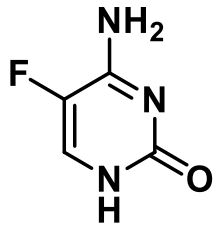
Process Development Report

The Medicines for All Institute

5-Fluorocytosine



M4ALL – 5-FC Team

31 January 2019

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Executive Summary:
A key intermediate in the synthesis of Emtricitabine (FTC) is the nucleobase 5-fluorocytosine (5FC). Herein, we describe a new route to 5FC starting from inexpensive precursors. Our process eliminates the use of gaseous fluorine to install the fluorine in 5FC. Fluorination with molecular fluorine requires specialized equipment and requires significant safety features in the manufacturing plant. The route combines inexpensive guanidine carbonate and another acyclic precursor to access 5FC efficiently. Further efficiencies are achieved through telescoping reactions and use of inexpensive reagents. The process is still being optimized and we predict there is room for improvement to reduce the overall environmental impact. Telescoping the processes will reduce the PMI which currently ranges from 9 to 27. The overall isolated yield currently stands at 48%. Further improvements will continue to be investigated.

Introduction:

The nucleoside reverse transcriptase inhibitor (nRTI) Emtricitabine **1** (FTC, 5-fluoro-1-(2R,5S)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine), Figure 1, is a key medicine in the fight against HIV. Discovered at Emory University, FTC was approved by the FDA in 2003 and marketed by Gilead Sciences. In combination with Tenofovir and Efavirenz, FTC is now one of the most important treatment regimens for limiting HIV load. Increasing access to this compound is considered vital to the worldwide battle against this infectious disease.

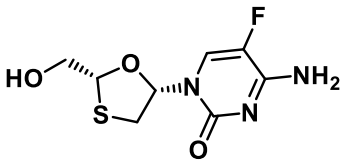

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Figure 1. Nucleoside reverse transcriptase inhibitor, Emtricitabine (FTC).

An important strategy for improving access to FTC is to reduce the manufacturing costs associated with the active ingredient. The current market price of FTC reported in the India Import/Export database is ~$280/kg. There are several routes to manufacture Emtricitibine such as the Ranbaxy process (US Patent 8748604) and the Lupin process (WO2013021290). The Ranbaxy process (Figure 2) can be used as a benchmark for process improvements. The synthesis of FTC proceeds with (L)-menthyl glyoxylate and the corresponding dithianediol. In the presence of acid the menthyl ester of the oxathiolane core of FTC is obtained in one step. Chlorination in the presence of thionyl chloride affords the precursor to the completed scaffold of FTC.

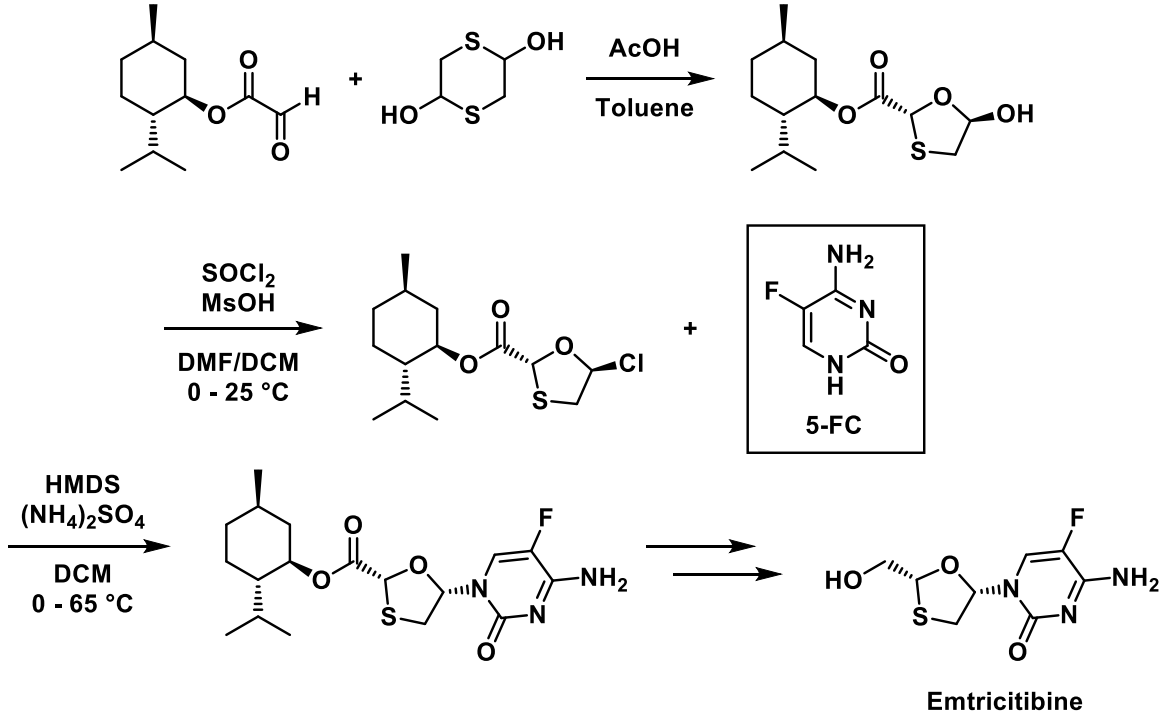

Figure 2. The Ranbaxy (US Patent 8748604) route to Emtricitibine.

Silylation of 5-fluorocytosine with HMDS and subsequent coupling with the oxathiolane core affords the completed scaffold. The ester funcational group is reduced to the alcohol with concomitant removal of the menthol auxilliary yielding FTC. Subsequent purifcations yield pure FTC.

