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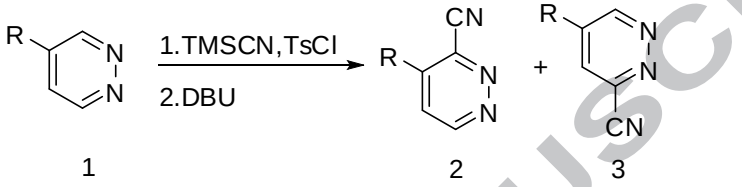

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Efficient synthesis of 5-substituted-3-pyridazine carbonitrile via regioselective Reissert–type reaction

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ABSTRACT

Various 5-substituted-3-pyridazine carbonitrile derivatives were synthesized by regioselective Reissert–type reaction with 4-substituted pyridazine, 4-methylbenzene-1-sulfonyl chloride and trimethylsilyl cyanide, the reaction can be carried out under the conditions with $AlCl_3$ as catalyst, THF as solvent at 10 ^{o}C, followed by treating with DBU gave a moderate yields and good regionselectivity.

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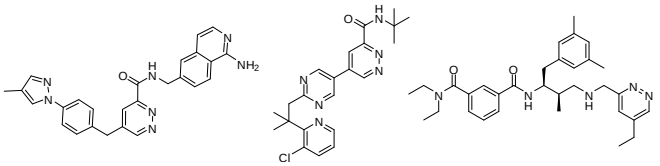
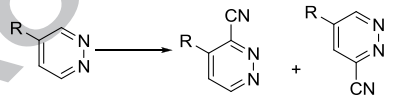
Introduction

Compounds containing pyridazine motifs are known to show a variety of biological activities[1], there have also been found several types of applications in agrochemistry[2], material science[3] and supramolecular chemistry[4]. Pyridazine nitriles represent versatile intermediates, the nitriles can be converted to a multitude of different functional groups. The functionalized 5-substituted pyridazine-3-carbonitrile are present in an increasing numbers of pharmaceutical products[5] (**Scheme 1**), but few synthetically useful examples have been reported. In order to explore more functional heterocyclic derivatives for drug design projects[6], we were interested in developing convenient methods for the synthesis of this kind of pyridazine nitriles scaffold.



Scheme 1. Examples of functionalized 5-substituted pyridazine-3-carbonitrile derivatives in active molecule

The Sandmeyer[7] and Rosemund-Von Braun[8] reactions are traditional methods for preparing aromatic nitriles. More recently, the transition-metal-catalyzed cyanation of aromatic halide in synthesis aromatic nitriles has attracted the most attention[9]. But due to the instability and the synthetic difficulty of halopyridazine, their application is severely limited. Another attractive method is through Reissert intermediates directly introduced nitriles on heterocycles (quinoline, isoquinoline, pyridazine etc)[10]. In 1981, Popp et al reported 3-methylpyridazine was treated with trimethylsilyl cyanide (TMSCN) and freshly distilled benzoyl chloride (BzCl) gave a 41% yield of the pyridazine Reissert compounds[11]. In 1986, Gottfried research group first obtained 4-methylpyridazine-3-carbonitrile through Reissert–type reaction with 4-methyl-pyridazine, 4-methylbenzene-1-sulfonyl chloride (TsCl) and trimethylsilyl cyanide[12]. Theoretically, direct cyanation of 4-substituted pyridazine by Reissert-type reaction has a regionselectivity at C-3 or C-6 position, respectively leads to 4- or 5-substituted pyridazine-3-carbonitrile (**Scheme 2**). In this paper, we described the synthesis of 5-substituted pyridazine-3-carbonitrile through regioselective Reissert-type reaction.

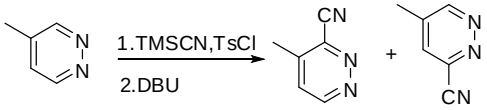


Scheme 2. Regioselective Reissert–type reaction of 4-substituted pyridazine

Results and Discussion

In the initial investigation, we studied the reaction of 4-methylpyridazine with TMSCN/TsCl to get pyridazine Reissert compounds based on the literature[12]. To our delight, after treating the crude pyridazine Reissert compounds with 1.8-diazabicyc1o[5.4.0]undec-7-ene (DBU) in THF, we can get a mixture of 4-methyl and 5-methyl pyridazine-3-carbonitrile in a ratio of 1:0.39. The 5-methylpyridazine-3-carbonitrile was first obtained through Reissert–type reaction.

