



Aromatic Nucleophilic Substitutions Using X-Cube Flash™ Continuous Flow Reactor

INTRODUCTION

Fluorine aromatic ring substitution using *N*-based nucleophiles normally requires either harsh conditions and/or transition metal catalysis [1].

In the presence of electron-withdrawing groups (EWGs), non-catalyzed aromatic substitution takes place in *ortho*- and *para*-position in good yields. In the case of *meta*-substituted compounds, long reaction times (about 50 - 100 h) at 100 °C are required.

It is well-known that fluoroaromatics undergo nucleophilic substitution much more rapidly than other halides since fluorine is more inductively electron withdrawing than, for instance, the best leaving group iodine, and effectively reduces the electron density on the aromatic ring enhancing the rate of nucleophilic attack. This effect is further enhanced by aprotic solvents like DMSO or NMP [2].

In the presence of phenyl ring containing donor groups, palladium chemistry must be used in order to obtain acceptable results. The use of MW techniques in organic synthetic chemistry offered novel opportunities and MW controlled heating was applied in many areas including nucleophilic aromatic substitution [3].

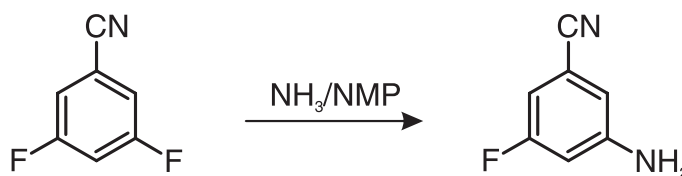
Brown et al. reported the amination of *meta*-difluorobenzonitriles accelerated by MW heating and the reaction



time was reduced from a few days to 2 - 5 h at 100 °C. However, these conditions resulted in increased levels of disubstitution [4].

ThalesNano has developed a high pressure/high temperature continuous flow reactor, called X-Cube Flash™, as a viable alternative to MW-chemistry. Several reactions previously reported under MW conditions were realized in the X-Cube Flash™ with improved yield and radically shortened reaction time under safe operation [5].

Our objective was to study the nucleophilic aromatic substitution reaction (F-amine exchange) in *metapositions*, since the substituted mono- and diaminobenzonitriles are important biological active molecules [6].



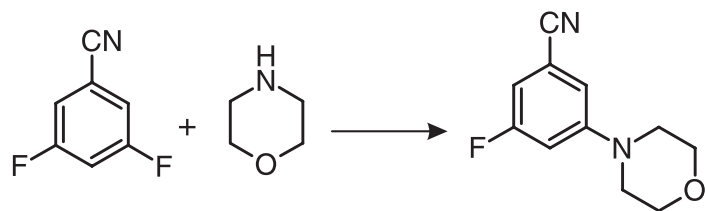
Scheme 1. F-amine exchange reaction between 3,5-difluorobenzonitrile and ammonia dissolved in NMP

F-AMINE EXCHANGE REACTION WITH AMMONIA

The batch preparation of 3-amino-5-fluorobenzonitrile from 3,5-difluorobenzonitrile was reported using NH_3 gas in dimethylsulfoxide (Time = 48 h, $T = 90^\circ\text{C}$) and the isolated yield was 70% [6]. Alternative routes toward this product include the reduction of 3-fluoro-5-nitrobenzonitrile [7], and multistep synthesis involving Pd-catalyzed cyanation [8]. Our approach employed an X-Cube Flash™ reactor [9] with ammonia gas, which was previously absorbed in the solvent of the reaction (NMP). The reaction could be performed and the monoaminated product could be prepared with >99% yield and selectivity within an effective residence time of 16 min (Loop = 8 mL, $T = 275^\circ\text{C}$, $p = 200$ bar, flow rate = 0.5 mL/min). The selectivity and conversion were dependant on the applied concentration. 0.05 M concentration gave the best result.

PARAMETER OPTIMIZATION

Based on the results of the previous experiment, 3,5-difluoro-benzonitrile and morpholine were chosen as starting materials for the optimization of the F-amine replacement reaction (Scheme 2.). The *N*-methyl pyrrolidine, in the presence of 6% MeOH to avoid precipitation, was found to be the best solvent and stable at temperatures above 200°C . The reaction parameters that afforded the highest conversion and selectivity are displayed in Table 1. The reaction conditions were $c = 0.2$ mol/L, $T = 200 - 275^\circ\text{C}$, $p = 200$ bar. Using lower pressure, below 100 bar, resulted in lower conversion. In all cases only the monoaminated product was observed.



Scheme 2. F-amine exchange reaction between 3,5-difluorobenzonitrile and morpholine

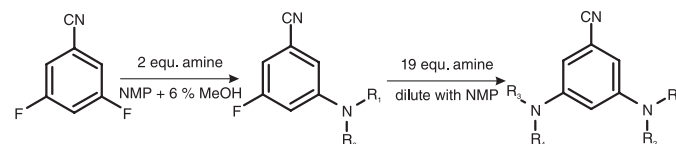
Flow rate (mL/min)	Volume of loop (mL)	T (°C)	Conversion (%)
1	8	200	86
1	8	225	93
1	8	250	>99
1	8	275	>99
0.5	4	270	>99

Table 1. Parameter optimization in F-amine exchange reaction

The experiments were carried out in two different sized loops (4 mL and 8 mL) and the residence time of 8 mins was found to be sufficient for total conversion using a 0.5 mL/min flow rate in the 4-mL-loop and a 1 mL/min in the 8-mL-loop respectively. The other advantage of our continuous process is its speed (productivity: 12 mmol/h) and the reaction can be performed using only 2 equ. of amine instead of the large excesses (6 equ.) used in the batch process.

