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Reaction of *N*-fluoropyridinium fluoride with isonitriles and diazo compounds: a one-pot synthesis of (pyridin-2-yl)-1*H*-1,2,3-triazoles

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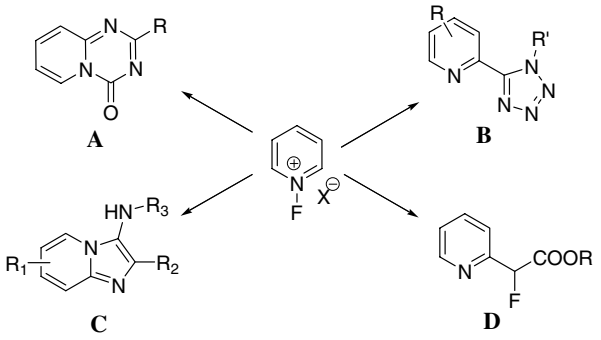
Abstract—Reaction of *N*-fluoropyridinium fluoride generated in situ with a series of isonitriles and diazo compounds led to the formation of the corresponding (pyridine-2-yl)-1*H*-1,2,3-triazoles in good yields (37–59%). Best outcome was consistently achieved with both aromatic isonitriles and stabilized diazo derivatives. The proposed reaction mechanism involves the intermediate formation of a highly reactive carbene species.

The synthetic potential of *N*-fluoropyridinium salts conveniently generated in situ 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] Pyridine-2-yl acetates,[7] 2-acetamidopyridines,[8] and picolinamides[9] were successfully prepared in a one-pot procedures from in situ generated *N*-fluoropyridinium salts. A three-component cyclization protocols based on this chemistry to yield pyrido[1,2-*a*][1,3,5]triazin-4-ones (**A**),[10] tetrazol-5-yl pyridines (**B**),[11] and imidazo[1,2-*a*]pyridines (**C**)[12] have been described (Scheme 1). In our attempt to further expand the synthetic utility of these useful substrates, we studied the reaction of *N*-fluoropyridinium fluorides with isonitriles in the presence of diazo compounds. The reaction with diazo ethylacetate in absolute EtOH was reported by us earlier to yield the respective fluorinated species **D** (Scheme 1).[13]



Scheme 1.

Initially, we found that one-pot reaction of diazo ethylacetate with **2** and a series of isonitriles furnished (pyridine-2-yl)-1*H*-1,2,3-triazoles **3a**–**p** (Scheme 2, 32–59% isolated yields). Varying amounts of 2-picolinamides **4** (15–34% yields) were also isolated from the reaction mixtures, along with a respective ethyl 2-fluoro-2-(pyridin-2-yl)acetates **5** (10–16% yields).[2,7] The reaction outcome was relatively independent of the nature of the isonitrile component (Scheme 2, entries **a**–**h**).[14,15]

Reactions with *p*-trifluoromethylphenyl isocyanide (Scheme 2, entries **e**, **i**–**p**) were most practical as they both (i) afforded the highest yields and (ii) allowed for the easy isolation of the desired products **3** by trituration of the concentrated reaction mixtures with EtOAc/Et_2O (1:1 mixture) followed by recrystallization of the solid residue from EtOH. Regiochemistry of the reaction has been confirmed by NOE experiments.[14,15]

Keywords: *N*-Fluoropyridinium; (Pyridine-2-yl)-1*H*-1,2,3-triazoles; Isonitriles; Carbene; Three-component reaction.
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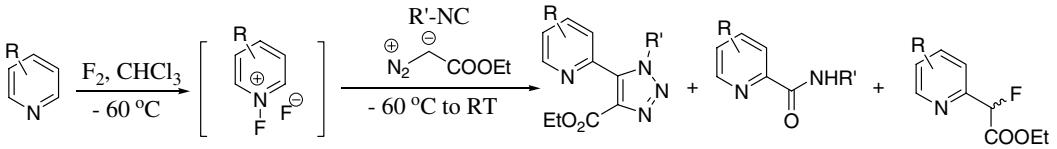
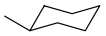
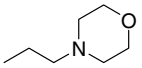


1 **2** **3a-p** **4a, i-p** **5**[a]

