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Reaction of *N*-fluoropyridinium fluoride with isonitriles and $TMSN_3$: a convenient one-pot synthesis of tetrazol-5-yl pyridines

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Abstract—Reaction of *N*-fluoropyridinium fluoride generated in situ with a series of isonitriles and $TMSN_3$ led to the formation of the corresponding tetrazol-5-yl pyridines in good yields (37–84%). A similar reaction sequence for quinoline yielded the respective derivatives of 2-quinoline. The proposed reaction mechanism involves the intermediate formation of a highly reactive carbene species.

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]

In our attempt to further expand the synthetic potential of these useful substrates,[9] we studied the reaction of *N*-fluoropyridinium fluorides **1** generated in situ with isonitriles in the presence of $TMSN_3$.[10] This one-pot reaction yielded tetrazol-5-yl pyridines **3a**–**p** in good yields (Scheme 1).[11,12] Varying amounts of 2-picolinamides **4** were also isolated from the reaction mixtures along with tetrazolo[1,5-*a*]pyridines.[2,7,10] The reaction outcome was independent of the nature of the isonitrile component (Scheme 2, entries **a**–**h**). In general, yields of the desired compounds **3** exceeded 50%. Reactions with *p*-trifloromethylphenyl isocyanide 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 (1:2 mixture) followed by recrystallization of the solid residue from EtOH.[11]

We also studied the effect of pyridine substitution on the reaction outcome (entries **i**–**p**). Consistent with our earlier observations,[10] 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 **3** and significant formation of side products, including the respective picolinamides **4**.[10] 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 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 76% overall isolated yield (Scheme 1, **1j**). Similar regioselectivity was observed by us earlier.[8] Ratio 1:2, pyridine to isonitrile, and pyridine to $TMSN_3$ furnished the best yields of the desired products **3**. $TMSN_3$ afforded significantly higher yields (by ca. 35–40%) than NaN_3 or a Bu_4NF/NaN_3 system, presumably due to the mild and quantitative in situ generation of N_3^- anion. Larger molar excess of pyridines led to increased amounts of the respective picolinamides **4** and tetrazolo[1,5-*a*]pyridines **5**. In addition, significant amounts of 2-chloro- and 2-fluoropyridines were detected in the reaction mixtures

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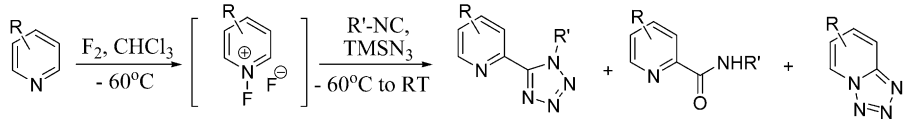
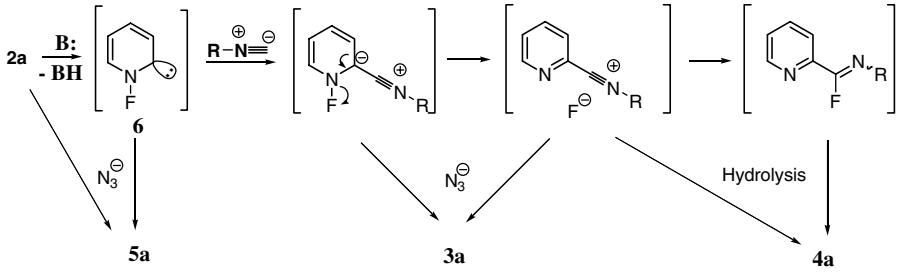


1 **2** **3a-p** **4a, i-p** **5**[a]

Entry, **1**	R	R'	Yields, % **3**	**4**	Entry, **1**	R	R'	Yields, % **3**	**4**
a	H	n-Bu	67	12	**i**	2-Me	*p*-CF_3-C_6H_4-	61	16
b	H	t-Bu	69	19	**j**	3-Me	*p*-CF_3-C_6H_4-	76[b]	10[b]
c	H		73	11	**k**	4-Me	*p*-CF_3-C_6H_4-	75	14
d	H	Ph	75	13	**l**	2-Cl	*p*-CF_3-C_6H_4-	70	13
e	H	*p*-CF_3-C_6H_4-	81	8	**m**	4-Cl	*p*-CF_3-C_6H_4-	84	9
f	H	CH_2COOEt	52	31	**n**	2-OMe	*p*-CF_3-C_6H_4-	41	36
g	H	CH_2Ph	45	27	**o**	2-Ph	*p*-CF_3-C_6H_4-	37[c]	24
h	H	*p*-NO_2-C_6H_4-	83	8	**p**	2-COOMe	*p*-CF_3-C_6H_4-	34[d]	28

