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Increasing global access to the high-volume HIV drug nevirapine through process intensification†

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Access to affordable medications continues to be one of the most pressing issues for the treatment of disease in developing countries. For many drugs, synthesis of the active pharmaceutical ingredient (API) represents the most financially important and technically demanding element of pharmaceutical operations. Furthermore, the environmental impact of API processing has been well documented and is an area of continuing interest in green chemical operations. To improve drug access and affordability, we have developed a series of core principles that can be applied to a specific API, yielding dramatic improvements in chemical efficiency. We applied these principles to nevirapine, the first non-nucleoside reverse transcriptase inhibitor used in the treatment of HIV. The resulting ultra-efficient (91% isolated yield) and highly-consolidated (4 unit operations) route has been successfully developed and implemented through partnerships with philanthropic entities, increasing access to this essential medication. We anticipate an even broader global health impact when applying this model to other active ingredients.

Introduction

Synthetic processes for active pharmaceutical ingredients (APIs) often evolve directly from medicinal chemistry routes that are designed to access a variety of structural analogs, with limited regard for commercial consideration.[1] In many cases, early routes can help define the final process for a drug in order to expedite commercial implementation. However, legacy API processes are also frequently carried forward into the product lifecycle post-patent expiration, impacting the cost structure of many generic and global health drugs. In both cases, the small molecule API cost represents 65 to 75% of the total drug product cost.[1c,2] As a result, these sub-optimal synthetic routes can have a major impact on affordability and subsequent access to medicines. In the case of the global healthcare supply, the resulting high cost often necessitates that API purchases be underwritten by philanthropic organizations in order to increase patient access.

We and others have demonstrated that new approaches using state-of-the-art chemical methods and novel reactor platforms can yield significant improvements to API production costs and efficiency.[3] Based on these observations, we have established a set of core principles for API process development, which are derived from fundamental elements of process intensification that are commonly known but often neglected. These principles include (a) implementation of innovative chemical methodologies and new manufacturing platforms, (b) consolidation of high-yielding reactions into a minimal number of unit operations with common solvents and limited intermediate isolations, and (c) vertical integration of advanced starting materials prepared from commodity chemicals. Assessment of cost drivers guides the initial development plan for a target molecule. Sub-optimal portions of the existing route are identified and alternative reaction conditions are developed that are both high yielding and chemically compatible with the overall synthetic sequence. This

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approach allows for process consolidation to reduce intermediate isolations.

Comparison of Process Development Principles

Typical Commercial API Process Development

Medicinal Chemist – Maximize Discovery Rate

1. Use advanced commercial intermediates
2. Use reactions that maximize expediency
3. Maximize modularity to create target family

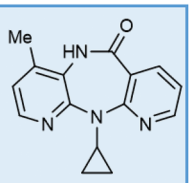
Development and Process Chemist – Maximize Scale-up Rate

1. Maximize safety
2. Minimize time to increased scale
3. Leverage insights from medicinal chemist route

Process Intensification to Increase Global Access

Core Principles to Minimize Cost

1. Implement innovative chemical methods
2. Leverage new manufacturing platforms
3. Vertically integrate intermediates
4. Consolidate unit operations
5. Minimize solvent exchanges
6. Use techno-economics to guide process



Nevirapine (**1**)

Incorporation of commodity chemicals often has the greatest impact when applied to the vertical integration of registered starting materials that tend to be complex and highly functionalized, and thus represent a major expense. The cost driver analysis during our initial evaluation highlights those API precursors of greatest impact, and significant effort is then placed on the use of commodity chemicals to prepare these compounds using our process principles. Cost drivers are further intensified as the potential increase in process complexity resulting from additional transformations is offset by telescoping reaction steps.

For our initial application of these core principles we selected nevirapine (**1**), a widely-prescribed treatment for HIV-1, as our target. Nevirapine is the first non-nucleoside reverse transcriptase inhibitor approved for the treatment of HIV-infected patients and is a high volume component of HIV combination drug therapies.[4] Two commercial processes have been reported by Boehringer Ingelheim (B.I.), both of which construct the central diazapine ring system from two multifunctional pyridines, 2-chloro-3-amino-4-picoline (CAPIC, **2**) and a nicotinic acid derivative, either **3** or **4** (Fig. 1), as the registered starting materials.[5] These processes provide moderate yields, but require multiple synthetic steps, solvent exchanges, and intermediate isolations that add to process complexity and waste generation. In order to iteratively score and identify process improvement opportunities, routes are not only evaluated by yield and unit operations, but also by chemical efficiency using Process Mass Intensity (PMI, total mass of all materials used in the process to produce 1 kg of product), a metric that has been widely accepted by the pharmaceutical industry.[6] With emphasis placed on value and efficiency rather than quantifying waste, PMI has been used to motivate and evaluate process improvements of various pharmaceuticals and pharmaceutically-relevant building blocks.[7] In our case, PMI is an especially appropriate metric, as it emphasizes the value generated by telescoping reactions in a common solvent system.