Entry, **1**	R	R'	Yields, % **3**	**4**	Entry, **1**	R	R'	Yields, % **3**	**4**
a	H	n-Bu	38	34	**i**	2-Me	*p*-CF_3-C_6H_4-	53	20
b	H	t-Bu	41	26	**j**	3-Me	*p*-CF_3-C_6H_4-	48[b]	19[c3]
c	H		45	21	**k**	4-Me	*p*-CF_3-C_6H_4-	59	15
d	H	Ph	52	18	**l**	2-Cl	*p*-CF_3-C_6H_4-	37	31
e	H	*p*-CF_3-C_6H_4-	56	16	**m**	4-Cl	*p*-CF_3-C_6H_4-	39	25
f	H		32	27	**n**	2-OMe	*p*-CF_3-C_6H_4-	47	31
g	H	CH_2Ph	44	21	**o**	2-Ph	*p*-CF_3-C_6H_4-	28[d]	25
h	H	*p*-NO_2-C_6H_4-	57	17	**p**	2-COOMe	*p*-CF_3-C_6H_4-	37	18

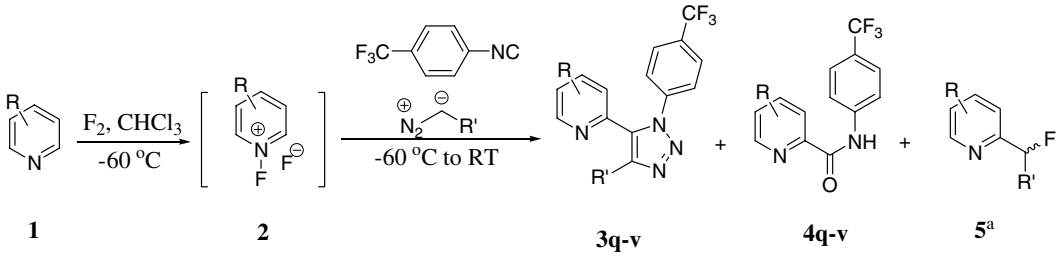
[a]Yields of **5** did not exceed 10-16% (isolated yields, 15-20% LC MS yields); [b]Mixture of 2- and 6-substituted derivatives, *ca.* 2:1 isolated ratio, respectively; [c]Mixture of 2- and 6-substituted derivatives, *ca.* 2:1 isolated ratio, respectively; [d]Mixture contained products of fluorination of the Ph ring (*ca.* 25%, LC MS).

Scheme 2.

We then studied the effect of pyridine substitution on the reaction outcome (Scheme 2, entries **i**–**p**). Consistent with our earlier observations,[11,12] 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**, **p**) as well as aromatic substituent (entry **o**) on the pyridine ring led to a considerably lower yields of the targeted compounds **3** and a significant formation of side products, including the respective picolinamides **4**.[9] Possible reasons for this outcome are (a) electrophilic fluorination of pyridine ring for **1n** or phenyl ring for **1o** under the reaction conditions (ca. 15–25% of fluorinated materials by ^{19}F NMR and LC MS) and (b) relative instability of the intermediate *N*-fluoropyridinium fluoride species for **2p**.[1,2] 3-Substituted pyridine yielded mixture of the respective 2- and 6-regioisomers in ca. 2:1 ratio and 48% overall isolated yield (Scheme 1, entry **j**). Similar regioselectivity was observed by us earlier.[8,9] A ratio of pyridine:isonitrile:diazo ethylacetate of 1:2:2 furnished the best yields of the desired products **3**. Larger molar excess of pyridines led to formation of the increased amounts of the respective picolinamides **4**. In addition, both 2-chloro and 2-fluoropyridines were detected in the reaction mixtures (ca. 10–15% by LC MS).[1,2] Chloroform was the optimal solvent for this reaction. Similar procedures conducted in CH_3CN (−42 °C) resulted in lower yields of the desired materials **3** and formation of side products (2-acetamidopyridines).[8] Thorough temperature control was found to be critical for securing good yields of the desired materials. Specifically, it was important for both the generation of **2** as well as for the addition of isonitriles to maintain the reaction temperature at less than −60 °C. At higher reaction temperatures (>−40 °C), the white suspension of **2** generated in situ rapidly changed color to dark yellow/brown. Significant amounts of the respective 2-chloro and 2-fluoropyridines were observed in the mixtures.[1,7]

We further investigated the effect of a substituent in diazo reagents on the reaction outcome. Specifically, we varied the diazo component, while maintaining the optimized nitrile input (*p*-CF_3–C_6H_4–NC). The results of these studies are summarized below (Scheme 3).

