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Highly Efficient Synthesis of HIV NNRTI Doravirine

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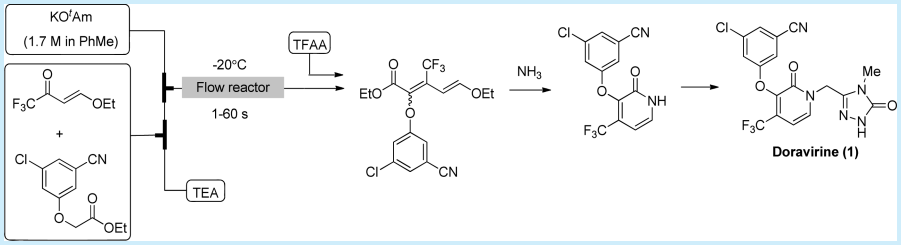
Supporting Information



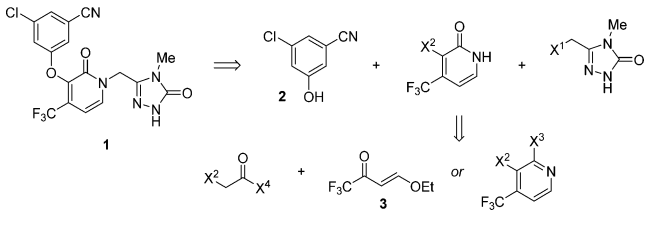
ABSTRACT: The development of an efficient and robust process for the production of HIV NNRTI doravirine is described. The synthesis features a continuous aldol reaction as part of a de novo synthesis of the key pyridone fragment. Conditions for the continuous flow aldol reaction were derived using microbatch snapshots of the flow process.

As of 2011, the World Health Organization estimated that 34 million individuals globally were living with Human Immunodeficiency Virus (HIV).[1] Since the mid-1990s, first line therapies for the treatment of HIV-positive patients employed a combination of medicines selected from at least two different mechanistic classes, including non-nucleoside reverse transcriptase inhibitors (NNRTIs), nucleos(t)ide reverse transcriptase inhibitors (NRTIs), integrase strand inhibitors (InSTIs), and protease inhibitors (PIs), known collectively as highly active anti-retroviral therapy (HAART).[2] This strategy decreases the patient's viral load, maintains the immune system, and prevents opportunistic infections which often lead to mortality for HIV-positive individuals. However, there remains a significant unmet medical need for new therapies which can improve lifespan, combat drug resistance, improve patient compliance, and decrease adverse effects. Doravirine (**1**) is a clinical candidate under development as a next-generation NNRTI with the potential to offer an improved balance of safety, tolerability, efficacy, and simplicity of administration over the current standard of care.[3]

The initial chemical synthesis of **1** was used to support the development program from preclinical toxicity studies into Phase IIB; however, the route lacked convergence in the endgame and relied on functional group manipulations.[4] A redesigned approach to doravirine was envisioned where both the triazolinone heterocycle and pyridone core were generated directly with the required functionality from readily available precursors. Successful execution of this retrosynthetic strategy was expected to result in a far more efficient and productive approach to the target structure (Scheme 1).

The 3,4-disubstituted 2-pyridone is a central structural feature of doravirine, and installation of this fragment via either the 2-halo- or 2-oxy-substituted pyridine is a well-documented strategy. However, the selective preparation of

Scheme 1. Retrosynthetic Design for Doravirine (1)



differentially substituted pyridines often requires lengthy synthetic sequences incongruent with the goals of an efficient process.[5] An inspiring report from Jiang and co-workers described the preparation of 4-(trifluoromethyl)-2(1*H*)-pyridinone by a Blaise reaction between vinylogous ester **3**[6] and chloroacetonitrile, followed by cyclization.[7]

Adapting this approach toward doravirine requires an extension of this strategy to include α-substituted organometallic precursors as a means of introducing the C3-aryloxy group on the pyridone. Having little success introducing α-substitution into the Blaise reaction, we turned toward ester enolates. In one of our early attempts, treatment of ester **4** with zinc powder and TMS-Cl delivered an organozinc reagent which upon reaction with **3** provided Reformatsky adduct **5** (Scheme 2). After amination, cyclization, and dehydration, the resulting 3-fluoro-4-(trifluoromethyl)pyridone **6** was converted to **1** through a series of steps including a protection−deprotection sequence to install the C3 phenol appendage.[8]