We now report a scalable, streamlined process route to nevirapine that results directly from the application of our core principles. This improved route, which uses CAPIC (**2**) and methyl 2-(cyclopropylamino)nicotinate (MeCAN, **5**) as starting materials for the registered portion of the synthesis, is marked by use of high atom-economy transformations and a high-throughput design that minimizes waste generation and maximizes product yield (Fig. 2). Furthermore, the ability to achieve high yields in each individual reaction allowed us to directly recycle a major portion of the solvent distillate, which was not possible with the previous commercial routes due to by-product impurities resulting from low-yielding reaction steps. Moreover, this new process has been applied in both batch and continuous synthesis regimes. Overall, the impact of these process improvements on yield, unit operations, and waste generation are profound (Fig. 2). The most noteworthy improvement was observed in the product yield of 91%, compared to 1st and 2nd generation process yields of 59% and 63%, respectively. This parameter is particularly important because it directly impacts the other two metrics and represents a major underpinning of our core process intensification principles.

Results and discussion

Our route to nevirapine (Fig. 2) relies on a new strategy for construction of the 7-membered central lactam ring. By using **5** in place of the free carboxylate **4**, amide bond formation with **2** could be telescoped with the final S_NAr conversion to produce **1** in a streamlined, one-pot process. Accordingly, we additionally decreased the PMI associated with the preparation of **2** and **5** by starting from commodity raw materials.

Our efficient synthesis of MeCAN included process improvements for the preparation of **4** (Scheme 1a). Using only one equivalent of cyclopropylamine, we achieved 98% conversion by pressurizing the reaction vessel to 10 psi with nitrogen. Moreover, we identified conditions for the sequential one-pot amination and nitrile hydrolysis, furnishing **4** in higher yields (91% *vs.* 70% for the B.I. process).[5d] Esterification of **4** with thionyl chloride in methanol afforded **5** in 95% yield, resulting in an overall yield of 86%, a PMI of 12, and a total number of 8 unit operations from **8** to MeCAN (**5**).

Techno-economic projections indicated that CAPIC (**2**) comprises 64% of the production cost of the nevirapine API. We previously reported a novel approach to build **2** from the commodity-based raw materials acetone (**9**) and malononitrile (**10**).[3e,8] While our previously reported route was a significant advance, we found additional improvements including reduction of waste by maximizing reaction concentrations and optimizing relative reagent input (Scheme 1b). We iteratively re-evaluated cost drivers for new opportunities and found that dimethyl formamide-dimethyl acetal (DMF-DMA) became the most expensive reagent in our improved route, leading to the replacement of DMF-DMA with dimethyl formamide-dimethyl sulfate (**14**) as a surrogate formylating agent.[9] This air-stable

