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Development of a Leuckart–Wallach Reaction in Flow for the Synthesis of Abemaciclib

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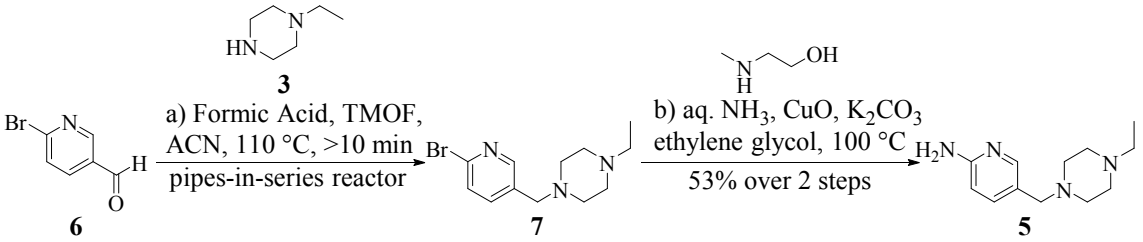


KEYWORDS: abemaciclib, reductive amination, Leuckart-Wallach, Ullmann coupling, CDK 4/6 inhibitor

ABSTRACT. The development of a route for a key building block in the synthesis of abemaciclib is described. The route proceeds through a Leuckart–Wallach reductive amination in flow followed by an Ullmann amination with aqueous ammonia. Key to the Leuckart–Wallach reductive amination was the addition of trimethyl orthoformate for water removal, running the reaction continuously in a pipes-in-series reactor for rapid heat-up, and building a kinetic model to understand time and temperature parameters for the feed tank storage. The product of the Leuckart–Wallach reductive amination is forward processed in batch and telescoped with the Ullmann amination and subsequent work-up. The development resulted in a robust process that has successfully been run on production scale.

Abemaciclib is a selective ATP-competitive inhibitor of cyclin dependent kinases (CDK) 4 and 6 that inhibits phosphorylation of the Rb tumor suppressor protein and thereby induces G1 cell cycle arrest. Abemaciclib is being studied for the treatment of multiple types of cancer and recently achieved positive Phase III results for metastatic breast cancer.[1]

In looking at the molecule of abemaciclib, two disconnections can be envisioned to simplify the synthesis (Figure 1). The first approach would be a reductive amination between ethyl piperazine (**3**) and aldehyde **2** as previously described.[2] A second, more convergent approach breaks the molecule into previously described pyrimidine chloride **4**[2] and pyridyl amine **5** through a Buchwald–Hartwig coupling.[3] A further disconnection, and the focus of this paper, is

to break amine **5** into ethyl piperazine (**3**) and 6-bromonicotinaldehyde (**6**) through a reductive amination followed by an Ullmann amination.[4]

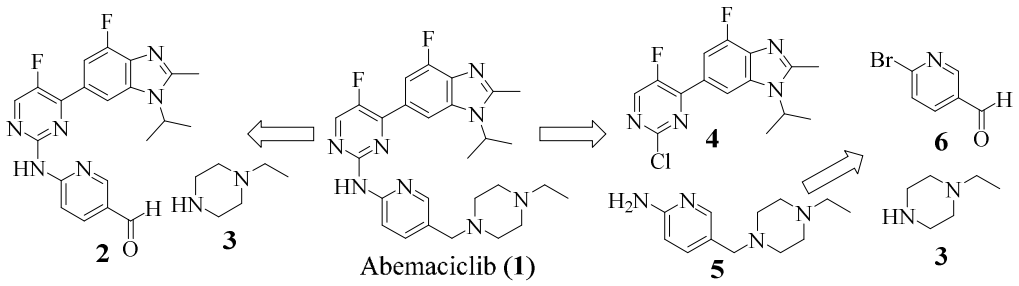
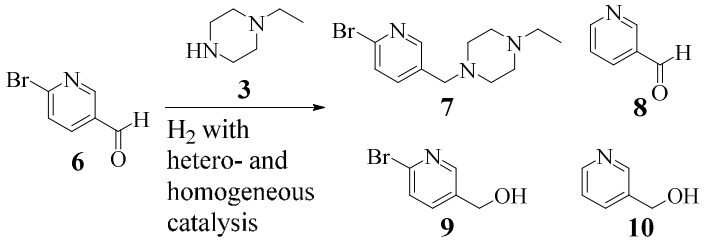


