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Opinions and Suggestions

1.1 Be a “Doctor,” Not Just a “Drug Fetcher”

Even after more than 40 years, I still vividly recall the advice my professor shared with us during my college organic chemistry experiments. He said, “When conducting a synthetic reaction, it’s essential to grasp the reaction mechanism and the principles behind each step of the process. It’s similar to how a physician prescribes medication based on a patient’s condition. If you merely follow the prescription to prepare the medication, you’ll always remain a ‘drug fetcher,’ never a doctor.” I don’t intend to diminish the role of a “drug fetcher” in any way. The key issue is that our aim in training organic chemists is to cultivate “doctors,” not just “drug fetchers.” Understanding the reaction mechanism allows you to master it, draw connections, design better experimental procedures, and tackle challenges in your research. For this reason, comprehending the mechanisms of organic reactions is a fundamental skill for any synthetic organic chemist.

1.2 Synthetic Organic Chemistry: Still as Much an Art as a Science

During my tenure as a university professor, one of my responsibilities was overseeing students conducting organic chemistry experiments in the laboratory. I frequently came across an intriguing scenario: despite following the same experimental procedure, students would obtain varying yields and qualities of the product. In certain extreme cases, some students failed to produce any of the intended product, resulting in a failed experiment. This highlighted the challenges of reliability and reproducibility in synthetic chemistry.

When it comes to the reliability and reproducibility of published articles, I consider the annual journal *Organic Syntheses* to be the top-ranked among organic chemistry journals. This is primarily because the procedures featured in this journal are rigorously verified by an independent group of chemists. However, even in such cases, each synthetic reaction typically yields a range of results or varying yields across different batches, rather than a fixed value.

The yield of a reaction is influenced by numerous factors, including temperature, concentration, the order and speed of reagent addition, stirring method and speed, solvent choice, catalyst, the suppliers and purities of starting materials and reagents, reaction scale, workup procedures, and purification methods. Even when all these external factors are carefully controlled, different chemists may still achieve different yields. Furthermore, for a particular chemist, yields can vary from one batch to another. This indicates that the yield of a synthesis depends not only on the reaction conditions but also on the individual performing the experiment—the chemist.

In this sense, while synthetic organic chemistry is undeniably a science, it also retains a significant degree of artistry. The skill, intuition, and experience of the chemist play a crucial role in the success of a reaction, making it as much an art as it is a scientific discipline.

1.3 Synthetic Organic Chemistry Is an Experimental Science under the Guidance of Theory

Whether an organic reaction is described in detail in a textbook, in a reference book, or in a journal-published article, replicating or referencing these experimental procedures can sometimes lead to issues of varying degrees. Any seemingly insignificant error could cause a reaction failure or lead to a different result from those reported. Occasionally, some planned synthetic reactions yield unexpected products or side products. On the other hand, many groundbreaking organic reactions have been discovered serendipitously. This unpredictability makes synthetic organic chemistry both challenging and fascinating. As a result, synthetic organic chemistry remains, and will continue to be, an experimental science.

Organic chemistry is grounded in a solid theoretical framework, which has been developed and refined by skilled chemists over centuries. These theories are built upon the vast body of experimental data accumulated through the collective efforts of countless chemists over hundreds of years. Understanding and explaining organic reaction mechanisms relies heavily on these established principles. In the field of medicinal chemistry, particularly in synthetic work, a deep mastery of organic chemistry theory and a thorough familiarity with various reaction mechanisms can significantly enhance the efficiency and productivity of our synthetic designs and practices. Therefore, organic synthesis is not merely an experimental science but one that is profoundly guided by theoretical insights.

1.4 Reduce Mistakes in Your Synthetic Work

Given the above considerations, it is imperative that chemists at all levels have opportunities to enhance their knowledge, experience, and skills throughout their careers. Many of us spend more than 8 hours a day in the lab, 6 days a week. But does this alone make us productive chemists? The answer is not necessarily. While dedicating

a certain number of hours to lab work each day is a necessary condition for productivity, it is not sufficient on its own. The true measure lies in the efficiency of our work.

A common question I receive from graduate students and colleagues I supervise is: How can we improve the efficiency and quality of our synthetic work? My response is straightforward: by minimizing or even eliminating mistakes in our work, thereby increasing the success rate of our synthetic reactions. If every reaction we conducted were successful, it would undoubtedly be the most efficient way to work. However, in practice, this is nearly impossible. Therefore, the best approach to enhancing productivity is to reduce errors and improve the success rate of our synthetic reactions.

To achieve this, it is crucial to completely understand the mechanism of every synthetic reaction we perform. We can drastically reduce mistakes by anticipating potential problems and devising strategies to avoid them. This proactive approach not only improves the quality of our work but also enhances overall efficiency, making us more productive chemists in the long run.