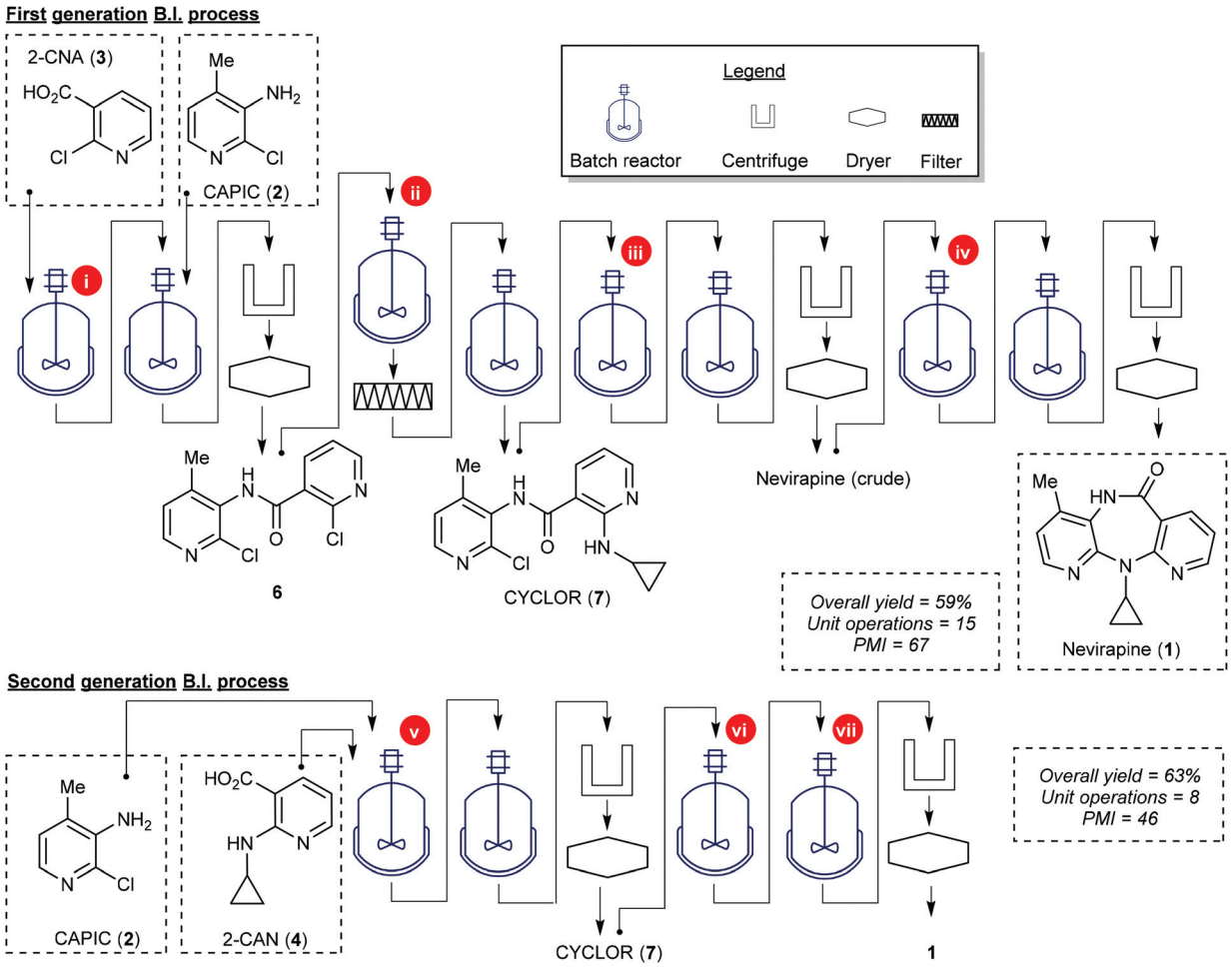


Fig. 1 Prior commercial nevirapine process routes. Conditions: i. $SOCl_2$, PhMe ii. cyclopropylamine (CPA), diglyme iii. NaH, diglyme iv. dimethyl formamide v. $SOCl_2$ vi. diglyme vii. NaH, diglyme. 2-CNA = 2-chloronicotinic acid, 2-CAN = 2-(cyclopropylamino)nicotinic acid, CYCLOR = *N*-(2-chloro-4-methylpyridin-3-yl)-2-(cyclopropylamino)nicotinamide.

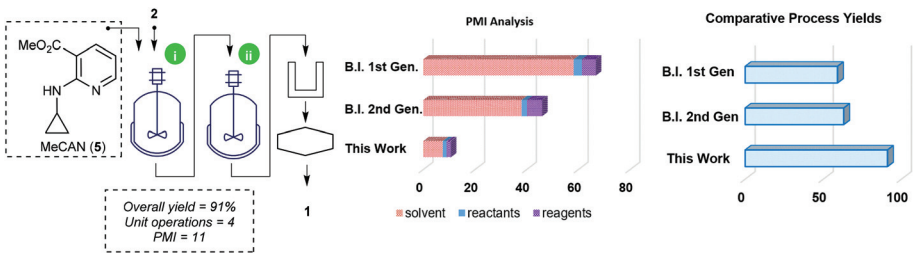
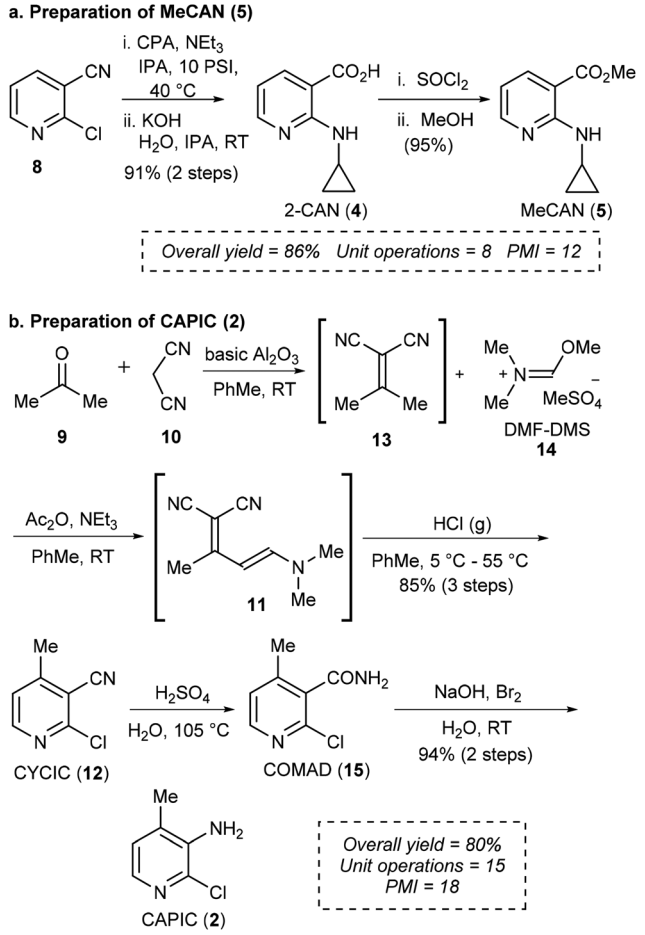


