are unstable under nonreducing conditions and undergo hydrolysis to yield **3**. Other reducing agents, namely $NaBH_4$ and $NaBH_3CN$ also afforded **2**, although the yields did not exceed ca. 30–35% presumably due to their poor solubility in the reaction system. The postulated intermediacy of the carbene ***C*** is in agreement with the lack of formation of the respective derivatives **2** and **3** 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 *N*-fluoroquinolinium- and isoquinolinium salts **5**, **9**[10] with *t*-BuNC as described above (**6**, **10**; 39% and 32% yields, respectively, Scheme 3).[11,12] Yields of the desired materials were lower than those observed for the similar reaction protocols with *N*-fluoropyridinium salts **1**, although the reaction pattern was similar. In addition, significant amounts of high molecular weight products were detected in the reaction mixtures (LC–MS analysis).

In summary, we described the reaction of *N*-fluoropyridinium salts with isonitriles in acetonitrile and propionitrile in the presence of $NaBH(OAc)_3$ to yield the respective imidazo[1,2-*a*]pyridine-3-amines in good yields. Similar transformations were observed for both quinoline and isoquinoline. Formation of a highly reactive carbene intermediate is proposed to explain the outcome of this reaction.

References and notes

1. (a) Umemoto, T.; Fukami, S.; Tomizawa, G.; Harasawa, K.; Kawada, K.; Tomita, K. *J. Am. Chem. Soc.* **1990**, *112*, 8563; (b) Umemoto, T.; Tomita, K.; Kawada, K. In *Organic Synthesis*; John Wiley and Sons: New York, NY, 1990; Vol. 69, p 129; (c) Umemoto, T.; Harasawa, K.; Tomizawa, G.; Kawada, K.; Tomita, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1081.
2. (a) Umemoto, T.; Tomizawa, G. *J. Org. Chem.* **1989**, *54*, 1726; (b) Hebel, D.; Rozen, S. *J. Org. Chem.* **1991**, *56*, 6298; (c) Hebel, D.; Rozen, S. *J. Org. Chem.* **1988**, *53*, 1123.
3. Van Der Puy, M.; Nalewajek, D.; Wicks, G. E. *Tetrahedron Lett.* **1988**, *29*, 4389.
4. Umemoto, T.; Tomizawa, G. *Tetrahedron Lett.* **1987**, *28*, 2705.
5. Kiselyov, A. S.; Gakh, A. A.; Kagramanov, N. D.; Semenov, V. V. *Mendeleev Commun.* **1992**, 128.
6. Kiselyov, A. S.; Strekowski, L. *J. Heterocycl. Chem.* **1993**, *30*, 1361.
7. Kiselyov, A. S.; Strekowski, L. *J. Org. Chem.* **1993**, *58*, 4476.
8. Kiselyov, A. S.; Strekowski, L. *Synth. Commun.* **1994**, *24*, 2387.
9. (a) Kiselyov, A. S. *Tetrahedron Lett.* **1994**, *35*, 8951; (b) Kiselyov, A. S.; Strekowski, L. *Tetrahedron* **1993**, *49*, 2151; (c) Kiselyov, A. S. *Tetrahedron Lett.* **2005**, *46*, 2279.
10. Other bases, including Et_3N, Hunig's base and Bu_4NF afforded a mixture of **3** and **4** exclusively, the targeted imidazo[1,2-*a*]pyridines **2** were not detected in the reaction mixtures. All *N*-fluoropyridinium-, quinolinium, and isoquinolinium salts were synthesized as described earlier.[1,2,8] *N*-Fluoropyridinium salts with BF_4^- counterion reacted in a similar fashion, however the yields of imidazo[1,2-*a*]pyridines **2** were significantly lower (ca. 15–30%), presumably due to the poor solubility of tetrafluoroborates in nitriles at lower temperature. Attempted reactions with other nitriles (*i*-PrCN and *t*-BuCN) were not successful as the mixtures were frozen under the reaction conditions. Increased temperatures afforded complex reaction mixtures. Reactions in a binary solvent systems

(nitrile/CH_2Cl_2, nitrile/THF, nitrile/acetone, various ratios) afforded very low yields of the desired imidazo[1,2-*a*]pyridines **2** even at low temperatures (−50 °C). Instead, products of solvent addition to pyridine (e.g., 2-chloropyridines, 2-pyridones) were detected in the reaction mixtures.[1,8]