Despite the inefficiencies associated with converting pyridone **6** to **1**, the Reformatsky disconnection was a powerfully simplifying transformation which enabled the use

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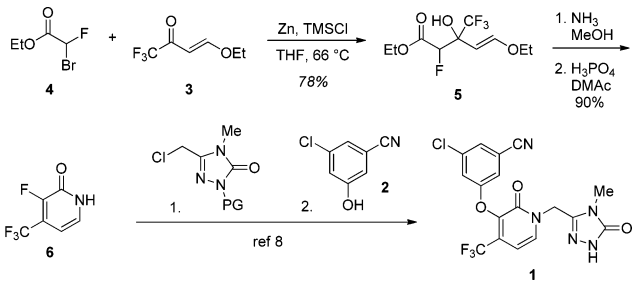
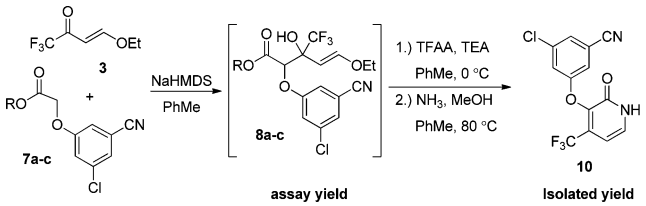
Scheme 2. 3-Fluoropyridone S_NAr Route to Doravirine



of vinylogous ester **3** as a trifluoromethyl-containing raw material. Exploiting this bond construction but redesigning the nucleophile to incorporate the aryloxy group was identified as a means to further improve access to doravirine. To investigate this approach, the aldol reaction of esters **7a–c**[9] with **3** in the presence of sodium hexamethyldisilazide was examined (Scheme 3).[10]

Scheme 3. Aldol Reaction Optimization in Batch



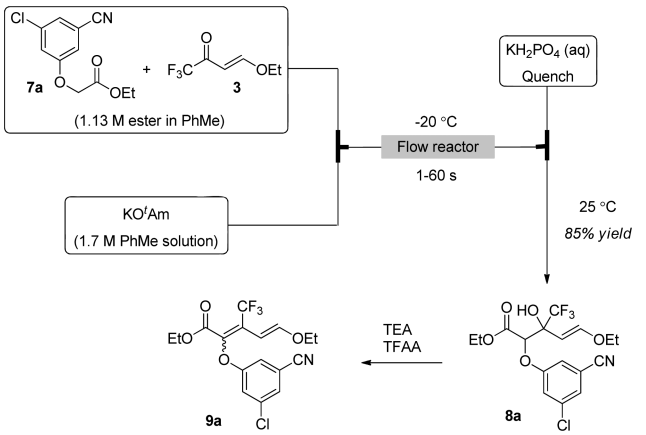
		assay yield	isolated yield
R = Et (**7a**)	t = -40 °C	65%	60%
R = ^{i}Pr (**7b**)	t = -40 °C	70%	46%
R = ^{t}Bu (**7c**)	t = -10 °C	77%	49%

Ethyl and isopropyl esters **7a** and **7b** were inferior reaction partners relative to the *tert*-butyl ester **7c**, as the hindered enolate proved more stable over a wider temperature range and provided an improved yield in the aldol reaction. However, in the downstream chemistry from aldol adducts **8a–c** it was observed that increasing the steric bulk of the ester alkyl group resulted in a lower yield of pyridone **10**. After further investigation into the overall stability of the preformed ester enolates, it was concluded that *t*-Bu ester **7c** was preferred even though the overall yield to pyridone **10** was lower.[11] Driven by the desire to maximize the chemical yield and provide a robust synthesis, alternative processing technologies were considered which could address the problem of enolate instability encountered with esters **7a–c**. Particular focus was placed on substrate **7a** to take advantage of the improved yield in the subsequent steps to pyridone **10**.