In collaboration with CHAI and USAID, the Medicines for All Institute (M4ALL) has identified two major cost drivers for the synthesis of FTC – establishing high enantiopurity of the oxathiolane core **2** and the 5-fluorocytosine. The major expense associated with setting the optical purity of **2**, (Figure 3) is the use of L-menthyl glyoxalate. This starting material costs approximately $14 – 20/kg and is 61% of the cost of the initial first step and 11% of the overall process – as defined in US Patent 8748604. New routes that reduce the cost of the oxathiolane core and 5-FC represent low barrier to entry opportunities to reduce the overall costs of the active pharmaceutical ingredient.

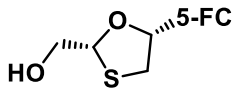

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Figure 3. The oxathiolane core of FTC.

The most expensive starting material used in the commercial preparation of FTC is the 5-fluorocytosine **3** (5-FC), Figure 4. In 2017 the price of 5-FC was $35/kg. Recently, the prices for both cytosine and fluorocytosine have increased. At the time of this report 5-FC and cytosine prices were $80/kg and $28/kg, respectively. The major cost driver of the synthesis of FTC is the installation of fluorine which accounts for 56% of the cost for the third step and 25% of the overall process of FTC. M4ALL has determined that an alternative route to 5-FC is needed to increase market participation. Herein, we describe a process that has lower raw material costs relative to known approaches to 5-FC.

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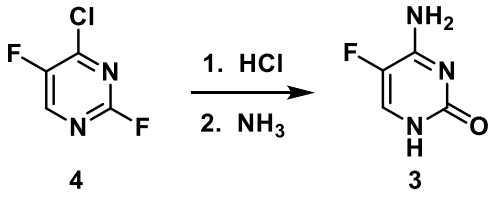
Figure 4. 5-fluorocytosine (5-FC)

Prior Art for 5-Fluorocytosine Synthesis:

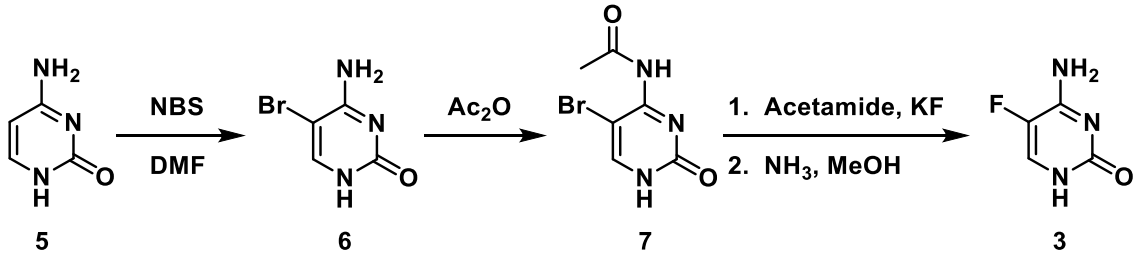
The fluorinated nucleobase 5-FC has been synthesized through several different patented approaches. The first class of routes start from fluorinated heterocycles to access 5-FC. The second general pathway is the direct fluorination of cytosine.

Bayer patented a route to 5-fluorocytosine starting from pre-fluorinated cyclic materials in 1987. Hydrolysis of the fluorinated pyrimidine in concentrated hydrochloric acid followed by ammonolysis afforded 5-fluorocytosine, Scheme 1. Starting from cyclic materials to access 5-fluorocytosine is expensive and refinement of this approach is unlikely to offer meaningful cost savings.



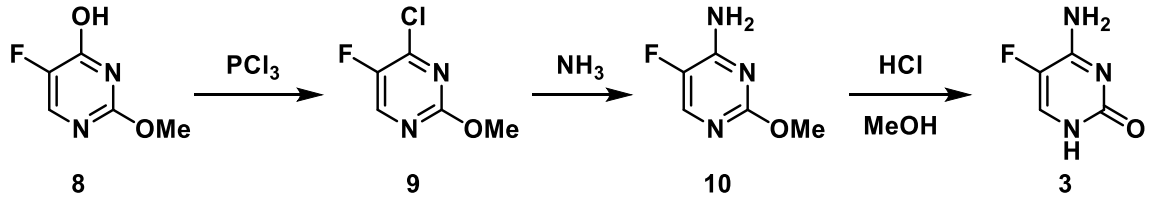
Scheme 1. Bayer's (US Patent US4703121 A1) patented route to 5-fluorocytosine from fluorinated heterocycles.

Zhejiang Xianfeng Technologies Co. patented a route to 5-fluorocytosine starting from cytosine, Scheme 2. Bromination with *N*-bromosuccinimide in DMF provided 5-bromocytosine that was subsequently acylated with acetic anhydride. The acylated 5-bromocytosine was treated with potassium fluoride in acetamide and then deprotection in methanolic ammonia yielding 5-fluorocytosine. This route relies on brominating reagents, protecting groups, and late stage fluorination – all potential cost drivers. Introduction of fluorine from inexpensive fluoride sources could be a potential cost saver for the synthesis of 5-fluorocytosine.