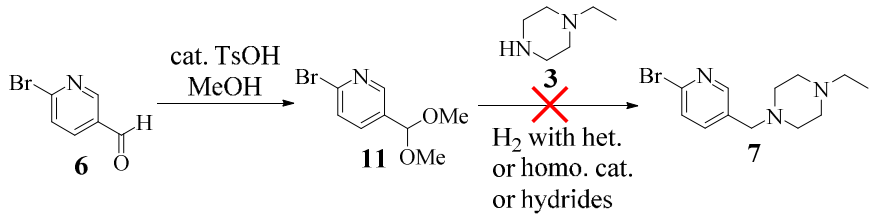
Figure 1. Two retrosyntheses for abemaciclib (**1**).

The reductive amination to form **7** from amine **3** and aldehyde **6** was studied extensively to find conditions to maximize conversion while minimizing impurities.[5] A process using sodium triacetoxyborohydride was initially developed,[6] and produced multiple kg's of product in respectable purity. Although high yielding, the corresponding alcohol (**9**) formed in measurable amounts (>1%) and could not be rejected through subsequent crystallizations and downstream chemistry. More atom economical approaches were investigated to minimize this impurity, especially hydrogenations with both heterogeneous and homogeneous catalysts, but they led to large amounts of desbromo-aldehyde **8**, bromo-alcohol **9** and desbromo-alcohol **10**.



Scheme 1. By products of the reductive amination.

Another option that was explored was the synthesis of the corresponding dimethyl acetal **11**. Although the acetal formed cleanly (cat. TsOH, MeOH), the subsequent reductive amination was never successful as the acetal proved quite stable (Scheme 2).[7]

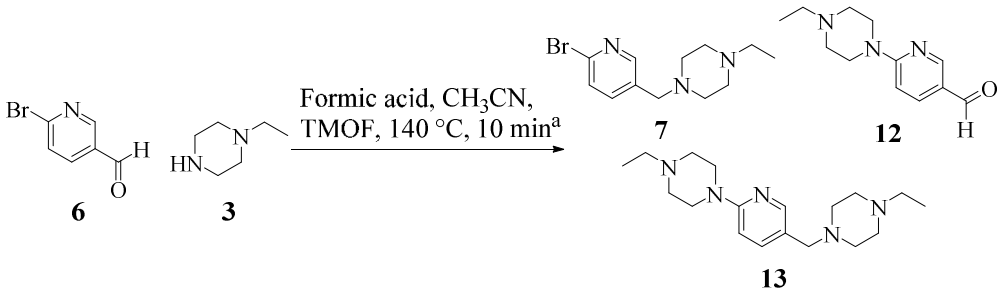


Scheme 2. Formation of and attempted reductive amination with dimethyl acetal **11**.

Our final efforts focused on Leuckart–Wallach conditions[8] with formic acid as the reducing agent and no catalyst under high temperatures. These conditions were expected to minimize both debromination and aldehyde reduction while maximizing conversion. As expected, des-bromo and alcohol products were not observed, unfortunately, two new impurities appeared, a S_NAr product **12** and the product of **12** undergoing reductive amination with ethyl piperazine (**13**). In addition to the new impurities, nearly 18% of the starting aldehyde remained due to the consumption of ethyl piperazine through formylation with formic acid (Table 1, entry 1). Varying equivalents of ethyl piperazine and formic acid had varying levels of success, but never provided full conversion and impurities **12** and **13** remained at significant levels (entries 2–6).[9] It was hypothesized that since the formation of the imine is an equilibrium driven process, the equivalent of water produced slowed the desired reaction with the formylation of ethyl piperazine dominating (Scheme 3). Various water scavengers such as molecular sieves were screened to prevent the reaction from stalling, but no positive impact was found until trimethyl orthoformate was used (Table 1, entries 7–9).[10] Not only was full conversion reached, but since

