One-Pot Reactions

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One-Pot Reactions Accelerate the Synthesis of Active Pharmaceutical Ingredients**

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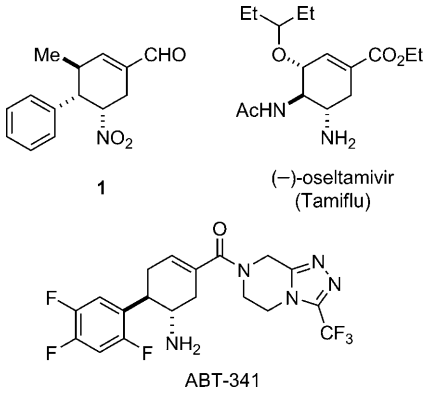
The word "Eintopf" (lit. Engl. one pot) is used generically in the German language to describe a simplistic technique of cooking all the ingredients of a meal in a single pot. It has also found its way into the chemical language as "one-pot reaction" or "one-pot process", in particular to emphasize that a sequence of chemical transformations is run in a single flask. Similar to the cook in the kitchen, synthetic chemists strive to save time and resources by avoiding purifications between individual steps within a multistep synthesis, thus minimizing the transfer of material between vessels.[1] In the strategic planning stage, several concepts are introduced so that alternative synthetic routes can be validated. Thus, the comparison of easy-to-measure parameters serves as a yardstick to identify the most economic approach. In atom economy,[2] the efficiency quotient of the simple reaction A + B→C + D is derived from the molecular weight of the desired product C divided by the combined molecular weight of the reactants (A + B). For 100% atom efficiency, D must be non-existent, that is, all the atoms in A and B end up in the product C. Such "ideal" reactions include the Diels–Alder reaction and catalytic hydrogenations, whereas the Gabriel synthesis (phthalimide used as the synthetic equivalent of ammonia) and Hantzsch ester hydrogenations (with dihydropyridines used as dihydrogen equivalents) are examples of reactions with lower atom efficiency. The quality and quantity of the synthetic steps (step economy[3]) as well as the changes in the oxidation state (redox economy[4]) have been suggested as decisive parameters for a comparative analysis of the multistep syntheses. Clarke et al. recently added pot economy[5] to the above list, with the ultimate aim "to complete an entire multi-step, multi-reaction synthesis in a single pot". Now, this ambitious goal has been achieved by the Hayashi research group in their one-pot total synthesis of the dipeptidylpeptidase IV (DPP4) selective inhibitor ABT-341 (Scheme 1). Before discussing the synthesis, it is important to outline the development of the enabling methodology. It is



Scheme 1. A cyclohexene derivative **1** from Enders' triple cascade, (−)-oseltamivir (Tamiflu), and ABT-341.

well understood that domino reactions[6] and multicomponent reactions[7] are the silver bullets for the rapid construction of complex molecular scaffolds in an economic fashion, with built-in step and pot economy. In this direction, organocatalysis[8] has opened up new vistas by allowing the merger of different modes of activation under the typically mild reaction conditions. The triple cascade of Enders et al.[9] was an early example which unleashed the full potential of organocatalytic domino reactions. The cyclohexene derivatives obtained by Enders et al. (for example, **1**) bear a remarkable resemblance to the carbocyclic core of (−)-oseltamivir (Tamiflu)[10] and ABT-341 (Scheme 1).

In a classical one-pot reaction, all the reagents are added sequentially to the reaction flask, followed by work-up and purification. Hayashi and co-workers have disclosed a strategy called an "uninterrupted sequence of reactions". In contrast to the classical one-pot reaction or telescoped synthesis,[11] where the number of different operations (extractions, distillations) is minimized, the removal of volatiles from the reaction vessel by distillation is explicitly allowed. An initial application, in their pursuit to minimize the transfer of material between flasks, was the development of an organocatalytic synthesis of (−)-oseltamivir. The first published synthesis,[12] which consisted of three one-pot reactions, was later shortened to two consecutive one-pot processes (Scheme 2).[13] In the design of an uninterrupted sequence of reactions it is advantageous to use low-boiling solvents, which are easily removed under high vacuum, and reagents that are