Table 1. Effects of catalysts and loading on the reaction of 4-methylpyridazine with TMSCN/ TsCl, and DBU[a]



1 2 3

Entry	Lewis acid	Loading (mol%)	Yield[b](%)	Ratio 2/3[c]
1	$AlCl_3$	0.4	78	1/0.39
2	$ZnCl_2$	0.4	35	1/0.25
3	$FeCl_3$	0.4	18	1/0.26
4	$BF_3{\cdot}OEt_2$	0.4	15	1/0.17
5	$AlCl_3$	1	80	1/0.1
6	$AlCl_3$	2	76	1/0.09
7	$AlCl_3$	5	75	1/0.06
8	$AlCl_3$	0.2	65	1/0.39

[a] Reaction conditions: 4-methylpyridazine (25 mmol), TMSCN (45 mmol), TsCl (43 mmol), DBU (45 mmol), DCM (100 mL), 25 °C.

[b] Total isolated yields of 2 and 3 based on 1.

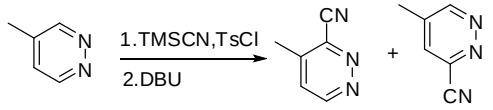
[c] Determined by H-NMR of the reaction mixture.

Encouraged by this result, we next tried to get 5-methylpyridazine-3-carbonitrile as the major product by changing the reaction conditions. The reaction of 4-methylpyridazine with TMSCN/TsCl, and DBU was investigated as a model reaction to explore the reaction condition (Table 1). The reaction time is determined by the complete conversion of the starting substance. Our initial study focused on the effects of the Lewis acid catalysts on the reaction. Various Lewis acid $AlCl_3$, $ZnCl_2$, $FeCl_3$, $BF_3{\cdot}OEt_2$ were investigated, unfortunately, only $AlCl_3$ can catalyze this reaction with a good yield (Table 1, entry 1). When $ZnCl_2$, $FeCl_3$, $BF_3{\cdot}OEt_2$ were used as Lewis acid catalysts, the conversion efficiency was greatly reduced, the combined yield of **2** and **3** is poor even when the material was completely consumed after a long time (Table 1, entries 2-4). Obviously, Lewis acid of $AlCl_3$ is more suitable in this system. Furthermore the loading of the catalyst was tested, the conversion efficiency is greatly improved when the Lewis acid catalyst loading increased. The higher catalyst loading does not benefit the generation of 5-methylpyridazine-3-carbonitrile (Table 1, entries 5-7). In contrast, a slight decrease of the Lewis acid catalyst loading will increase the ratio of the 5-methylpyridazine-3-carbonitrile to 4-methylpyridazine-3-carbonitrile. Too little catalyst loading will result in a long reaction time and low yield (Table 1, entry 8).

We also studied the effects of the amount of TMSCN/TsCl (1.1/1), temperature and solvents on this reaction by fixing 0.4 mol % $AlCl_3$ (Table 2). When 1.6 equiv or 2.0 equiv of TMSCN and 1.7 equiv or 2.2 equiv TsCl were used under the same catalytic system, similar results were obtained (Table 2, entries 1-2). Moreover a poor conversion and low yield were obtained, when 1.2 equiv of TMSCN and 1.3 equiv equiv TsCl were used (Table 2, entry 3). When the temperature was decreased from 25 °C to 10 °C, the similar yield and an excellent percentage of 5-methylpyridazine-3-carbonitrile can be obtained (Table 2, entry 4). When the reaction was taken at 0 °C, the starting material still remained after a long time (Table 2, entry 5). Higher temperature cause a poor percentage of 5-methylpyridazine-3-carbonitrile (Table 2, entry 6). Several solvents such as toluene, dichloromethane, THF, dichloroethane were examined in the

reaction (Table 2, entries 7-10). As the table shows, when THF was used as solvent, the yield and percentage of 5-methylpyridazine-3-carbonitrile are the highest. So, the combination of 1.6 equiv of TMSCN and 1.7 equiv TsCl and 0.4 mol % $AlCl_3$, in THF at 10 °C was chosen as an optimum condition. After purified by column chromatography we can easily get the desired products.

Table 2. Effects of the amount of TMSCN/TsCl, solvent, and temperature on the reaction of 4-methylpyridazine with TMSCN/TsCl and DBU[a]



1 2 3

Entry	TMSCN/TsCl (equiv)	Solvent	Temp (°C)	Yield[b] (%)	Ratio 2/3[c]
1	1.7/1.6	CH_2Cl_2	25	78	1/0.39
2	2.0/1.8	CH_2Cl_2	25	80	1/0.26
3	1.2/1.1	CH_2Cl_2	25	58	1/0.45
4	1.7/1.6	CH_2Cl_2	10	79	1/0.51
5	1.7/1.6	CH_2Cl_2	0	65	1/0.51
6	1.7/1.6	CH_2Cl_2	50	63	1/0.30
7	1.7/1.6	Toluene	10	75	1/0.75
8	1.7/1.6	THF	10	78	1/1.30
9	1.7/1.6	$CHCl_3$	10	78	1/0.68
10	1.7/1.6	CH_2ClCH_2Cl	10	78	1/0.33

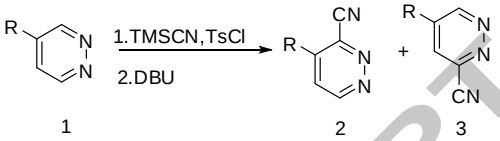
[a] Reaction conditions: 4-methylpyridazine (25 mmol), TMSCN, TsCl, $AlCl_3$ (24 mg), DBU (45 mmol), solvent (100 mL).