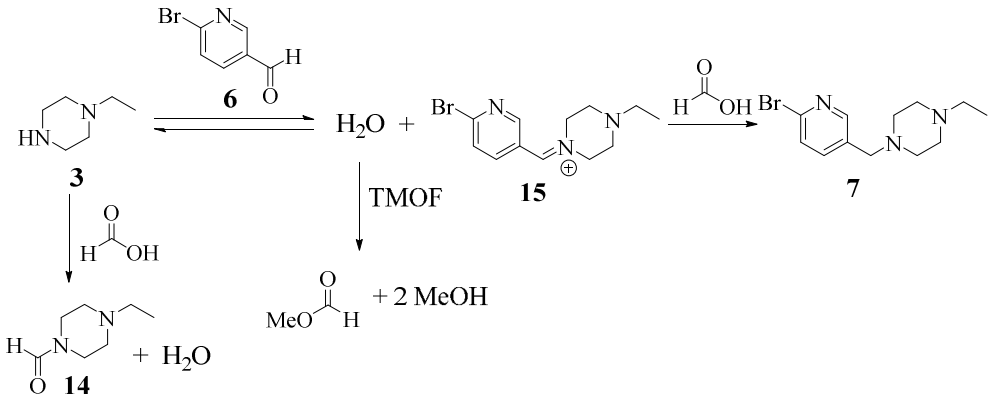
removing the water accelerated the desired reaction, there was less S_NAr related by-products observed (Table 1, entry 8).

Table 1. Leuckart–Wallach screening conditions.



Entry	**3** (equiv.)	Formic Acid (equiv.)	TMOF (equiv.)	**6**	**7**	**12**	**13**
1	1.5	5.0	0.0	17.8	79.8	2.2	0.2
2	2.0	5.0	0.0	4.0	87.8	5.2	3.0
3	2.5	5.0	0.0	0.7	90.6	5.4	3.3
4	2.0	3.0	0.0	0.0	79.0	2.3	18.7
5	2.0	4.0	0.0	0.1	87.1	4.6	8.2
6	2.0	10.0	0.0	53.0	45.5	1.5	0.0
7[b]	2.0	5.0	1.0	0.0	97.7	0.7	1.6
8[b]	2.0	5.0	2.0	0.0	99.5	0.1	0.4
9[b]	2.0	5.0	5.0	5.3	94.4	0.3	0.0

[a]Reactions run on 1 mmol scale in flow through a pipes-in-series reactor,
[b]Reactions carried out at 150 °C.



Scheme 3. Mechanistic explanation for the benefits of trimethyl orthoformate.

While successful on small scale, the reaction was not suitable for larger scale. The longer heating times resulted in more consumption of ethyl piperazine (**3**) to form formamide **14**, and therefore incomplete reaction of aldehyde **6**. It is reasoned that the formation of **14** has a lower activation energy than the desired formation of **7**. Therefore at intermediate temperatures it has a higher relative rate. As a result focus was shifted to exploring the reaction in flow through a heated pipes-in-series reactor to minimize heat-up time and maximize conversion and yield.[11]

The use of pipes-in-series reactors with near instantaneous heat-up times worked well to maximize conversion. A consequence of this reaction mode was that the solution needed to be stored before feeding through the pipes-in-series reactor, and during this storage the formylation occurs (albeit slowly).[12] In order to scale up, the relationship between formylation and storage time and temperature needed to be understood, so a kinetic model was built. Two nominal reactions at 50 and 70 °C were monitored by React NMR[13] and the data was fit using Dynochem.[14] This resulted in parameters of a kinetic constant (k) of 1.40E-06 L/mol•s and an activation energy (Ea) of 85.06 kJ (Figure 2).

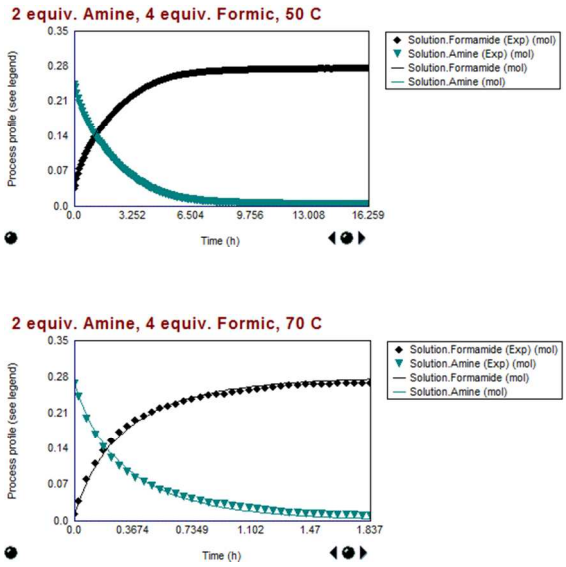


Figure 2. Fitting the formylation using Dynochem for the equation [**3**] + Formic Acid → [**14**]. Black diamonds and green triangles represent experimental data, black and green lines represent the fitted results.