Continuous reactions are being pursued with increasing frequency in both academic and industrial laboratories for the synthesis of small molecules,[12] and one power of this technology is the ability to address in a robust manner the very challenges posed by the aldol addition reaction.[13] However, the transition from an aldol reaction in batch mode to a continuous process required re-evaluation of several reaction parameters, including base, solvent, temperature, stoichiometry, concentration, and reaction duration. To examine all of these parameters in a flow reactor would be a formidable task. Therefore, prior to evaluating the chemistry in a flow reactor, reaction parameters were re-examined in 1–5 mg scale batch experiments where mixing, heat transfer and time-cycle concerns were minimal.[14] The miniature reactions served as microbatch "snapshots" of a flow process, and we believed this protocol would serve as an efficient tool to narrow down optimization parameters. Unlike in the optimization of the batch process where the enolate was preformed, the microbatch reactions were run under Barbier conditions with the base added as the final component.[15] This simple technique enabled rapid evaluation of several hundred conditions by incorporating high-throughput screening tools. The reaction of ethyl ester **7a** with **3** mediated by potassium *tert*-amyloxide (1.5 equiv) in toluene at −20 to −30 °C proved most efficient.[16]

The flow reactor illustrated in Scheme 4 was then designed to test the continuous process. One feed was a toluene solution

Scheme 4. Flow Reactor Schematic for Aldol Reaction



of ester **7a** and vinylogous ester **3**. The second feed was a commercially available 1.7 M solution of potassium *tert*-amyloxide in toluene. After the streams were combined at a T-mixer, the reaction was quenched at a second T-mixer with aqueous phosphoric acid buffer. The continuous reaction provided the desired aldol adduct **8a** in up to 85% assay yield as a mixture of diastereomers.[17] The toluene solution of aldol adduct **8a** was dried by distillation, and the tertiary alcohol underwent elimination promoted by trifluoroacetic anhydride and triethylamine to afford diene **9a** as a mixture of stereoisomers.

To maximize efficiency, a streamlined process was targeted where the aldolate intermediate is converted directly to the desired diene. In-line elimination was considered, but ultimately not pursued, as reagents which promote this reaction invariably produce an insoluble inorganic byproduct and present a risk of clogging in the reactor. Rather, the aldol condensation was carried out as a semicontinuous process where the unquenched aldol exit stream from the flow reactor was collected in a cooled receiver vessel to which trifluoroacetic anhydride was added synchronously (Scheme 5). In this manner, the desired diene could be obtained directly in comparable purity to the two-step process, without recourse to a separate elimination step.[18] The resulting heterogeneous mixture, consisting of diene **9a** and precipitated potassium trifluoroacetate, was treated with methanol to provide a homogeneous solution poised for the subsequent ammonia-mediated reaction.

Diene **9a** bears the appropriate terminal oxidation states for direct cyclization to a 2-pyridone. Literature precedence for the heterocyclization of acyclic species such as **9a** exists, though examples of substrates bearing α-oxygenation are scarce.[19] The cyclization reaction performed best with an excess of ammonia

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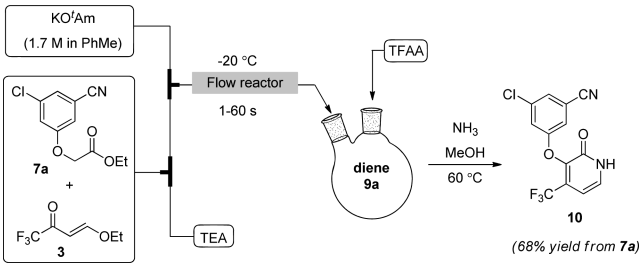
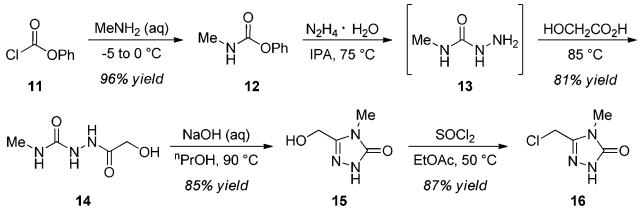
Scheme 5. Streamlined Continuous Aldol Reaction



(28 equiv) at 60 °C. Crystallization of the product was induced by switching the solvent from a mixture of methanol, toluene, and ammonia to pure methanol, and from this mixture pyridone **10** was isolated in 68% yield with high purity. Previous synthetic approaches to **1** involved alkylation of pyridone **10** with an *N*-H triazolinone and subsequent *N*-methylation. This sequence provided **1** in only modest yield due to incomplete chemoselectivity for methylation of *N*-4[20] and the resultant challenging purification. A more convergent approach to **1** would employ *N*-methylated electrophile **16** directly in the alkylation of **10**.