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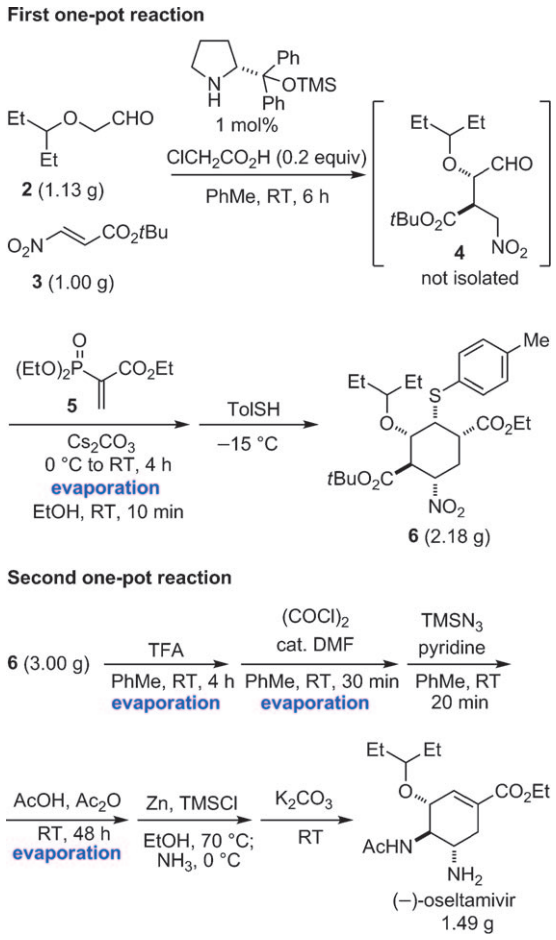
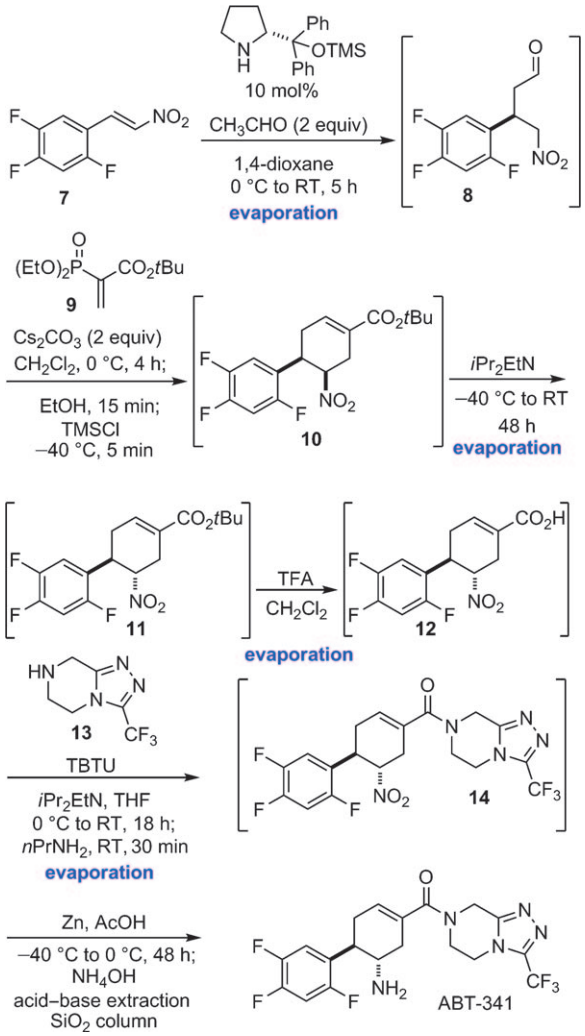


Scheme 2. Synthesis of (−)-oseltamivir by Hayashi and co-workers. TMS = trimethylsilyl, Tol = tolyl.



Scheme 3. One-pot synthesis of ABT-341 in an "uninterrupted sequence of reactions" by Hayashi and co-workers. TBTU = *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate.

themselves volatile or form volatile by-products. The evaporation under high vacuum also prevents accumulation of reactive waste. Moreover, high-yielding and selective steps are a requirement for the success of this strategy. The first one-pot sequence of oseltamivir commenced with an organocatalytic Michael addition of aldehyde **2** to nitroalkene **3**, carried out in the presence of the Jørgensen–Hayashi catalyst (1 mol%), which proceeded with excellent stereoselectivity (97% *ee*). A domino transformation with vinylphosphonate **5** (a Michael reaction and an intramolecular Horner–Wadsworth–Emmons (HWE) reaction), followed by a conjugate addition of toluenethiol and epimerization yielded the highly functionalized cyclohexane **6**. At this stage, the only chromatographic separation of the synthesis was performed. The second "one-pot" process was initiated by cleavage of the *tert*-butyl ester (with TFA) and subsequent conversion of the product into an acyl azide. A Curtius rearrangement at room temperature, reduction of the nitro group, and potassium carbonate induced retro-Michael reaction took place during the second one-pot operation. Finally, acid/base extraction provided pure (−)-oseltamivir.

As a further refinement of his concept, Hayashi and coworkers recently disclosed the one-pot synthesis of ABT-341, a DPP4-selective inhibitor (Scheme 3).[14] Similar to the synthesis of Tamiflu described above, the synthesis of ABT-341 commenced with an organocatalytic Michael addition of acetaldehyde to the nitroalkene **7**, followed by the addition of the resulting nitroalkane **8** to the vinylphosphonate **9** and a HWE ring closure. After a base-promoted epimerization (**10**→**11**), the *tert*-butyl ester **11** was cleaved (with TFA), and the resulting carboxylic acid **12** was subjected to a TBTU-mediated amide formation with amine **13**. The coupling was performed in THF instead of DMF because of its better volatility. Reduction of the nitro group of **14** with Zn/AcOH and purification by chromatography afforded the target compound in a one-pot operation.

Clarke et al. also made an attempt to combine pot, atom, and step economies (PASE) into a unified concept.[5] A few relevant parameters were calculated to compare the efficiency of the concept of an "uninterrupted sequence of reactions" with the stepwise synthesis (Table 1). The mass intensity[5] (defined as the total mass used divided by the mass of the product) and the volume of solvents used provide useful data that help to highlight the resource- and time-economic

Table 1: Comparison of stepwise (A) versus one-pot synthesis (B).

	(−)-Oseltamivir		ABT-341	
Metric	A	B	A	B
mass intensity[a]	241.2	56.4	90.5	53.7
pots	9	2	6	1
yield [%]	49	60	73	63
solvent[b]	319	18.5	180.6	54.5

[a] In $g\,g^{-1}$. [b] In $mL\,mmol^{-1}$.

aspects of this process. Unfortunately, no general tendency could be observed when comparing the overall yields.

In conclusion, it appears conceivable that one-pot reactions in combination with organocatalysis will join the restricted circle of techniques that chemists can apply for the accelerated synthesis of biologically active molecular scaffolds. In addition, from a medicinal chemist's point of view, one-pot reactions are attractive for the synthesis of analogues by permutation of the reactants. It is to be seen if this approach is robust enough for the (automated) synthesis of a focused library of an active pharmaceutical ingredient, thereby rendering this method complementary to other approaches such as flow chemistry and solid-phase synthesis.

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