Experimentally, it was known that 1.2 equivalents of ethyl piperazine were needed to be present at the time the reaction started to make acceptable material.[15] Combining the kinetic model with our understanding, created a design space seen in Figure 3. With this design space, we set a holding time limit of 96 h at 0 °C to ensure successful production of material.[16]

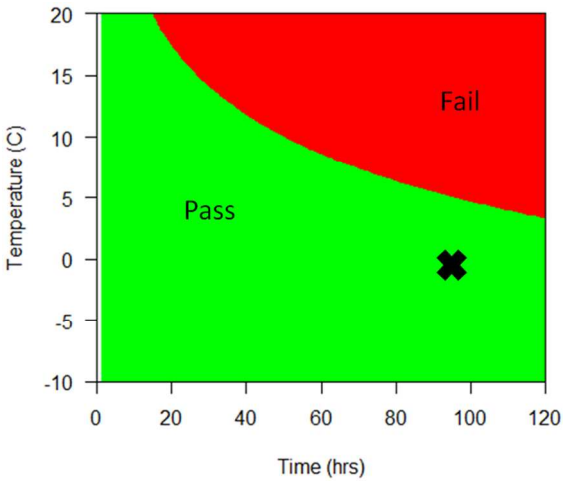
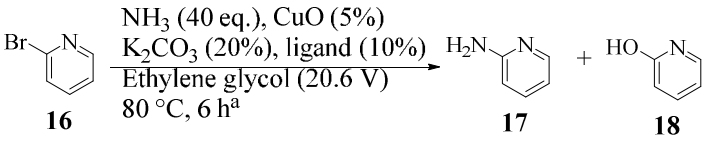


Figure 3. Reaction holding time/temperature design space. The black "X" marks the targetted maximum temperature (0 °C) and time (96 h) for holding before everything is fed through the reactor.

The product of the Leuckart–Wallach reductive amination was a low-melting solid so we planned to use the product without isolation in the next step. To this end, the reductive amination product was worked up with aqueous washes (aq. NaOH followed by aq. $NaHCO_3$ washes[17]). The aqueous washes were followed by solvent removal and dissolution in a minimal amount of ethylene glycol for use in the next step.

For the Ullmann amination, the original process used condensed liquid ammonia. Due to equipment limitations and safety concerns it was desired to use aqueous ammonia. The starting ligand screen used 40 equiv. of aqueous ammonia, 5 mol% of CuO, 20 mol% K_2CO_3, and 20.6 V ethylene glycol at 80 °C for 6 hours. Various ligands were used at 10 mol% for the amination of 2-bromopyridine in this model system (**16**, Table 2).[18] In all cases, the reactions were clean, however with entries 1-9, conversion was less than 30%. Fortunately the use of 2-(methylamino)ethanol at elevated temperature of 100 °C provided conversion of 99.0%, with the main impurity being the corresponding hydroxypyridine (**18**).



16 **17** **18**

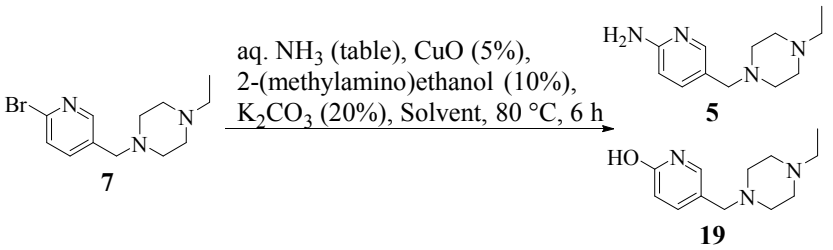
Entry	ligand	Conversion[b]	%**18**
1	none	<1.0	0.0
2	tetramethylethylenediamine	16.7	0.0
3	dimethylethylenediamine	23.9	0.0
4	2-(methylamino)ethanol	29.8	0.0
5	2-aminoethanol	18.1	0.0
6	piperazine	8.2	0.0
7	diethanolamine	20.7	1.6
8	2-(ethylamino)ethanol	22.9	1.5
9	2-(2-aminoethylamino)ethanol	7.1	0.8
10[c]	2-(methylamino)ethanol	99.0	4.7

[a]Reactions run on 1 mmol scale, [b] Conversion based on remaining SM [c]Reaction at 100 °C.

Table 2. Ligand screening for the Ullmann amination.