To reduce this approach to practice an efficient synthesis of **16** was required.[4b] Base-mediated cyclodehydration of acylated semicarbazides is an established method to produce the desired 1,2,4-triazol-3-one architecture and was targeted as the key bond-forming step for the optimal synthesis of **16**.[21] Starting from phenyl chloroformate, carbamate formation with aqueous methylamine provided **12** in 96% isolated yield (Scheme 6).[22]

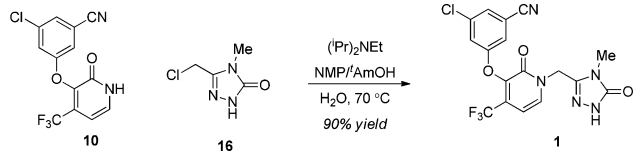
Scheme 6. Streamlined Synthesis of Triazolinone 16



Semicarbazide **13** was generated by the addition of hydrazine in hot 2-propanol and converted without isolation to acylated adduct **14** in 81% yield over the two steps. Base-mediated cyclization with sodium hydroxide in *n*-propanol/water afforded triazolinone **15** in 85% isolated yield. Chlorination of the primary alcohol with thionyl chloride in ethyl acetate provided the key fragment **16** in 87% isolated yield.

Having demonstrated an efficient route to *N*-Me triazolinone **16**, we evaluated the final alkylation reaction to generate **1** directly (Scheme 7). Extensive evaluation of the reaction conditions identified Hünig's base in a mixture of NMP and *tert*-amyl alcohol[23] as optimal for the formation of **1**. At the conclusion of the reaction, the solution was warmed to 70 °C

Scheme 7. Final Alkylation



and water was added to induce crystallization. The product was then isolated in 90% yield with excellent purity.

In conclusion, a novel chemical synthesis of doravirine was developed which utilizes a continuous aldol reaction as the key step for de novo construction of advanced pyridone intermediate **10**. Microbatch snapshot experiments aided in optimizing conditions for the continuous aldol reaction. Ultimately, the high-yielding, robust conversion of ester **7a** to pyridone **10** was enabled through continuous flow by avoiding preformation of an unstable enolate intermediate. *N*-Methylated triazolinone **16** was synthesized in high yield from the bulk commodity reagents phenyl chloroformate, methylamine, hydrazine, and glycolic acid. Ultimately, doravirine was prepared in 52% overall yield along the longest linear sequence with excellent control of chemical purity. The described synthesis is convergent and productive and lays the foundation for a robust scalable process toward doravirine.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure/data and discussion. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) *UNAIDS Report on the Global AIDS Epidemic*, 2013 (UNAIDS/JC2502/1/E).

(2) Lohse, N.; Hansen, A.-B. E.; Pedersen, G.; Kronborg, G.; Gerstoft, J.; Sørensen, H. T.; Væth, M.; Obel, N. *Ann. Int. Med.* **2007**, *146*, 87.

(3) (a) Gatell, J. M.; Morales-Ramirez, J. O.; Hagins, D. P.; Thompson, M.; Keikawus, A.; Hoffmann, C.; Rugina, S.; Osiyemi, O.; Escoriu, S.; Dretler, R.; Harvey, C.; Xu, X.; Teppler, H. *J. Int. AIDS Soc.* **2014**, *17*, 19532. (b) Gulick, R. *J. Int. AIDS Soc.* **2014**, *17*, 19528.

(4) (a) Côté, B.; Burch, J. D.; Asante-Appiah, E.; Bayly, C.; Bédard, L.; Blouin, M.; Campeau, L.-C.; Cauchon, E.; Chan, M.; Chefson, A.; Coulombe, N.; Cromlish, W.; Debnath, S.; Deschênes, D.; Dupont-Gaudet, K.; Falgueyret, J.-P.; Forget, R.; Gagné, S.; Gauvreau, D.; Girardin, M.; Guiral, S.; Langlois, E.; Li, C. S.; Nguyen, N.; Papp, R.; Plamondon, S.; Roy, A.; Roy, S.; Seliniotakis, R.; St-Onge, M.; Ouellet, S.; Tawa, P.; Truchon, J.-F.; Vacca, J.; Wrona, M.; Yan, Y.; Ducharme, Y. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 917. (b) Tucker, T. J.; Tynebor, R.; Sisko, J. T.; Anthony, N.; Gomez, R.; Jolly, S. M. PCT Int. App. WO 2009067166 A2, US 2008012774, 2009. (c) Burch, J.; Coté, B.; Nguyen, N.; Li, C. S.; St-Onge, M.; Gauvreau, D. PCT Int. App., 2011120133 A1, CA 2011000320, 2011.