1.5 Your Knowledge, Experience, and Skills Can Never Be Too Much

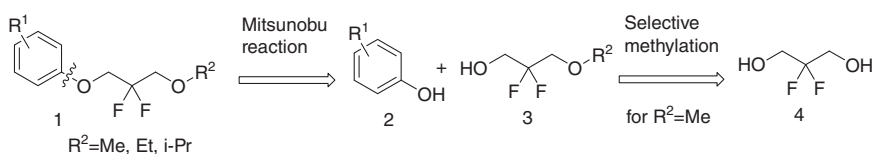
For any entry-level synthetic chemist fresh out of university—whether you hold a bachelor's degree or a Ph.D. with postdoctoral research experience—working as a medicinal chemist in drug discovery, your knowledge, experience, and skills will always feel insufficient. Mistakes are inevitable in the early stages of your career. However, if you are a quick learner, you will rapidly grow by learning from your own work and the expertise of others. By striving to understand the mechanism behind every reaction you perform, your problem-solving abilities will improve significantly. Over time, as you accumulate more knowledge and experience, the frequency of errors in your synthetic work will steadily decrease.

I've heard hiring managers or HR professionals use the term "overqualified" as a reason to reject certain applicants for a position. However, when it comes to performing a synthesis, no chemist, regardless of their experience level, can ever be considered "overqualified." For even the most experienced chemist, a lack of caution during a synthetic reaction can result in failure. Experience doesn't eliminate the need for careful attention to detail—it reinforces it.

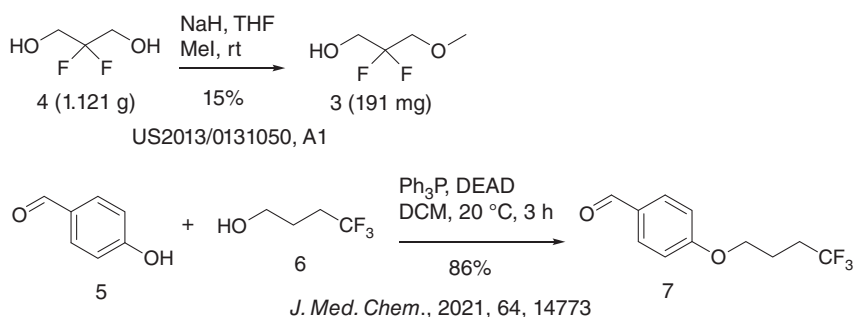
Synthetic organic chemistry is a rapidly evolving field, continuously advancing with the emergence of new synthetic methods, innovative reagents, and cutting-edge technologies. These developments are documented in a growing number of articles published across various organic chemistry journals. The volume of published research is expanding, and new journals dedicated to organic synthesis are also being established. Given the finite nature of time and energy, it is challenging to keep up with every new paper relevant to your work. Nevertheless, it is feasible to efficiently skim through titles and abstracts to identify key publications. When a paper particularly captures your interest, you can delve into it in greater detail. While the papers you read may not always directly contribute to your current projects, maintaining this habit over the long term can significantly enhance your expertise and benefit your career.

1.6 What Is a Mistake?

What is a mistake? From my perspective, it is a relative term or concept. A synthetic plan or experimental design created by a relatively junior chemist might be considered reasonable or acceptable. However, the same plan could be seen as an obvious mistake if it were designed by a more experienced, senior-level chemist. For instance, consider a medicinal chemistry project where the goal is to synthesize a series of aromatic ethers (**1**) featuring a difluoro alkyl branch, aiming for final compounds in the range of 5–10 mg. Your proposed synthesis design for compound **1** ($R^2 = \text{Me}$) is shown below.



The target compounds could be synthesized from phenol **2** (suppose **2** have been prepared or commercially available) and alcohol **3**. You find **3** ($R^2 = \text{Me}$) is commercially available, but very expensive (Sigma-Aldrich, US\$1746/1 g, US\$220/mmol). So, you decide to prepare **3** ($R^2 = \text{Me}$) from the relatively less expensive diol **4** (AK Scientific, US\$162/5 g, US\$3.63/mmol) by iteroselective monomethylation. You also find references (*a*, US2013/0131050, A1. *b*, *J. Med. Chem.*, **2021**, 64, 14773) supporting your design. The analogs **3b** ($R^2 = \text{Et}$) and **3c** ($R^2 = i\text{-Pr}$) could be prepared similarly.



If you are a junior-level chemist and have proposed such a design, the two-step synthesis appears reasonable at first glance, making your design acceptable in principle. However, this acceptance does not necessarily mean your design is suitable for actual synthesis. While the Mitsunobu reaction step is unlikely to pose significant issues, a more thorough analysis reveals that the first step—preparing ether **3** from diol **4**—could be problematic. If you were to attempt this synthesis in the lab, you would almost certainly encounter difficulties in isolating product **3** from the reaction mixture.

The patent procedure for this step involves diluting the reaction mixture with water, extracting with ethyl acetate, evaporating the solvents under reduced pressure, and further purifying the crude product via silica gel column chromatography using an ethyl acetate-hexane eluent, followed by another round of solvent evaporation. Despite this extensive process, the yield of product **3** was only 15%. If you were to replicate this procedure, you might initially obtain no product at all. Detecting compound **3** would also be challenging, as it lacks ultraviolet (UV) absorption, making it difficult to identify using thin-layer chromatography (TLC) or high-performance liquid chromatography (HPLC).