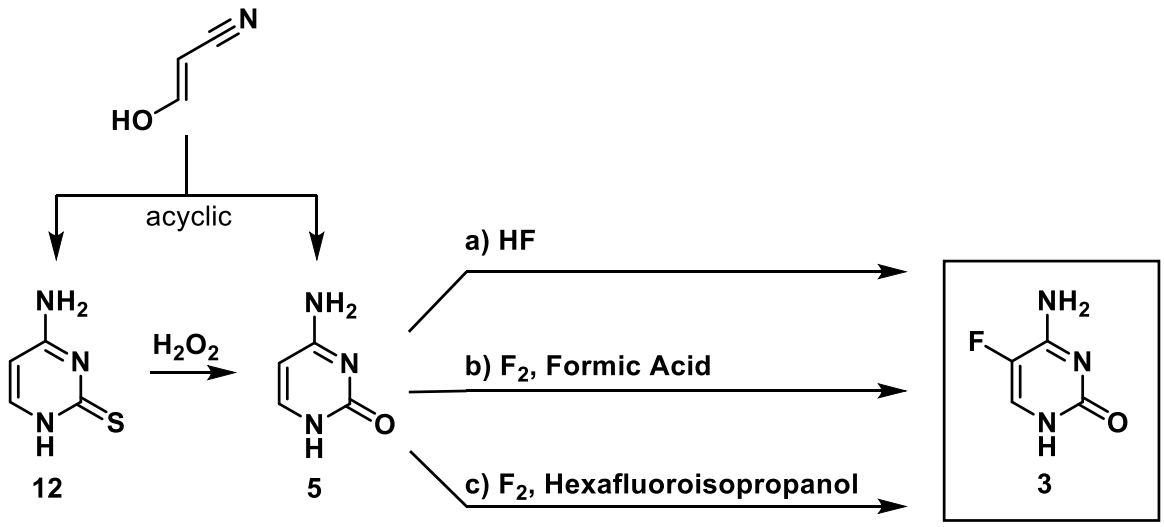
Scheme 2. Zhejiang Xianfeng Technologies Co. (CN103819412) late stage halogen exchange of cyclic precursors.

Shanghai Dixinuo Chemical Pharmaceutical Co. patented a route to 5-fluorocytosine starting from the monomethylated fluorinated pyrimidine **8** (Scheme 3). Chlorination in the presence of phosphorus chloride affords the chlorinated heterocycle **9**. Ammonolysis of the chloride yields **10**. Acidic hydrolysis of the methoxy ether in methanol affords 5-fluorocytosine **3**.



Scheme 3. Shanghai Dixinuo Chemical Pharmaceutical Co. patented route to 5-fluorocytosine. Shenyang Sinochem Pesticide Chemical CN105801492 A, 2016.

Finally, a more direct route to 5-FC involves the direct fluorination of cytosine. Starting with cytosine, Shaoxing Shangyu Hualun Chemical Industry Co. demonstrated a direct fluorination method using hydrofluoric acid (Scheme 4, route a). In 2016, the University of Durham patented the fluorination of cytosine using fluorine gas and formic acid (Scheme 4, route b) and Zhejiang Chemical Industry Research Institute patented the fluorination of cytosine using fluorine gas and hexafluoroisopropanol (HFIP) (Scheme 4, route c) in 2017. Cytosine can be produced using acyclic precursors by combing 3-hydroxyacrylonitrile with urea and sodium *tert*-butoxide or through a two-step procedure where 3-hydroxyacrylonitrile is cyclized with thiourea (Scheme 4, acyclic).

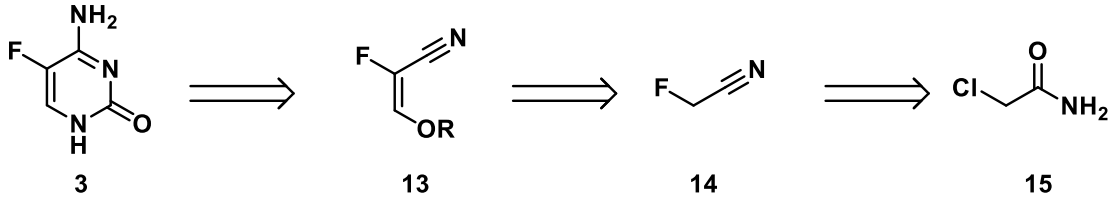


Scheme 4. Direct fluorination of cytosine as described in patents: CN104326990 B, 2016; CN106432099 A, 2017; WO2016/30662 A1, 2016.

Although direct fluorination routes are atom economical there are drawbacks. Facilities must be specialized to handle large quantities of these reagents and even with proper equipment the scale of these reactions are limited by regulations and safety concerns. This approach also does not address the rising cost of cytosine (see above).

Retrosynthetic Analysis:

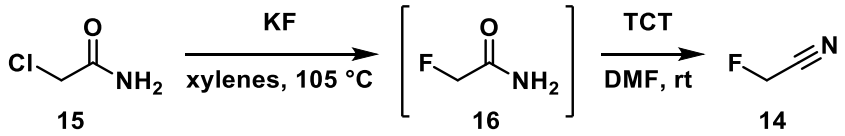
M4ALL envisioned that 5-fluorocytosine synthesized from inexpensive and readily available starting materials would lower the cost of 5-FC production (Scheme 5). The most obvious and desirable disconnection would be breaking the initial C – N bonds of the heterocyclic ring. Cyclization with urea was anticipated to directly access 5-FC and require no further functional group manipulation. The fluorinated acrylonitrile derivative **13** was might be accessible from a condensation of fluoroacetonitrile **14**. The required fluoroacetonitrile imagined to form through dehydration of the primary amide after introduction of fluorine through a Finkelstein reaction on chloroacetamide **15**. These reactions were anticipated to be readily telescoped to reduce costs and reduce the overall environmental impact. The reagents and starting materials required for these transformations are produced in industrial quantities assuring supply of raw materials. Introduction of the fluorine atom early using an inexpensive fluoride source eliminates the need for specialized equipment to handle F_2 and HF.



Scheme 5. Retrosynthetic analysis for the synthesis of 5-fluorocytosine.

