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Facile preparation of 3-substituted-2,6-difluoropyridines: application to the synthesis of 2,3,6-trisubstituted pyridines

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ABSTRACT

We report a facile method for the difluorination of 3-substituted-2,6-dichloropyridines using cesium fluoride as a fluorination reagent in dimethyl sulfoxide. It is proposed that this method for preparing 3-substituted-2,6-difluoropyridines is simpler and easier than those reported in previous literature. To examine the utility of 3-substituted-2,6-difluoropyridines in synthetic chemistry, we also demonstrate a subsequent conversion to 2,3,6-trisubstituted pyridines by a tandem nucleophilic aromatic substitution.

Introduction

Fluoropyridines are useful building blocks and easily react with nucleophiles because the fluorine atom with the highest electronegativity makes the carbon–fluorine bond susceptible to nucleophilic aromatic substitutions (S_NAr).[1] In particular, 3-substituted-2,6-difluoropyridines are considered as attractive intermediates in terms of synthetic and medicinal chemistry. Since they have two distinguishable carbon–fluorine bonds, a tandem S_NAr of 3-substituted-2,6-difluoropyridines can produce 2,3,6-trisubstituted pyridines, which are used in drug discovery[2] and found as scaffolds of biologically attractive compounds.[3]

The utility of 3-substituted-2,6-difluoropyridines in synthetic chemistry has been known for many years. However, only a few methods for preparing these compounds have been published. For example, the synthesis of 2,6-difluoro-3-nitropyridine from 2,6-dichloro-3-nitropyridine in low yield using a proton sponge [1,8-bis(dimethylamino)naphthalene] and triethylaminetris (hydrogen fluoride) was reported.[4] 2,3,6-Trichloropyridine was converted into 3-chloro-2,6-difluoropyridine in an autoclave reaction.[5] Various 3-substituted-2,6-difluoropyridines were prepared via lithiation of 2,6-difluoropyridine with lithium diisopropylamide.[6] The difluorination of methyl 2,6-dichloropyridine-3-carboxylate using freshly prepared anhydrous TBAF has been described.[7] In these previous reports, 3-substituted-2,6-difluoropyridines were prepared with only low yields or under either high temperature (at 200 °C) or low temperature (at −75 °C). Using other methods, freshly prepared TBAF was required. These limitations have prevented the field of synthetic chemistry having easy access to 3-substituted-2,6-difluoropyridines.

Herein, we describe a facile method for preparing 3-substituted-2,6-difluoropyridines derived from 3-substituted-2,6-dichloropyridines using a simple reaction where chlorine is replaced by fluorine. We also show the utility of these compounds for chemical synthesis by demonstrating their subsequent conversion to 2,3,6-trisubstituted pyridines (Scheme 1).

Reaction conditions for the difluorination of 3-substituted-2,6-dichloropyridines

As many methods for the monofluorination of chloropyridines have been reported,[8] we attempted to modify some of these procedures for the difluorination of 3-substituted-2,6-dichloropyridines. We started a screening of reaction conditions for the difluorination of 2,3,6-trichloropyridine (**1**). The progress of the fluorination reaction was measured by HPLC while monitoring UV absorption at 254 nm. Two types of well-known fluorination reagents [potassium fluoride (KF) and cesium fluoride (CsF)] were used to replace chlorine atoms at the 2- and 6-positions with fluoride in DMSO under atmospheric conditions (Table 1, entries 1–3). Both KF and CsF were found to be effective fluorination reagents for this reaction. When KF was used, a higher temperature and longer reaction time for completing the difluorination reaction were required compared to CsF due to the slower reaction rate of KF (Table 1, entries 2 and 3). A solvent screening revealed that DMSO was better than the other polar aprotic and non-polar solvents (Table 1, entries 4–8). The combination of

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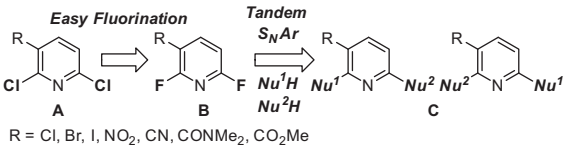
0040-4039/



Scheme 1. Synthetic approach to 2,3,6-trisubstituted pyridines **C**.

CsF and DMSO was the best reaction condition for the difluorination of 2,3,6-trichloropyridine.[9]

The versatility of the difluorination reaction was confirmed by applying it to 3-substituted 2,6-dichloropyridines (Table 2). Pyridines with electron-withdrawing groups at the 3-position reacted easily with CsF (80–100 °C, 0.5–8 h). Conversely, 2,6-dichloro-3-methylpyridine was converted into 2,6-difluoro-3-methylpyridine under harsher conditions (120 °C, 40 h). The yield of 2,6-difluoro-3-methylpyridine was low (13%, calculated from the NMR spectra of a crude mixture after a routine work-up) because 2,6-difluoro-3-methylpyridine was volatilized under the harsh conditions. Hence, we assume that alkyl substituents such as the methyl on the 3-position impaired the reactivity toward fluorine substitution and required a longer reaction time and higher temperature. The difluorinated products were so reactive that some of them may be hydrolyzed by reacting with moisture in the solvent.[10] We assumed that the moderate yields of the difluorinated products were due to this side reaction and the volatilization of the products in purification processes such as evaporation under reduced pressure.