Fig. 2 Our optimized nevirapine process and comparative metrics. Conditions: i. NaH, diglyme 65 °C ii. NaH, diglyme 115 °C. MeCAN = methyl 2-(cyclopropylamino)nicotinate.

reagent was formed quantitatively from commodity chemicals and was introduced directly into our process with equivalent performance. With these improvements, we were able to increase the isolated yield of **12** to 85% over three telescoped steps, providing CAPIC (**2**) in an overall yield of 80% from acetone.

With optimized processes for the key nevirapine starting materials in hand, we applied our core principles to the preparation of the nevirapine API. While amide bond formation is one of the most important chemical transformations in drug synthesis, these reactions typically possess poor atom economy.[10] Recent reports of lithium hexamethyldisilazide (HMDS) facilitating amide bond formation between anilines and esters[11] inspired our efforts to form intermediate **7** directly from **2** and **5**. As an improvement over the B.I. processes, this strategy presented an opportunity to telescope the reaction

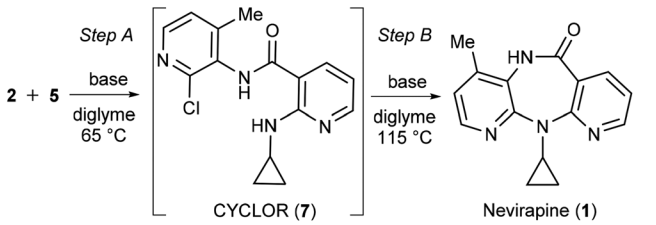


Scheme 1 Optimized routes towards **5** and **2**. CYCIC = 2-chloro-4-methylnicotinonitrile, COMAD = 2-chloro-4-methylnicotinamide, IPA = isopropyl alcohol, Ac_2O = acetic anhydride, DMF-DMS = dimethylformamide dimethylsulfate.

sequence, converting **7** to nevirapine without isolation. Indeed, sodium HMDS-mediated amide formation provided high conversions of **7** (Table 1, entry 1).

We then evaluated sodium hydride as a cost- and atom-economical alternative to achieve 95% conversion to **7** using 1.7 equivalents of sodium hydride (Table 1, entry 2). Moreover, upon treatment with additional base at an elevated temperature, **7** could be converted to **1** without isolation (Table 1, entry 3). After optimization (Table 1, entries 3–6), near-quantitative conversion to **1** was achieved, affording an isolated yield of 91% for the overall process. This streamlined synthesis not only improved the overall yield, but also cut the number of unit operations in half and reduced the PMI dramatically from 46 (2nd generation B.I. process) to 11 (our process, Fig. 2). Solvent losses to waste typically represent one of the largest contributors to high PMI values in API processes, and solvent recycling was prohibitive in both B.I. processes due to elevated impurity levels in the reaction mixtures. However, the yield improvements realized from the new process provided the additional benefit and opportunity to recover and recycle 80%

Table 1 Optimization of the batch process for **1**



Entry	**5** [equiv.]	Base	Base [equiv.] Step A	Base [equiv.] Step B	Conversion[a] to **7**	Conversion[a] to **1**
1	1.0	NaHMDS	1.7	—	95	—
2	1.05	NaH	1.7	—	95	—
3	1.05	NaH	2.0	1.0	94	70
4	1.0	NaH	2.0	2.0	99	97
5	1.05	NaH	1.8	1.8	99	97
6	1.05	NaH	1.8	1.7	99	97 (91[b])