The M4ALL 5-FC Route:

The M4ALL 5-FC route proceeds through telescoped steps using inexpensive and acyclic starting materials fluoroacetonitrile and guanidine carbonate. The route begins by transforming chloroacetamide to fluoroacetamide **16** *in situ* in near quantitative conversion as indicated by ^{1}HNMR (Scheme 6). Telescoping the reaction through the addition of cyanuric chloride (TCT) affords the key fluorinated intermediate fluoroacetonitrile **14**. The desired product can be isolated through distillation from the crude reaction mixture affording a clear colorless liquid in 70% yield with 99% purity as indicated by ^{1}HNMR.



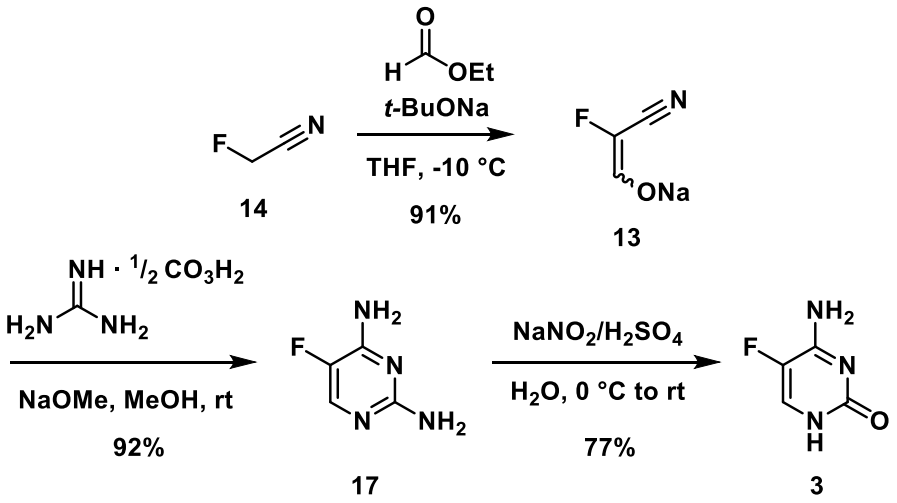
Scheme 6. Synthesis of fluoroacetonitrile.

Fluoroacetonitrile, **14**, in the presence of ethyl formate (-10 °C) and a hindered base, affords sodium-2-cyano-2-fluoroethen-1-olate **13** as a light brown solid, in 91% yield.

When bases such as sodium *tert*-butoxide or *tert*-amylate were used, small quantities of sodium formate can be observed, likely due to hydrolysis of ethyl formate by sodium hydroxide present in commercial samples of the alkoxide bases. The use of sodium hexamethyldisilazane can eliminate this impurity but with similar yield. The isolation of **13** was a source of variability in the process and we resolved this uncertainty by concentrating the reaction and using the concentrated material directly in the next step.

The concentrated solution of **13** was combined with the guanidine carbonate in the presence of sodium methoxide yielding 2,4-diamino-5-fluoropyrimidine **17** (Scheme 7, 92% yield). The purification was achieved by swapping the solvent with ethyl acetate and decolorizing with activated charcoal.

We attempted to produce 5-FC **3** directly by combining **13** and urea. Although we were able to generate the product under some conditions, we found the process to be highly sensitive to reaction conditions and starting material purity.

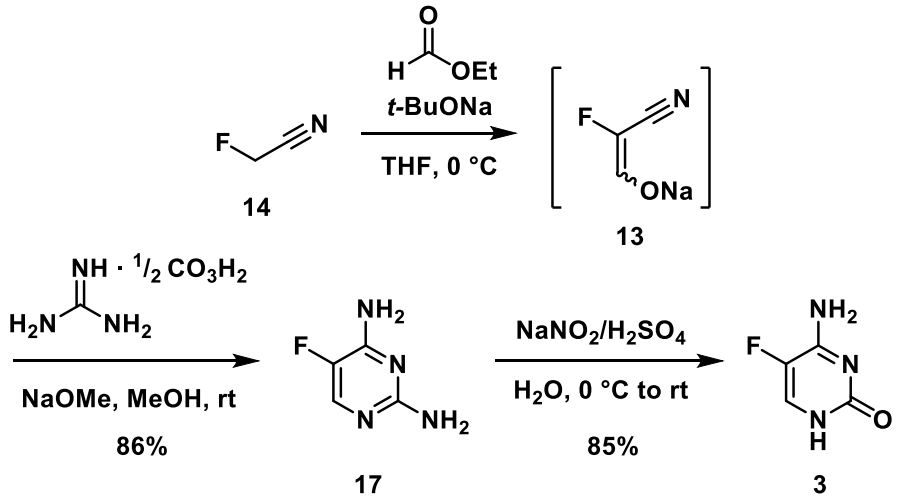


Scheme 7. Stepwise synthesis of 5-fluorocytosine from fluoroacetonitrile.

Regioselective diazotization of the pyrimidine using Sandmeyer conditions was developed to yield 5-FC **3**. One hour after addition of the sodium nitirite solution, all the starting material was consumed as indicated by NMR and the reaction mixture was neutralized to pH 7.4 with ammonium hydroxide to precipitate 5-FC **3** as an off-white solid in 85% yield.

The same sequence from fluoroacetonitrile to access **17** can be telescoped to reduce solvent consumption and unit operations (Scheme 8). A Knoevenagel-like condensation of ethyl formate with fluoroacetonitrile in the presence of sodium *tert*-butoxide in THF

afforded the sodium acrylonitrile salt **13**. The reaction mixture can be concentrated to half or lesser volume and telescoped into the next step. In a separate reactor, guanidine carbonate is reacted with sodium methoxide in methanol to liberate the freebase. The concentrated reaction mixture of **13** can be transferred via cannula to the guanidine solution. Stirring at room temperature for 24 hours afforded **17** (86% yield).