It was found that the difluorination reaction was applied to the monofluorination of 3-substituted-2-chloropyridines although it required more tough reaction conditions (90–130 °C, 4–40 h).[11]

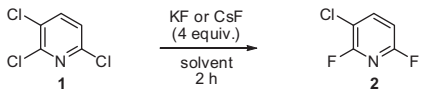
Preparation of 2,3,6-trisubstituted pyridines by a tandem S_NAr reaction of 3-substituted-2,6-difluoropyridines

It is well-known that fluoropyridines are reacted with nucleophiles.[12] Especially, 3-substituted-2,6-difluoropyridines are known to be transformed into 2,3,6-trisubstituted pyridines by successive reactions with nucleophiles.[13] Herein, we provide new examples of 2,3,6-trisubstituted pyridines prepared from 3-substituted-2,6-difluoropyridines. We demonstrate the utility of 3-substituted-2,6-difluoropyridines in synthetic chemistry by using them to synthesize 2,3,6-trisubstituted pyridines via a tandem S_N-Ar reaction. Since two fluorine atoms on the pyridine ring make the scaffold reactive to nucleophiles, the reaction of 3-chloro-2,6-difluoropyridine (**2**) with benzylamine was completed within 2 h at room temperature (Scheme 2). The fluorine substitution occurred preferentially at the 2-position (yield of **2D**/**2E** = 66%:9%). Conversely, the reaction of 2,3,6-trichloropyridine (**1**) with benzylamine produced only trace amounts of products.

The reactions of the 3-substituted-2,6-difluoropyridines with benzylamine were examined (Table 3). The fluorine substitution smoothly proceeded at room temperature with good yields although the ratio of **D** to **E** was dependent on the substituent groups on the 3-position.[14] When bromine- or nitro-groups were introduced at the 3-position, the major products were observed to be **3D** and **5D**, respectively. (Table 3, entries 1 and 3). However when cyano- or methyl-ester-groups were introduced at the 3-position, fluorine substitution preferentially proceeded at the 6-position (Table 3, entries 4 and 6).

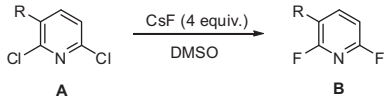
Next, we examined the reactivity of 3-chloro-2,6-difluoropyridine (**2**) toward other nucleophiles (Table 4). We found that an amine **9**, amide **10**, alcohol **11**, and a sulfur **12** were good substrates for the fluorine substitution (Table 4, entries 1–4) although an aromatic amine such as aniline was unsuitable for this reaction (data not shown). Note that carbon nucleophiles such as sodium cyanide (**13**) and dimethyl malonate (**14**) easily produced moderate to high yields with good regioselectivity (Table 4, entries 5 and 6).

Table 1
Screening of reaction conditions for the preparation of 3-chloro-2,6-difluropyridine (**2**) from 2,3,6-trichloropyridine (**1**)

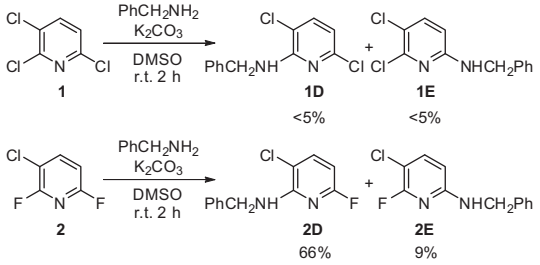


Entry	Reagent	Solvent	Temp	**2**	Mono-F	**1**
1	KF	DMSO	80 °C	0	29	71
2	KF	DMSO	120 °C (20 h)	100	0	0
3	CsF	DMSO	80 °C	100	0	0
4	CsF	DMF	80 °C	26	68	6
5	CsF	NMP	80 °C	4	55	41
6	CsF	Toluene	80 °C	0	0	100
7	CsF	CH_3CN	80 °C	0	12	88
8	CsF	THF	Reflux	0	0	100

Table 2
Difluorination of 3-substituted 2,6-dichloropyridines

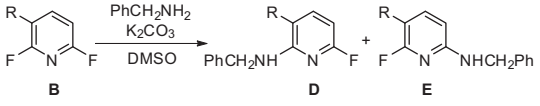


Entry	**A**	R	Temp (°C)	Time (h)	Yield (%)
1	**3A**	Br	80	8	64 (**3B**)
2	**4A**	I	90	1.5	52 (**4B**)
3	**5A**	NO_2	90	0.5	64 (**5B**)
4	**6A**	CN	80	1.5	56 (**6B**)
5	**7A**	$CONMe_2$	100	3	67 (**7B**)
6	**8A**	CO_2Me	80	1	51 (**8B**)



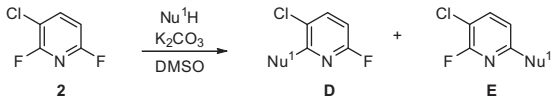
Scheme 2. Reactions of 2,3,6-trichloropyridine (**1**) and 3-chloro-2,6-difluoropyridine (**2**) with benzylamine.