11. *In a typical reaction sequence*, a solution of *N*-fluoropyridinium triflate (**1**, 2 mmol) in a dry degassed nitrile (25 mL) was added dropwise to a vigorously stirred mixture of isonitrile (4 mmol) and $NaBH(OAc)_3$ (4.5 mmol) in the same solvent (25 mL) under Ar at −40 °C (water/ethylene glycol bath). The temperature of the mixture was thoroughly controlled so as not to exceed −35 °C during the addition of **1**. The resultant mixture was stirred for additional 4 h at this temperature, 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 **1**. 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. Solid residue was re-dissolved in EtOAc and purified by column chromatography on silica gel. Elution with hexanes/EtOAc (1:1) furnished imidazo[1,2-*a*]pyridine-3-amines **2** as main products along with varying quantities of **3** (9–22% isolated yields) and **4** (5–8% isolated yields).
12. *Representative examples*: 7-Isopropyl-2-methyl-*N*-(4-nitrophenyl)*H*-imidazo[1,2-*a*]pyridin-3-amine (**2h**): mp 225–227 °C, 65% yield, ^1H NMR (400 MHz, DMSO-d_6): δ 1.32 (d, J = 7.6 Hz, 6H, *i*-Pr), 2.25 (s, 3H, Me), 3.15 (m, 1H, *i*-Pr), 4.74 (br s, 1H, exch. D_2O, NH), 6.61 (d, J = 8.0 Hz, 1H), 6.76 (d, J = 9.2 Hz, 2H), 7.43 (s, 1H), 7.92 (d, J = 9.2 Hz, 2H), 8.12 (d, J = 8.0 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 10.1, 23.6, 36.5, 114.8, 117.6, 121.6, 122.1, 124.0, 124.8, 134.1, 138.7, 144.2, 149.3, 155.1. ESI MS: (M+1) 311, (M−1) 309; HR ESI MS: Exact mass calcd for $C_{17}H_{18}N_4O_2$ 310.1430. Found: 310.1427. Elemental analysis calcd for $C_{17}H_{18}N_4O_2$: C, 65.79; H, 5.85; N, 18.05. Found: C, 65.66; H, 5.94; N, 18.14.

2-Ethyl-5-methyl-*N*-(4-nitrophenyl)*H*-imidazo[1,2-*a*]pyridin-3-amine (**2m**): mp 212–214 °C, 73% yield, NMR (400 MHz, DMSO-d_6): δ 1.25 (t, J = 7.6 Hz, 3H, Et), 2.52 (q, J = 7.6 Hz, 2H, Et), 2.57 (s, 3H, Me), 4.46 (br s, 1H, exch. D_2O, NH), 6.56 (d, J = 8.0 Hz, 1H), 6.76 (d, J = 9.2 Hz, 2H), 7.01 (m, 1H), 7.35 (d, J = 6.8 Hz, 1H), 7.92 (d, J = 9.2 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 14.2, 18.1, 22.9, 117.1, 119.3, 122.1, 124.2, 124.5, 128.2, 135.1, 136.3, 138.8, 144.5, 149.4; ESI MS: (M+1) 297, (M−1) 295; HR ESI MS: Exact mass calcd for $C_{16}H_{16}N_4O_2$ 296.1273. Found: 296.1264. Elemental analysis calcd for $C_{16}H_{16}N_4O_2$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.72; H, 5.61; N, 18.75.

2-Ethyl-5-methoxy-*N*-(4-nitrophenyl)*H*-imidazo[1,2-*a*]pyridin-3-amine (**2n**): mp > 250 °C, 55% yield, ^1H NMR (400 MHz, DMSO-d_6): δ 1.26 (t, J = 7.6 Hz, 3H, Et), 2.52 (q, J = 7.6 Hz, 2H, Et), 3.75 (s, 3H, OMe), 4.27 (br s, 1H, exch. D_2O, NH), 5.98 (d, J = 8.0 Hz, 1H), 6.52 (d, J = 6.8 Hz, 1H), 6.74 (d, J = 9.2 Hz, 2H), 7.02 (m, 1H), 7.93 (d, J = 9.2 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 14.3, 18.0, 56.5, 108.8, 110.6, 117.3, 122.0, 124.3, 135.2, 138.0, 138.2, 149.2, 144.6, 165.3. ESI MS: (M+1) 313, (M−1) 311; HR ESI MS: Exact mass calcd for $C_{16}H_{16}N_4O_3$ 312.1222. Found: 312.1213. Elemental analysis calcd for $C_{16}H_{16}N_4O_3$: C, 61.53; H, 5.16; N,17.94. Found: C, 61.38; H, 5.27; N, 17.82.

N-*tert*-Butyl-2-methyl-*H*-imidazo[2,1-*a*]isoquinolin-3-amine (**10**): mp > 250 °C, 32% δ 1.11 (s, 9H, *t*-Bu), 2.29 (s, 3H, Me), 4.52 (br s, 1H, exch. D_2O, NH), 7.48–7.52 (m, 2H), 7.58 (m, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 6.8 Hz, 1H), 8.43 (d, J = 8.0 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 9.6, 30.2, 53.1, 121.1, 124.3, 124.9, 125.1, 126.7, 127.1, 128.2, 130.1, 133.9, 136.5, 144.3. ESI MS: (M+1) 254, (M−1) 252; HR ESI MS: Exact mass calcd for $C_{16}H_{19}N_3$ 253.1579. Found: 253.1575. Elemental analysis calcd for $C_{16}H_{19}N_3$: C, 75.85; H, 7.56; N, 16.59. Found: C, 75.71; H, 7.68; N, 16.43.

13. Chen, J. J.; Golebiowski, A.; McClenaghan, J.; Klopfenstein, S. R.; West, L. *Tetrahedron Lett.* **2001**, *42*, 2269, and references cited therein.