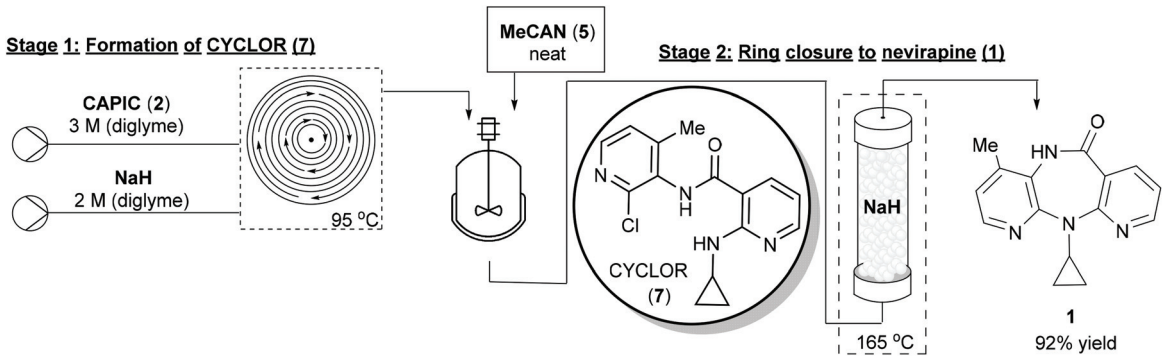
[a] Conversions determined by HPLC. [b] Yield (wt%) of isolated product.

of the diglyme solvent, which is reflected in our PMI. Nevirapine produced by this method exceeded the purity of prior processes.

Having established a highly-consolidated batch process for **1**, nevirapine became an ideal candidate for a continuous manufacturing platform. While API manufacturing relies predominantly on batch reactor technology, continuous manufacturing of APIs has recently seen a surge of interest. Continuous chemical operations not only provide exceptional control of critical reaction parameters and minimize process safety hazards[12] but also provide access to short-lived intermediates, minimize by-product and waste formation, and increase overall productivity.[6b,12b,c,13]

For the continuous preparation of nevirapine, we envisioned a system that would be capable of safely handling solid sodium hydride[14] as well as the off-gassing of hydrogen required to drive both reactions to completion. Thus, a continuous, thin-film reactor was used as sodium hydride (2 M suspension) and **2** (3 M solution) were delivered to the reactor simultaneously and the resulting salt was fed into a continuous stirred tank reactor containing **5**, affording conversion to **7** (Scheme 2). This intermediate was directed to a packed bed reactor of sodium hydride to affect the diazepine ring formation with high conversion as the packed bed system provided excellent stoichiometric leverage, maximizing the instantaneous solid-solution phase concentrations.[15]

For the purposes of scoring the efficiency and sustainability of the continuous process, our group has elected to adopt the measure of Volume-Time Output (VTO). Briefly, VTO measures throughput in the context of reactor space and is an excellent indicator of the intrinsic economy of a particular manufacturing platform. The overall continuous process provided excellent throughput with a volume-time output (VTO) of 7.01×10^{-3} m^3 h kg^{-1} and 92% isolated yield. For comparison, typical manufacturing processes strive to reach a VTO of <1.[1b]



Scheme 2 Continuous process for **1**.

Conclusions

Integrating principles derived from the basic tenets of process intensification, we have demonstrated a process development model that has been successfully applied to the preparation of nevirapine and its starting materials. We streamlined routes to both API starting materials by pinpointing conditions that minimize unit operations while incorporating commodity chemicals as raw materials into the consolidated process. In doing so, we were able to increase the isolated yield of nevirapine from 63% to 91% while reducing the PMI value for the process from 46 to 11. The details of this streamlined nevirapine batch process were transferred to the Clinton Health Access Initiative (CHAI) and rapidly adopted by their supply chain network. CHAI estimates that implementation of our optimized process will result in a minimum of 30% savings in nevirapine cost of goods.

Furthermore, we successfully transitioned our streamlined synthesis into a continuous process, demonstrating high conversions and throughput in a consolidated reactor space (7.01×10^{-3} m^3 h kg^{-1}). We anticipate that this process intensification model will serve as a template for the optimization of other drugs that support the global healthcare network, providing the greatest impact in areas where access to essential medications is limited.

Acknowledgements

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