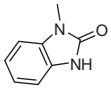
Table 3
Reactions of 3-substituted-2,6-difluoropyridines with benzylamine



Entry	**B**	R	Time (h)	Yield (%)	
1	**3B**	Br	6	51 (**3D**)	13 (**3E**)
2	**4B**	I	24	33 (**4D**)	30 (**4E**)
3	**5B**	NO_2	0.5	47 (**5D**)	<5 (**5E**)
4	**6B**	CN	0.5	25 (**6D**)	64 (**6E**)
5	**7B**	$CONMe_2$	24	40 (**7D**)	43 (**7E**)
6	**8B**	CO_2Me	2	27 (**8D**)	60 (**8E**)

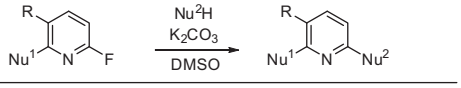
Table 4
Reaction between 3-chloro-2,6-difluoropyridine (**2**) and nucleophiles

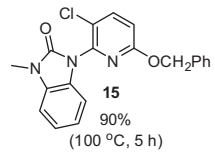


Entry	Nucleophiles		Temp (°C)	Time (h)	Yield (%)	
1		9	50	0.5	83* (**9D**)	8* (**9E**)
2		10	50	3	68 (**10D**)	6 (**10E**)
3	$PhCH_2OH$	11	80	20	78* (**11D**)	16* (**11E**)
4	$PhCH_2SH$	12	rt	0.5	93 (**12D**)	<5 (**12E**)
5	NaCN	13	50	0.5	55 (**13D**)	<5 (**13E**)
6	$CH_2(CO_2Me)_2$	14	80	2	87 (**14D**)	7 (**14E**)

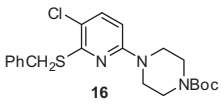
* The regioselectivity was calculated from the NMR spectra.

Table 5A
Second fluorine substitution

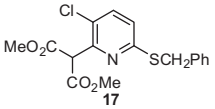




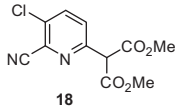
15
90%
(100 °C, 5 h)



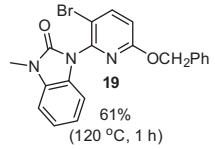
16
82%
(100 °C, 20 h)



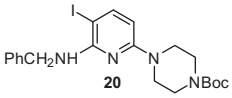
17
33%
(100 °C, 3 h)



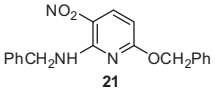
18
56%
(100 °C, 1 h)



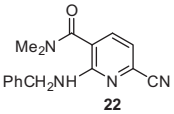
19
61%
(120 °C, 1 h)



20
43%
(110 °C, 40 h)

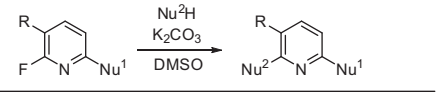


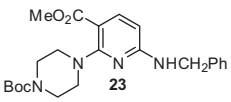
21
60%
(90 °C, 2 h)



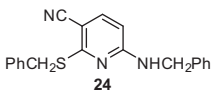
22
78%
(100 °C, 20 h)

Table 5B
Second fluorine substitution





23
73%
(100 °C, 5 h)



24
88%
(100 °C, 0.75 h)

Since the major products in Tables 3 and 4 still had a carbon–fluorine bond remaining on the 2- or 6-position, a second fluorine substitution was performed (Tables 5A and 5B). Although almost all of the substrates required a slightly higher temperature to complete the second fluorine substitution, it was observed that various nucleophiles could be used in this reaction producing moderate to high yield. Consequently, numerous different 2,3,6-trisubstituted pyridines could be prepared.

We presented a facile method for the difluorination of 3-substituted-2,6-dichloropyridines, which were used to synthesize 2,3,6-trisubstituted pyridines using a tandem fluorine substitution. 2,3,6-Trisubstituted pyridine is a popular scaffold found in many drug candidates and biologically attractive compounds. This synthetic approach provides organic and medicinal chemists with new insights in designing synthetic routes for their target materials.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.09.057.

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14. The regiochemistry of the products was determined by the coupling constants ($^3J_{HF}$ or $^5J_{HF}$). See Supporting information for the details.