Using the above conditions, a number of primary (e.g. isopropyl amine) and secondary amines (e.g. open chain: diethylamine, and cyclic: morpholine, pyrrolidine, piperidine, *N*-methyl piperazine, etc.) were reacted with 3,5-difluoro-benzonitrile and the monoamination reaction was monitored by GC-MS. In all cases the desired mono fluoro-exchanged products were detected and produced with good yield.

After the successful introduction of the first *N*-substituent by nucleophilic aromatic substitution (monoamination of 3,5-difluoro-benzonitrile), we decided to perform the second amination step which could afford unsymmetrical diaminated products (Scheme 3.).



Scheme 3. Synthesis of diaminated products

After optimal parameters were determined, a small library of 3,5-substituted diamino-benzonitriles (Table 2.) were synthesized together with one symmetrical diamino-benzonitrile (Table 2. Entry 10). For the second substitution reaction harsh conditions were required such as higher temperature, higher excess of amine, and a longer residence time ensured by using a longer loop in the second X-Cube Flash™ reactor after eluting from the first X-Cube Flash™ system and dilution with NMP. The optimized conditions and the results of each reaction are displayed in Table 2.



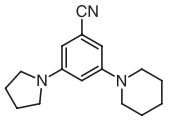


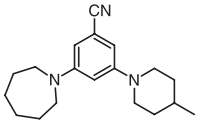


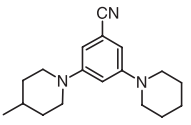


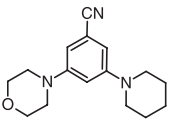


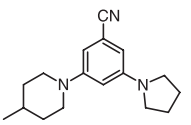


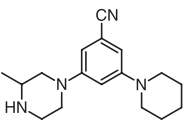


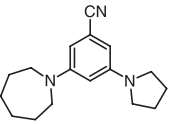


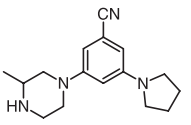


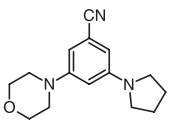


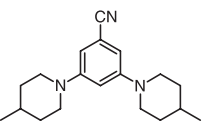


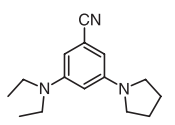


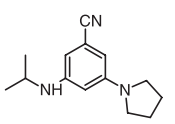
Entry	Amine A (2 equ.)	Conversion (% GC-MS)	Amine B (2 equ.)	Product	Conversion (% GC-MS)	Overall yield (% GC-MS)	Isolated yield (%)
1		>99			>99	>94	>89
2		>99			>99	>98	>92
3		>99			>99	>93	>92
4		>99			>99	>95	>87
5		>99			>99	>96	>98
6		>99			>99	>98	>98
7		>99			>99	>99	>96
8		>99			>90	>86	>86
9		>99			>99	>99	>98
10		>99			>99	>99	>99
11		>99			>99	>98	>90
12		>99			>99	>98	>90

Table 2. The synthesized 3,5-substituted diamino-benzonitrile derivatives

Reaction conditions of monoamino derivate synthesis: T = 270 °C, p = 100 bar, Loop = 4 mL, Flow rate = 0.5 mL/min.
 Reaction conditions of diamino derivate synthesis from the corresponding monoamino compound: T = 350 °C, p = 100 bar, Loop = 16 mL, Flow rate = 0.5 mL/min



GENERAL PROCEDURES OF F-AMINE EXCHANGE REACTIONS

General procedures for preparing symmetrical or unsymmetrical diamino-benzonitriles in two consecutive flow aminations.

First amination step:

The X-Cube Flash™ #1 reactor was preheated to 270 °C by pumping NMP + 6% MeOH solvent through the reactor with a 0.5 mL/min flow rate. In the meantime a 0.2 M solution was prepared containing 1 equ. of difluoro-benzonitrile and 2 equ. of the corresponding amine. When the system reached the optimal parameters (T = 270 °C, p = 100 bar, flow rate = 0.5 mL/min), the solvent was switched to the starting material solution. The main fraction was collected after 8 min of residence time for analysis.

Second amination step:

The reaction mixture from the first amination step was diluted with NMP to reach a 0.05 M concentration and 19 equ. of the second amine was added. In the meantime the X-Cube Flash™ #2 reactor was heated and allowed to reach the required parameters (p = 100 bar; T = 350 °C; flow rate = 0.5 mL/min.) having solvent pumped through the system. After reaching the above parameters the system was switched to the solution containing the reactants.

Since the residence time is 32 min (Loop = 16 mL; flow rate = 0.5 mL/min) the fractions could be collected after this time period.

Product isolation:

To the resulting fractions solid K₂CO₃ (1.5 g) was added. The mixture was stirred for 5 min and filtered. To the filtrate 500 mL diethyl ether was added and washed twice with 50 mL of saturated NaHCO₃, then 50 mL water and 50 mL brine. The organic phase was dried over Na₂SO₄, filtered and evaporated to dryness.

The crude material was analyzed by GC-MS and ¹H-NMR. Further purification was not required since the product purity reached 90 - 95 %.

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