With appropriate conditions for the model system, some screening was done with the desired substrate **7** (Table 3). The focus was on reducing the amount of ethylene glycol to make the subsequent product isolation more straightforward. Replacing ethylene glycol with simple alcohols (entries 9–12) resulted in poor conversion. Fortunately, the equivalents of ethylene glycol could be lowered with minimal impact to conversion, with as low as 0.15 equivalents

being acceptable. Although conversion was 100%, the hydroxy-impurity (**19**) could not be avoided. Fortunately it rejected readily in the final isolation, so we ultimately accepted the yield loss.



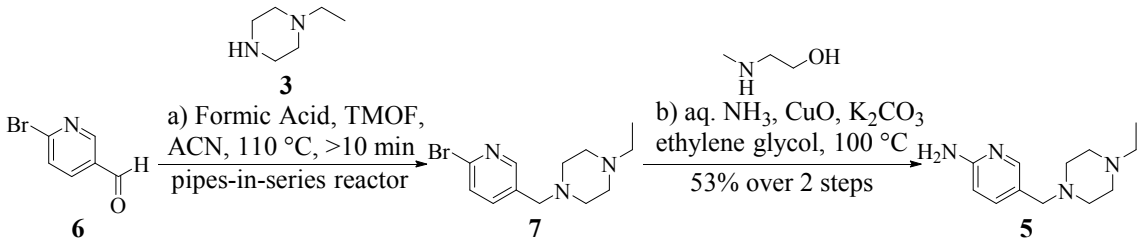
Entry	NH_3 (eq.)	Solvent (V)	Conversion[a]	%**19**
1	40	EG (9.2)	100.0	10.7
2	20	EG (9.2)	100.0	11.1
3	20	EG (2.3)	100.0	9.1
4	10	EG (2.3)	99.7	15.4
5	20	EG (1.2)	100.0	9.9
6	20	EG (0.6)	99.1	10.0
7	20	EG (0.3)	95.3	7.9
8	20	EG (0.15)	98.3	8.6
9	20	MeOH (4.6)	52.8	17.5
10	20	EtOH (4.6)	67.6	11.1
11	20	*i*PrOH (4.6)	57.0	8.0
12	20	*n*BuOH (4.6)	24.2	7.4

[a]Conversion based on remaining SM.

Table 3. Solvent and aq. NH_3 screen.

The isolation of amine **5** from the ethylene glycol/aqueous ammonia solution proved difficult due to the hydrophilicity of **5**. There was also a need to develop an efficient method for copper removal from the product stream. By salting out the aqueous layer with 3.0 equivalents of K_2CO_3 and extracting the product into *n*-butanol, the copper was well rejected to the aqueous phase with nearly quantitative product recovery in the organic phase. A solvent exchange into acetonitrile was then performed for product crystallization, however the product had a high amount of inorganic material. Dissolving the wetcake up in warm acetonitrile allowed the inorganic material to be filtered away. Subsequent cooling of the filtrate allowed crystallization

of the desired product in high purity and free of inorganic impurities. The second crystallization was also effective at reducing ethylene glycol levels to below 100ppm.



Scheme 4. Overall process for the conversion of aldehyde **6** to amine **5**.

In summary, a robust process was developed to make amine **5** through two telescoped steps. The first step was a Leuckart–Wallach reductive amination in flow and the second was an Ullmann coupling with aqueous ammonia. The process has been run at production scale, making high quality material that could be forward process to abemaciclib.

ASSOCIATED CONTENT

Supporting information: Manufacturing procedure is contained in the supporting information.

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[15] 1.2 equivalents of ethyl piperazine (**3**) were minimally required to achieve full conversion. We chose this as a conservative target, since it is a flow reaction, material produced when less than 1.2 equivalents were present, would make acceptable material when averaged out with earlier parts of the feed solution

[16] Reagent addition leads to solid formation at lower temperatures, so they need to be charged at no more than (NMT) 15 °C. To be conservative we calculated the amount of ethyl piperazine remaining after 20 hours at 15 °C then used this amount as the input for constructing the design space in Figure 3. So in summary the total holding parameters were addition of reagents at NMT 15 °C over NMT 20 hours and the remaining holding at NMT 0 °C for NMT 96 h to conservatively ensure full conversion.

[17] The aqueous NaOH wash was to quench and remove the formic acid. The aqueous $NaHCO_3$ washes worked well to remove excess formylated ethyl piperazine (**14**).

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