Scheme 8. Telescoped synthesis of 5-fluorocytosine from fluoroacetonitrile.

Route Details

Preparation of fluoroacetonitrile from chloroacetamide with cyanuric chloride:

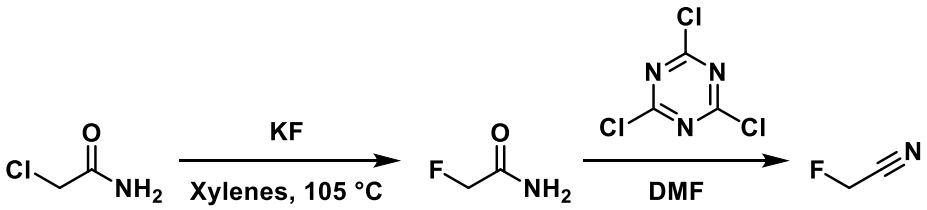


Table 1: Reagents and quantities for the synthesis of fluoroacetonitrile.

Material	Mol. Wt. (g/mol)	mmol	Eq.	Amount	Density
Chloroacetamide	93.5	427	1.0	40.0 g	-
Potassium Fluoride	58.1	522	1.2	29.8 g	-
Xylenes				300 mL	
Cyanuric chloride	184.4	149	0.4	31.4 g	-
DMF	73.1	427	1.0	35 mL	-

Safety Precautions:

1. Chloroacetamide is suspected of reproductive toxicity and teratogenicity.
2. Fluoroacetamide is a known metabolic poison.
3. Fluoroacetonitrile is potentially toxic and could potentially hydrolyze to fluoroacetic acid, another poison.

Procedure:

1. Into a 250 mL three-neck round bottom flask equipped with magnetic stirring bar, thermocouple was charged with anhydrous 2-chloroacetamide (40 g, 427 mmol, 1.0 eq), anhydrous potassium fluoride (29.8 g, 513 mmol, 1.2 eq), and xylenes (300 mL, 1.5M).
2. The reaction mixture was heated to 105 °C for 6 hours with low speed stirring. Excessive stirring will increase solid deposits on the reactor wall.
4. The reaction mixture turned brown, but the brown solid settled to the outside of flask. The reaction mixture was clear while at temperature. The reaction mixture was analyzed by ^{1}H NMR and found to have a conversion of greater than 99% after 6 hours. ^{1}H NMR ($CDCl_3$, 600 MHZ) δ 6.27 (br, 1H), 5.56 (br, 1H), 4.82 (d, *J* = 47.44 Hz, 2H).
5. Dimethylformamide (35 mL, 427 mmol) was added to the reaction mixture and then cooled to room temperature.

6. Cyanuric chloride (31.4 g, 171 mmol, 0.4eq) was added slowly. Calorimetry data indicated the dehydration released 38.1 kJ/mol of heat.
7. The reaction was stirred at room temperature for 30 minutes until complete consumption of the fluoroacetamide. (The reaction mixture was tested by ^{1}H NMR to find a conversion of greater than 99%: ^{1}H NMR ($CDCl_3$, 600 MHZ) δ 5.00 (d, *J* = 47 Hz, 2H).)
8. The reaction mixture was filtered to remove residual solids and fitted with a distillation apparatus.
9. Distillation 120 °C to collect at 79 - 81 °C afforded fluoroacetonitrile as a colorless liquid, (17.6 g, 70%). The purity of the isolated material was 98% (^{1}HNMR) with xylenes and DMF as the only observed impurity.(^{1}H NMR ($CDCl_3$, 600 MHZ) δ 5.00 (d, *J* = 47 Hz, 2H). ^{19}F NMR (*d*6-DMSO, 300 MHz) δ -77.00 (d, *J* = 47 Hz, 2H))

Notes:

1. Fluoroacetamide can co-distill with the solvent and/or sublime and will deposit on the sides of the reaction vessel. This is of no consequence to the halogen exchange but care should be taken to return all material to the reaction vessel prior to the dehydration.
2. Fluoroacetonitrile is relatively volatile and an efficient condenser should be used during distillation from the reaction mixture.

Preparation of 4-amino-5-fluoropyrimidin-2(1H)-one from fluoroacetonitrile:

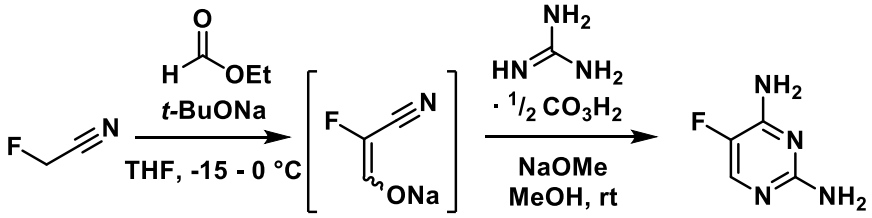


Table 2: Reagents and quantities for the synthesis of 4-amino-5-fluoropyrimidin-2(1H)-one.