In our hands, the best yields of the targeted triazoles **3** were achieved with diazo compounds stabilized with ArCO-functionality (Scheme 3, entries **q**, **t**–**v**). Reactions



Entry, **1**	R	R'	Yields, % **3**	**4**	Entry, **1**	R	R'	Yields, % **3**	**4**
q	H	COPh	52	12	**t**	H	CO-C_6H_4-*p*Cl	48	14
r	H	COMe	29[b]	27	**u**	4-Me	COPh	55	11
s	H	-	12[b]	29	**v**	4-Cl	COPh	41	28

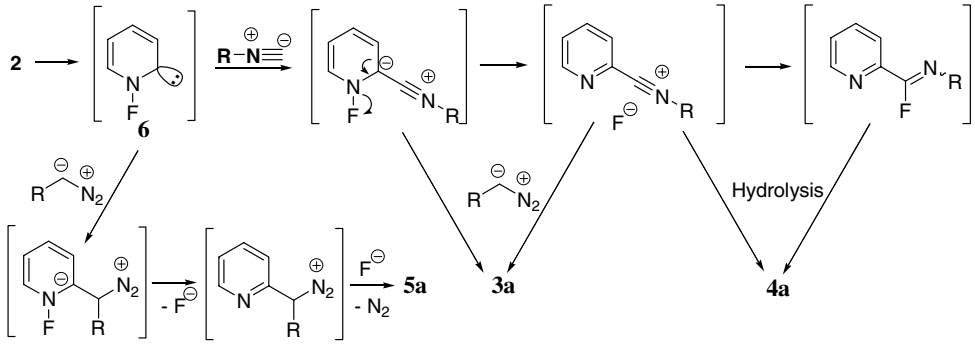
[a]Yields of **5** did not exceed 8-13% (isolated yields, 12-15% LC MS yields); [b]Extensive formation of a high MW products was observed under a variety of experimental conditions.

Scheme 3.

with both diazoacetone (entry **r**) and diazomethane (entry **s**) resulted in the excessive formation of high-molecular weight products (>40%) under a variety of experimental conditions.

The outcome of the reported reaction could be explained by an initial formation of *N*-fluoropyridinium species **2**. These undergo proton abstraction from the strongly activated position 2 of the *N*-fluoropyridinium cation by fluoride anion to yield the electrophilic carbene **6** (Scheme 4).[1,2] We suggest that **6** undergoes a subsequent reaction with isonitrile to afford the respective isonitrilium ylid. This ylid reacts with diazo molecule to yield the observed product **3**. Product **5** is likely to originate from the direct addition of diazo compound to either carbene species **6** or to *N*-fluoropyridinium fluoride **2** followed by the elimination of HF (*cine*-substitution step) and displacement of N_2 with nucleophilic F^-.[13] Apparently, the reaction of **6** with isonitrile to yield the ylid intermediate seems to be the main route for this conversion as the yields of 2-fluoro-2-(pyridin-2-yl)acetates **5**, products of the side reaction of **6** with carbanion do not exceed 20% (LC MS data). Picolinamides **4** are likely to result from the hydrolysis of the isonitrilium ylid species.[9] Formation of 2-chloro and 2-fluoropyridines at elevated temperatures can be rationalized in terms of the reaction of highly reactive species **6** with the solvent ($CHCl_3$) or fluoride anion.[1,2] The postulated intermediacy of the carbene **6** is in agreement with the lack of formation of the respective derivatives **3** in an attempted reaction of 2,6-dimethylpyridine under the described conditions.

In summary, we described a one-pot reaction of in situ generated *N*-fluoropyridinium fluorides with isonitriles and diazo compounds to afford the respective (pyridine-2-yl)-1*H*-1,2,3-triazoles in a satisfactory yields (32–59%). Best outcome was consistently achieved with both aromatic isonitriles and stabilized diazo derivatives. Intermediate formation of a highly reactive carbene intermediate is proposed to explain the result of this reaction.



Scheme 4.