[a]Yields of **5** did not exceed 7-10% (isolated yields, 10-15% LC MS yields); [b]Mixture of 2- and 6-substituted derivatives, *ca.*2 :1 isolated ratio, respectively; [c]Mixture contained products of fluorination of the Ph ring (*ca.* 25%, LC MS); [d]considerable amount of unidentified side products (>30%) detected by LCMS

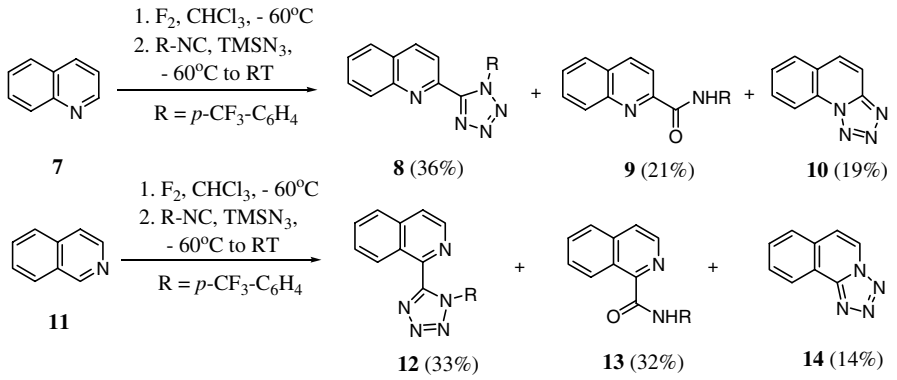
Scheme 1.



Scheme 2.

(LC–MS).[1,2] Chloroform was the optimal solvent for this reaction. Similar procedures conducted in CH_3CN (−42 °C) resulted in considerably lower yields of the desired materials **3** and formation of side products.[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 −50 °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.[1,7,10]

The outcome of the reported 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 electrophilic carbene **6** (Scheme 2).[1,2] We suggest that **6** undergoes a subsequent reaction with isonitrile to afford the respective isonitrilium ylide. This ylide undergoes subsequent reaction with in situ generated azide anion to yield the observed product **3**. Product **5** is likely to originate from the addition of azide anion to either carbene species or to *N*-fluoropyridinium fluoride **2** followed by the elimination of HF (*cine*-substitution step).[10] Apparently, the reaction of **6** with isonitrile to yield the ylide intermediate seems to



Scheme 3.

be the main route for this conversion. The yields of tetrazolo[1,5-*a*]pyridines, products of the side reaction of **6** with azide anion did not exceed 15%. Picolinamides are likely to result from the hydrolysis of the isonitrilium ylide species.[10] 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 and 2,6-dichloropyridine 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 followed by the reaction of the intermediary cationic species with isonitrile and $TMSN_3$ as described above (**8** and **12**; 36% and 33% yields, respectively, Scheme 3).[11,12] However, the yields of the desired materials were lower than for **3**. In addition, significant amounts of chlorinated species along with the high molecular weight products were detected in the reaction mixtures (LC–MS). Notably, pyrimidine, pyridazine, and pyrazine failed to produce the expected tetrazole derivatives under a variety of reaction conditions, presumably due to the liability of the intermediate *N*-fluorinated species. Instead, a complex mixture of fluorinated products (^{19}F NMR), none of them major was observed in each case.