Material	Mol. Wt. (g/mol)	mMole	Eq.	Amount	Density
Fluoroacetonitrile	59.1	160.7	1.0	9.5 g	
Ethyl formate	74.1	401.8	2.5	32.3 mL	
t-BuONa	96.1	241.1	1.5	23.2 g	
THF				80 mL	
Guanidine carbonate	90.1	225	1.4	20.2 g	

NaOMe	54.1	241.1	1.5	13.3 g	
Ethyl acetate	88.11			50ml	
Activated carbon	12			0.500 g	
Celite	60.08			3 gm	
MeOH	32.0			40 mL	

Safety Precautions:

1. All prior safety precautions are to be recognized.

Procedure:

1. A 500 mL 4-necked round bottom flask was fitted with an overhead stirrer, addition funnel and internal temperature probe.
2. The flask was charged with fluoroacetonitrile (9.5 g, 160.7 mmol, 1.0 eq), ethyl formate (32.3 mL, 401.8 mmol, 2.5 eq) and THF (40 mL).
3. The reaction mixture was cooled to an internal temperature of -15 °C using an external ice bath.
4. A solution of sodium *tert*-butoxide (23.2 g, 241.1 mmol, 1.5 eq) was prepared in THF (40 mL). **WARNING: The solvation of sodium *tert*-butoxide can be slightly exothermic, the flask was notably warmer.**[1]
5. The solution of sodium *tert*-butoxide in THF was added dropwise to the reaction mixture over the course of 15 minutes. There was no observed exothermic reaction upon addition of the base. The reaction mixture was stirred at 300 RPM at 0 °C for 6 hours. The observed mixture was a light brown suspension.
6. After complete consumption of the starting material as indicated by ^{1}HNMR. The reaction mixture was concentrated to one third volume. The reaction stirring was maintained until transfer to the next reactor.
7. A second 500 mL 4-necked round bottom flask was fitted with an overhead stirrer, addition funnel and internal temperature probe.
8. The flask was charged with methanol (40 mL) and with stirring NaOMe (13.3 g, 257 mmol, 1.6 eq) was added in one portion.
9. Stirring at 250 RPM, guanidine carbonate (20.2 g, 225 mmol, 1.4 eq) was added in several portions.
10. The reaction mixture was stirred at 250 RPM for 15 minutes until all the guanidine carbonate was dissolved.
11. With stirring, the previously completed reaction from step 6 was transferred rapidly to the guanidine solution prepared in step 7. There was no observed exotherm for this reaction.
12. The reaction was stirred at 22 °C for 24 hours until complete consumption of the starting materials as indicated by ^{1}HNMR analysis.
13. The reaction mixture was concentrated *in vacuo*.

14. The residue was dissolved in ethyl acetate, stirred and the solids filtered off. The organic phase was decolorized with activated charcoal and filtered through celite. The solvent was removed *in vacuo* to afford a light yellow or cream colored solid, (17.7 g, 86%).

Notes:

1. Small quantities of sodium formate can be present in the solid (5 - 15%). This impurity is not detrimental to the next step.
2. In the presence of NaHMDS, there was no observed sodium formate impurity. It is known that commercially available sodium and potassium *tert*-butoxide contain significant quantities of sodium and potassium hydroxide impurities.
3. In addition to impure *t*-BuONa, ethyl formate can contain notable quantities of formic acid which could add to the sodium formate content.
4. Any color impurity should have no ill effect on the following procedure. This presents a potential for telescoping the reactions. Impurities present should be extremely water soluble and be removed in the final step during crystallization.
5. This product is extremely water soluble, attempts to wash out the salts have required excessive quantities of organic solvent (EtOAc) to recover the product.

Preparation of 4-amino-5-fluoropyrimidin-2(1H)-one (5FC):

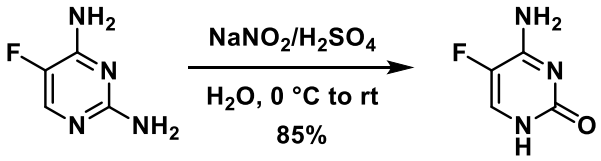


Table 3: Reagents and quantities for the synthesis of 4-amino-5-fluoropyrimidin-2(1H)-one.

Material	Mol. Wt. (g/mol)	mmol	Eq.	Amount	Density
5-fluoropyrimidine-2,4-diamine	128.1	45.27	1.0	5.8 g	-
$NaNO_2$	68.99	138	3	9.6 g	-
H_2SO_4	98.1	138	3	8.0 mL	-
H_2O	18.0	-	-	175 mL	-
NH_4OH	35	-	-	12.5 mL	-

Safety Precautions:

1. The addition of sodium nitrite to acidic reaction solution is extremely exothermic.
2. **Warning: Diazonium chemistry can be potentially explosive if the temperature increases rapidly.** Slow addition of the sodium nitrite solution prevents rapid temperature increase.

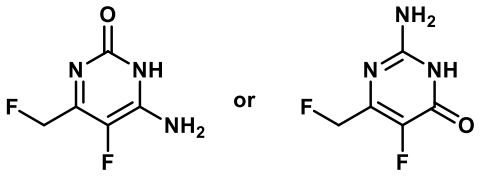
Procedure:

1. A 3-neck round bottom flask was fitted with an addition funnel and internal temperature probe.
2. The reaction flask was charged with 5-fluoropyrimidine-2,4-diamine and water (100 mL). The mixture was stirred until the solid was dissolved.
3. The reaction vessel was cooled to 0°C and cold sulfuric acid (8 mL, 138 mmol; diluted to 25 mL) was added dropwise to the diamine solution. A clear solution was observed. Significant heat was released, calorimetry data indicated 291 kJ/mol for the neutralization.
4. A solution of sodium nitrite (9.6 g, 138 mmol) was prepared in water (50 mL) and added to the addition funnel.
5. The reaction mixture was stirred at 500 RPM and heated to an internal temperature of 40°C.
6. The sodium nitrite solution was added dropwise to the reaction mixture with caution. Calorimetry data indicated that the addition of sodium nitrite released 210 kJ/mol of heat.
    a. Minimal evolution of NO_2 was observed, proper ventilation is recommended.
    b. Evolution of N_2 from the reaction mixture indicated the rapid consumption of the diazonium salt.
7. The reaction mixture was stirred for 1 hour at 40 °C until all starting material was consumed. Monitoring only consumption of starting material can be misleading by HPLC as the diazonium salt is undetected.
8. The acidic solution was decolorized with activated charcoal and filtered to yield a colorless solution.
9. The pH is adjusted to and maintained at 8.4 using commercial ammonium hydroxide (28-33% by wt) and the product crystallizes upon cooling at 10°C.
10. The reaction mixture is filtered to collect the desired product. The filtrate is washed with several small portions of ice-cold water to remove residual salts. The product is collected as an off white solid, (4.9 g, 85% yield; 95.5 wt%).