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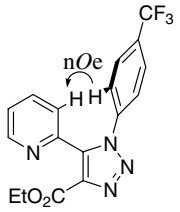
14. *In a typical reaction sequence*, an excess of fluorine gas (15–20 mmol) was bubbled through a solution of pyridine (0.79 g, 10 mmol) in $CHCl_3$ (50 mL) at such a rate that the initial temperature of −78 °C (acetone/dry ice bath) did not raise above −60 °C (*critical!*). The resultant white suspension of **2** was thoroughly flushed with nitrogen (*critical!*) to remove molecular fluorine and then treated dropwise (−60 °C) with a solution of isonitrile (20 mmol in 50 mL of $CHCl_3$) followed by a solution of diazo compound (20 mmol in 50 mL of $CHCl_3$). The resultant pale yellow mixture was stirred at −60 °C for 1 h, allowed to reach 0 °C within the next 2 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 $CHCl_3$. The solutions were combined, washed with water, dried (Na_2SO_4), and concentrated. Elution with hexanes/EtOAc (1:1) furnished (pyridine-2-yl)-1*H*-1,2,3-triazoles **3** as main products along with varying quantities of **4** (11–34%) and **5** (8–16%). Alternatively, for *p*-trifluoromethylphenyl isocyanide reaction mixtures, the resulting concentrate was washed with EtOAc/Et_2O, 1:1 (2 × 15 mL), the resultant solid residue was recrystallized from EtOH to afford analytically pure **3e**, **i**–**q**, **t**–**v**.
15. Regiochemistry of substitution in **3** was confirmed by NOE experiments:



3e

Analytical data for a representative (pyridine-2-yl)-1H-1,2,3-triazoles **3**:

Ethyl 5-(pyridin-2-yl)-1-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazole-4-carboxylate (**3e**), mp 226–228 °C, 56% yield, ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.36 (t, $J = 8.4$ Hz, 3H), 4.11 (q, $J = 8.4$ Hz, 2H), 7.13 (d, $J = 8.8$ Hz, 2H), 7.33 (dd, $J_1 = 7.6$ Hz, $J_2 = 3.6$ Hz, 1H), 7.38 (d, $J = 8.8$ Hz, 2H), 7.56 (d, $J = 6.8$ Hz, 1H), 7.75 (dd, $J_1 = 6.8$ Hz, $J_2 = 7.6$ Hz, 1H), 8.71 (d, $J = 3.6$ Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 15.0, 58.9, 119.5, 123.2, 124.7, 125.6, 127.5, 129.8, 130.7, 131.3, 137.3, 138.5, 150.1, 156.2, 168.2. ESI MS: (M+1) 363, (M−1) 361; Elemental analysis, calcd for $C_{17}H_{13}F_3N_4O_2$: C, 56.36; H, 3.62; N, 15.46. Found: C, 56.31; H, 3.49; N, 15.27.

Ethyl 5-(4-methylpyridin-2-yl)-1-(4-(trifluoromethyl)-phenyl)-1H-1,2,3-triazole-4-carboxylate (**3k**), mp >244–246 °C, 36% yield; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.31 (t, $J = 8.4$ Hz, 3H), 2.24 (s, 3H), 4.07 (q, $J = 8.4$ Hz, 2H), 7.16 (d, $J = 8.8$ Hz, 2H), 7.25 (d, $J = 4.0$ Hz, 1H), 7.41 (d, $J = 8.8$ Hz, 2H), 7.48 (s, 1H), 8.64 (d, $J = 3.6$ Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 14.3, 25.0, 58.6, 124.1, 124.6, 125.1, 125.3, 127.7, 129.9, 131.5, 132.2, 137.6, 147.8, 149.7, 156.1, 168.1. ESI MS: (M+1) 377, (M−1) 375; Elemental analysis, calcd for $C_{18}H_{15}F_3N_4O_2$: C, 57.45; H, 4.02; N, 14.89. Found: C, 57.22; H, 3.87; N, 14.66.

Phenyl(5-(pyridin-2-yl)-1-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl)methanone (**3q**); mp >250 °C, 52% yield; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.21 (d, $J = 8.4$ Hz, 2H), 7.35 (dd, $J_1 = 8.0$ Hz, $J_2 = 3.6$ Hz, 1H), 7.43–7.47 (m, 4H), 7.51 (m, 1H), 7.58 (d, $J = 8.0$ Hz, 1H), 7.80–7.83 (m, 3H), 8.66 (d, $J = 3.6$ Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 119.7, 123.8, 124.1, 124.9, 129.0, 129.6, 130.1, 130.7, 131.5, 133.2, 134.6, 137.4, 142.8, 144.7, 149.5, 156.1, 190.3. ESI MS: (M+1) 395, (M−1) 393; Elemental analysis, calcd for $C_{21}H_{13}F_3N_4O$: C, 63.96; H, 3.32; N, 14.21. Found: C, 63.77; H, 3.21; N, 14.02.