In summary, we described the reaction of in situ generated *N*-fluoropyridinium fluorides with isonitriles and $TMSN_3$ to yield the respective tetrazol-5-yl pyridines in good yields. A 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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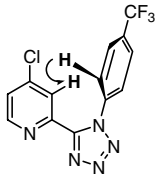
11. *In a typical reaction sequence*, an excess of fluorine gas (15–20 mmol) was bubbled through a solution of pyridine (0.79 g, 10 mmol) in $CHCl_3$ (50 mL), at such a rate that the initial temperature of −78 °C (acetone/dry ice bath) did not raise above −50 °C (*critical!*). The resultant white suspension of **2** was thoroughly flushed with nitrogen (*critical!*) to remove molecular fluorine and then treated dropwise (−50 °C) with a solution of isonitrile (20 mmol in 50 mL of $CHCl_3$) followed by a solution of $TMSN_3$ (20 mmol in 50 mL of $CHCl_3$). The resultant pale yellow mixture was stirred at −50 °C for 1 h, allowed to reach 0 °C within the next 4 h, and finally stirred for additional 4 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 ($MgSO_4$), and concentrated. Elution with hexanes/EtOAc (1:2) furnished 2-tetrazol-5-yl pyridines **3** as main products along with varying quantities of **4** (6–33%) and **5** (7–10% isolated yields). Alternatively, for *p*-trifluoromethylphenyl isocyanide reaction mixtures, the resulting concentrate was washed with EtOAc–Et2O, 1:2 (2 × 15 mL), the

resultant solid residue was recrystallized from EtOH to afford analytically pure **3i**–**p**.

12. Regiochemistry of substitution was confirmed by NOE experiments:



observed significant nOe's for 3m

Representative examples: 4-Chloro-2-(1-(4-(trifluoromethyl)phenyl)-1*H*-tetrazol-5-yl)pyridine (**3m**): mp 203–205 °C, 84% yield; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.21 (d, J = 7.6 Hz, 2H), 7.29 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 7.6 Hz, 2H), 7.66 (s, 1H), 8.72 (d, J = 8.0 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 122.9, 123.8, 124.3, 126.0, 129.5, 131.1, 132.2, 142.4, 150.4, 152.3, 156.7. ESI MS: (M+1) 327, (M−1) 325; HR ESI MS: Exact mass calcd for $C_{13}H_7ClF_3N_5$: 325.0342. Found: 325.0333. Elemental analysis, calcd for $C_{13}H_7ClF_3N_5$: C, 47.94; H, 2.17; N, 21.50. Found: C, 47.69; H, 2.35; N, 21.23.

2-(1-(4-(Trifluoromethyl)phenyl)-1*H*-tetrazol-5-yl)quinoline (**8**): mp >250 °C, 36% yield; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.24 (d, J = 7.6 Hz, 2H), 7.41 (d, J = 7.6 Hz, 2H), 7.48 (m, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.63 (m, 1H), 7.70 (d, J = 8.4 Hz, 1H), 8.02–8.06 (m, 2H); ^{13}C NMR (DMSO-d_6): δ 119.1, 124.4, 125.0, 125.5, 126.8, 128.2, 128.9, 129.8, 130.5, 131.3, 132.4, 137.2, 147.2, 155.4, 157.8. ESI MS: (M+1) 342, (M−1) 340; HR ESI MS: Exact mass calcd for $C_{17}H_{10}F_3N_5$ 341.0888. Found: 341.0881. Elemental analysis, calcd for $C_{17}H_{10}F_3N_5$: C, 59.83; H, 2.95; N, 20.54. Found: C, 59.66; H, 3.08; N, 20.37.

2-(1-(4-(Trifluoromethyl)phenyl)-1*H*-tetrazol-5-yl)quinoline (**12**): mp >250 °C, 33% yield; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.21 (d, J = 7.6 Hz, 2H), 7.46–7.53 (m, 5H), 7.73 (d, J = 7.2 Hz, 1H), 7.90 (d, J = 7.2 Hz, 1H), 8.44 (d, J = 7.2 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 116.5, 124.1, 124.8, 126.8, 127.1, 127.3, 128.2, 129.9, 130.4, 130.9, 132.1, 137.2, 141.6, 150.8, 160.5. ESI MS: (M+1) 342, (M−1) 340; HR ESI MS: Exact mass calcd for $C_{17}H_{10}F_3N_5$ 341.0888. Found: 341.0876. Elemental analysis, calcd for $C_{17}H_{10}F_3N_5$: C, 59.83; H, 2.95; N, 20.54. Found: C, 59.58; H, 3.11; N, 20.33.