    HPLC Purity (A%) 99.1; Wt% assay—95.5%-KF = 1.1%. The unaccounted mass is expected to be inorganic salts.

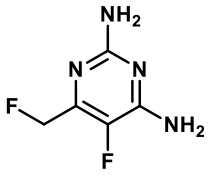
    The major impurity (0.9 Area %) is methanol soluble and can be removed with a small erosion in yield. The impurity is tentatively identified as one of the

regioisomers of compound **18** [^{1}H NMR ($DMSO_{d6}$, 600 MHZ) δ 10.72 (br, 1H), 7.54 (br, 2H), 5.21 (dd, *J* = 46.9, 1.7 Hz, 2H).]



Impurity 18

This impurity is believed to arise from dimerization of fluoroacetonitrile in the previous step giving rise to compound **19**. Slow addition of sodium *tert*-butoxide in the previous step minimizes this dimerization resulting in much lower levels of **18** in the 5-fluorocytosine product.



Compound 19

Notes:

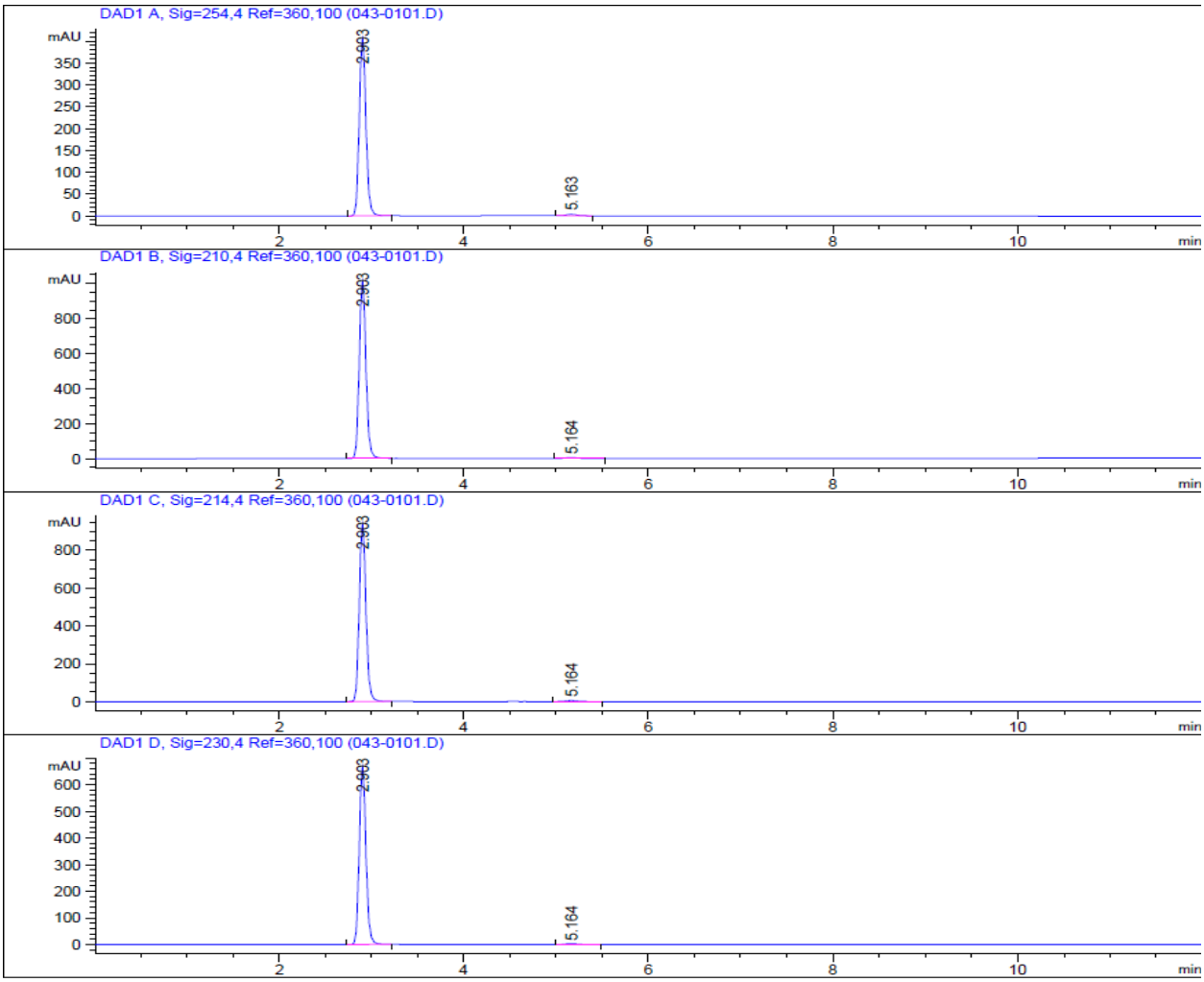
1. The product is extremely water soluble, care should be taken to avoid dissolving significant quantities while recovering the product from the reaction mixture.
2. Significant amounts of diazonium salts are immediately hydrolyzed, although mild heating (40°C) is required to completely hydrolyze the diazonium salt before isolation.
3. Decolorization of the mother liquor aids in crystallization of 5-FC. Colored impurities drastically slow the crystallization process.