DOI: 10.1021/ol503625z
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(5) Seeking to employ direct C−H trifluoromethylation, the reactivity of various pyridine precursors under either oxidative or photoredox conditions was examined. Unfortunately, of the various substrates tested, none underwent clean and selective direct trifluoromethylation. See: (a) MacMillan, D. W. C.; Nagib, D. A. *Nature* **2011**, *480*, 224. (b) Ji, Y.; Brueckl, T.; Baxter, R. D.; Fujiwara, Y.; Seiple, I. B.; Su, S.; Blackmond, D. G.; Baran, P. S. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 14411.
(6) Hojo, M.; Masuda, R.; Kokuryo, Y.; Shioda, H.; Matsuo, S. *Chem. Lett.* **1976**, *5*, 499.
(7) Jiang, B.; Xiong, W.; Zhang, X.; Zhang, F. *Org. Process Res. Dev.* **2001**, *5*, 531.
(8) Itoh, T.; Jeon, I.; Mangion, I.; Qian, G.; Sherry, B. D.; Gauthier, D. R.; Cao, Y. PCT Int. Appl. WO 2014089140 A1 20140612, 2014.
(9) Esters **7a−c** were prepared by alkylation of commercially available 3-chloro-5-cyanophenol with the appropriate alkyl bromoacetate (see the Supporting Information).
(10) For the addition of an ester enolate to electrophile **3**, see: Kondratov, I. S.; Gerus, I. I.; Kukhar, V. P.; Manoilenko, O. V. *Tetrahedron: Asymmetry* **2007**, *18*, 1918.
(11) For further discussion and results, see the Supporting Information.
(12) (a) Baumann, M.; Baxendale, I. R.; Ley, S. V. *Mol. Diversity* **2011**, *15*, 613. (b) Poechlauer, P.; Manley, J.; Broxterman, R.; Gregertsen, B.; Ridemark, M. *Org. Process Res. Dev.* **2012**, *16*, 1586.
(13) Viviano, M.; Glasnov, T. N.; Reichart, B.; Tekautz, G.; Kappe, C. O. *Org. Process Res. Dev.* **2011**, *15*, 858.
(14) Refer to the Supporting Information for a description of the Micro-Batch experimental design and a table of selected results.
(15) Barbier conditions in batch mode using various solvents produced the aldol product in only modest yield using sodium or potassium hexamethyldisilazide and poor yields with alkoxide bases.
(16) The major competing side reactions were 1,4-addition to enone **3** and Claisen condensation of ester **7a**.
(17) Crystallization of the crude stream from IPAc/heptane provided a single diastereomer from which X-ray quality crystals could be obtained, allowing independent confirmation of the molecular structure; see the Supporting Information for details.
(18) Diene **9a** in toluene was found to be exceptionally stable with no decomposition detected after 3 months at 23 °C.
(19) Ko, Y. K.; Lee, S. C.; Koo, D. W.; Jung, M.; Kim, D.-W. *Bull. Korean Chem. Soc.* **2001**, *22*, 234.
(20) Five isomeric impurities were formed using this strategy which include various mono-, bis-, and O-alkylated side products.
(21) For the base-mediated cyclization of semicarbazides to 1,2,4-triazol-3-ones, see: (a) Madding, G. D.; Smith, D. W.; Sheldon, R. I.; Lee, B. *J. Heterocycl. Chem.* **1985**, *22*, 1121. (b) Pieczonka, A. M.; Mlostón, G.; Heimgartner, H.; Linden, A. *Helv. Chim. Acta* **2012**, *95*, 1521.
(22) Ren, Y.; Karki, B.; Zhao, M. M.; Bidodeau, M. T. US Patent Application Publication, US 2004/0023981 A1.
(23) Interestingly, the cosolvent *tert*-amyl alcohol attenuated *O*-alkylation from 6% to 3%.

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