[b] Total isolated yields of 2 and 3 based on 1.

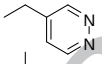
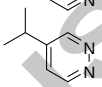
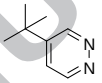
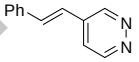
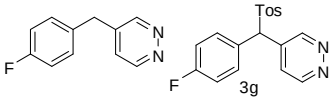
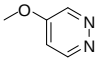
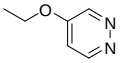
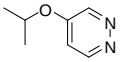
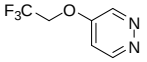
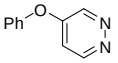
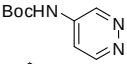
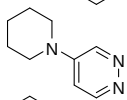
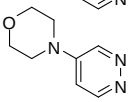
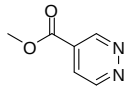
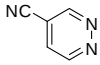
[c] Determined by H-NMR of the reaction mixture.

Under the optimized reaction conditions, the scope of 4-substitute-pyridazine derivatives were examined (Table 3). It could be noted that most reactions proceeded smoothly, providing the desired products in moderate yields and a good selectivity. The 4-ethylpyridazine gave a 78% combined yield, and the ratio of 2b:3b is 1:1.8 (Table 3, entry 2). 4-Isopropylpyridazine can provide a better ratio of 2c:3c (1:5) and a similar yield with 4-ethylpyridazine (Table 3, entry 3). As the steric hindrance increases (for t-butylpyridazine), the ratio of two isomers 2d:3d reached 1:10 (Table 3, entry 4). Meanwhile the 4-styrylpyridazine can also give the desired products with slightly poor regioselectivity, the ratio of 2e:3e was 1:0.8 (Table 3, entry 5). When the substrate changed to 4-phenylpyridazine, the ratio of 2f:3f changed to 1:2.5 (Table 3, entry 6). Unfortunately, the substrate of 4-(4-fluorobenzyl)pyridazine can not give the desired product, we can only get the byproduct (Table 3, entry 7). To our delight, the desired products were formed in good yields and excellent selectivity when the electron-donating group of 4-alkoxy-substituted (Table 3, entries 8-10) and 4-phenoxy-substituted pyridazine (Table 3, entry 11) were used in this reaction. Pleasingly, when nitrogen substituent group is the electron-donating group instead of alkoxy group, similar high regioselective results were achieved, but the yields slightly decreased (Table 3, entries 13-15). From the result we can see, the ratio of 2:3 was influenced by the steric as well as the electronic characteristics of the substituents. Compared with the electron-donating group, the electron-withdrawing group showed a negative effect on the reaction. The methyl pyridazine-4-carboxylate only provided trace products under this reaction condition even at higher temperature (Table 3, entry 16). The reaction could not be carried out when the pyridazine-4-carbonitrile was used as a starting material (Table 3, entry 17).

Table 3. Scope of 4-substitute-pyridazine under the optimized conditions[a]



1 2 3

Entry	Substrate	Product	Yield[b] (%)	Ratio (2:3)[c]
1		2a/3a	72	1:1.3
2		2b/3b	75	1:1.8
3		2c/3c	76	1:5
4		2d/3d	78	1:10
5		2e/3e	71	1:0.8
6		2f/3f	75	1:2.5
7		3g	64	
8		2h/3h	77	1:24
9		2i/3i	79	1:25
10		2j/3j	73	1:28
11		2k/3k	75	1:23
12		2l/3l	80	1:26
13		2m/3m	78	1:3
14		2n/3n	65	1:26
15		2o/3o	58	1:25
16		3p	trace	
17		3e	no	

[a] Reaction conditions: 4-substitute-pyridazine (25 mmol), TMSCN (45 mmol), TsCl (42 mmol), DBU (35 mmol), $AlCl_3$ (24 mg), THF (100 ml). 10 °C.

[b] Total isolated yields of 2 and 3 based on 1.

[c] Determined by H-NMR of the crude mixture.

Conclusion

In conclusion, we have demonstrated the selective cyanation of 4-substitute-pyridazine via regionselective Reissert–type reaction to get 5-substituted-3-pyridazinecarbonitrile. The regioselectivity was influenced by the steric effect as well as the electronic characteristics of the substituent, high steric hindrance or electron-donating group on the substrates benefit the generation of desired product. The functionalized 5-substituted pyridazine-3-carbonitrile are useful intermediates in bioactive molecules.

Acknowledgments

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Highlights

A series of 5-substituted-3-pyridazine carbonitrile derivatives were synthesized

One-pot two-step regioselective Reissert-type reaction was used

Regioselective cyanation of 4-substituted pyridazine was studied for the first time