Analytical Methods:

Reactions were monitored by crude aliquots using ^{1}HNMR analysis in an appropriate solvent. Chemical shifts of the compounds are described above. Analytical methods are being currently in development for low boiling and extremely polar compounds using GCMS and HPLC or LCMS.

HPLC Method:

The final product purity was determined with an HPLC. The chromatograms were acquired on an Agilent 1260 Infinity system using an Atlantis T3 column (5 µm, 4.6 mm x 150 mm). Isocratic elution with 1% methanol in pH = 7.6 phosphate buffered water at 1.0 mL/min at 30 °C resulted in a retention time of 2.8 minutes of 5-fluorocytosine. The HPLC below is for 5-FC from BPD1072 synthesized using the above route. 5-FC elutes at 2.9 minutes and an 0.9% (by area at 210 nm) impurity is observed at 5.2 minutes.



Assay against a commercial sample gave a weight % of 95.5% and Karl Fischer titration indicated 1.1% water content. This leaves 2.4% unaccounted mass, which is thought to be salts remaining in the isolated 5-FC. Experiments have shown that washing with water reduces the salt content and trituration with methanol removes the impurity observed in the HPLC. These results demonstrate that the quality of the isolated 5-FC can be improved with minimal yield losses.

Economic Analysis:

In this report the economic analysis of new processes to manufacture of 5-Fluorocytosine (5-FC) is restricted to chemical input costs. Other manufacturing and operating costs can be highly site-dependent, and the intent here is to compare approaches rather than predict final prices. An estimated economic analysis for the new M4ALL process for 5-FC is provided below in Table 4. The raw material costs shown (below) are based on chemical Marketing Reporter (ICIS), India import/export data, Datamyne, and from quotes from various vendors. Several routes were considered, and techno economic analyses were performed for each. The cost of raw materials to manufacture 5-FC is in the range of $ 24 and 35/kg with and without solvent recycle, respectively. For cost calculation 75% recycle of solvent is considered. The yield of the last step was adjusted for the 95.5% weight assay.

Table 4. 5-Fluorocytosine replacing P_2O_5 with Cyanuric Chloride

Fluorocytosine Route using Cyanuric Chloride												PMI w/o water	
Raw materials	M.Wt.	Amounts(g)	Moles	equivalent	density	CAS #	RMCost-	RM cost	Rmcost		kg RM /		kg RM /
Step -1							$/Kg	$/batch	/Kg Produ	kg RM	kg prod	kg RM	kg prod
Chloroacetamide	93.5	93.5	1	1.0		79-07-2	3.50	327.25		93.50		93.50	
Potassium Flouride	58.1	69.72	1.2	1.2	2.48	7789-23-3	1.59	110.85		69.72		69.72	
Dimethyformamide(DMF)	73.09	69.00	1	1	0.944	106-42-3	0.95	65.55		69.00		69.00	
Xylenes	106.16	140.88		-	0.861	106-42-3	0.72	101.43		140.88		140.88	
Cyanuric Chloride	184.4	73.76	0.4	0.4	1.32	108-77-0	1.22	89.99		73.76		73.76	
Product: Fluoroacetonitrile	59.04											0.00	
70%	59.04	41.328						695.07	16.82	446.86	10.81	446.86	10.81
Step 2 -													
Fluoroacetonitrile	59.04	59.04	1	1.0	1.06	503-20-8	16.82	992.96		638.37		638.37	
Ethylformate	74.08	185.20	2.5	2.5	0.917	109-94-4	1.20	222.24		185.20		185.20	
Sodium tert-butoxide	96.1	144.15	1.5	1.5	0.910	865-48-5	1.00	144.15		144.15		144.15	
THF	72.1	103.91		-	0.88	109-99-9	1.30	135.08		103.91		103.91	
Guanidine Carbonate	90.1	126.14	1.4	1.4	1,354	593-85-1	3.50	441.49		126.14		126.14	
NaOMe	54.03	105.36	1.5	1.5	1.3	124-41-4	0.45	47.41		105.36		105.36	
MeOH	32.04	46.64		-	0.79	67-56-1	0.40	18.66		46.64		46.64	
Activated carbon	12	2.95					1.20	3.54		2.95		2.95	
Celiet (filter aid)	60.08	11.81					0.20	2.36		11.81		11.81	
Ethylacetate	88.11	26.63		-	0.902	141-78-6	1.47	39.14		26.63		26.63	
Product: 2,4-Diamino-5-fluoropyrimidine	128.05												
86%	128.05	110.123						2047.04	18.59	1391.16	12.63	1391.16	12.63
Step -3													
2,4-Diamino-5-fluoropyrimidine	128.05	128.05	1	1.0	unknown		18.59	2380.28		1617.62		1617.62	
Sodium nitrite	68.99	206.97	3	3	2.17	7632-00-0	0.43	89.00		206.97		206.97	
conc. Sulfuric acid	98.08	294.24	3	3	1.84	7664-93-9	0.10	29.42		294.24		294.24	
H2O	18	638.33		-	0.997	7732-18-5	0.00	0.00		638.33			
Ammonium hydroxide (~28%)	35.05	157.725	5	5	0.9	144-55-8	0.10	15.77		157.73		157.73	
Product: 5-Fluorocytosine	129.09												
81%	129.09	104.782353						2514.47	24.00	2914.89	27.82	2276.56	21.73
					With Recycle Solvent				$Kg		PMI		PMI
					W/O Recycle				35.24		with H2O		W/O H2O
solvent recycle	75%												
			Over all Yi	48.9%									

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