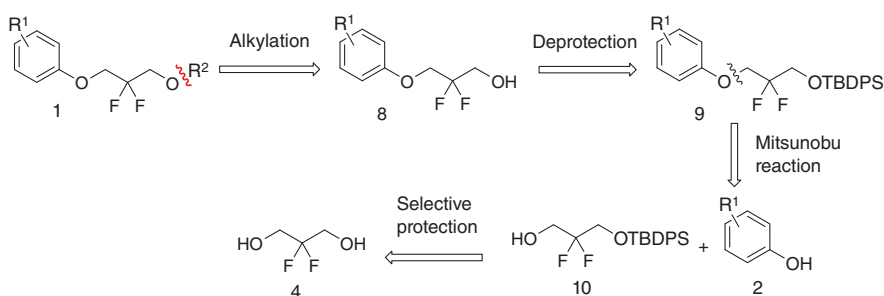
Moreover, the situation is further complicated by the likelihood that compound **3** is volatile. Although no boiling point is reported for **3**, a structurally similar compound, 3-methoxy-1-propanol, has a boiling point of approximately 150 °C at 760 mmHg or 45 °C at 10 mmHg. This suggests that during rotary evaporation, the product could easily be lost—either carried over into the receiving flask with the solvents or even drawn into the vacuum pump and released into the air. This issue is particularly pronounced when the reaction is conducted on a small scale (e.g., <5 g), which explains the poor yield (15%) reported in the patent.

Another limitation of this design is the lack of divergent synthesis. The iteroselective monomethylation of diol **4** in the initial step prevents the synthesis of other analogs (where $R^2 = \text{Et}$, $i\text{-Pr}$, etc.) from a shared intermediate.

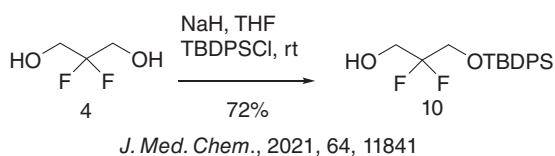
In summary, while your design is conceptually sound, practical challenges in isolating and purifying compound **3** make it less viable for actual laboratory synthesis.

Therefore, if you are a senior-level chemist, creating a design as described above would be considered an “obvious mistake.”

A more logical and appropriate design is presented below.



The iteroselective mono protection of diol **4** with tert-butyldiphenylsilyl chloride (TBDPSCl) was reported in many patents and journal articles (e.g., *J. Med. Chem.*, **2021**, 64, 11841).



In the synthesis of the methyl ether product **1**, although this design involves two additional reaction steps compared to the previous approach due to the introduction of the TBDPS-protecting group, the significantly higher molecular weight of compound **10** relative to ether **3** ensures that it is less prone to evaporation. This intermediate is also UV-active, as it contains two benzene rings, making it detectable by TLC and analytical HPLC. The subsequent steps, including the Mitsunobu reaction, deprotection, and methylation, are expected to proceed without issues. Additionally, this design positions alkylation as the final step, maintaining the flexibility to synthesize other homologues from the common intermediate **8**.

Nevertheless, if the goal is to synthesize hundreds of grams or even kilograms of compound **3**, the first design would be more practical. This is because, on such a scale, compound **3** could be purified by fractional distillation.

1.7 Beyond Experience: Combining Literature and Insight for Optimal Synthetic Design

In the field of medicinal chemistry, once the structures of a series of compounds to be synthesized are finalized, the subsequent step involves designing the synthesis. Even if you are a highly knowledgeable and experienced expert, it is essential to consult the literature while incorporating your own ideas. This approach ensures the development of the most rational and feasible synthetic route. Relying solely on personal experience for synthetic design often does not yield the best results.

Every stage of the reaction, from the raw materials to the final product, must be meticulously examined. It is also crucial to prepare contingency plans to address potential challenges and issues. For multi-step syntheses, the yield of each reaction step, as well as the overall yield, should be estimated. This allows for the determination of the initial reaction scale based on the required quantity of the target product.

In multi-step syntheses, it is imperative to avoid using all or most of an intermediate for the next reaction until a smaller-scale test reaction has been successfully completed. This precaution holds true even for traditional reactions that appear to be problem-free, as unexpected complications can arise.

1.8 Improve Your Decision-Making Ability

Modern online search engines like SciFinder and Reaxys are incredibly powerful tools. When searching for a specific reaction or the synthesis of a particular compound, these platforms can generate thousands of results in mere seconds. However, the challenge you face is not a lack of information but an overwhelming abundance of it. If you find yourself considering 10 out of 100 plausible options as worth trying, it essentially means you are uncertain. (Having too many

options can be as paralyzing as having none!) The key is to prioritize these reaction conditions and select only two or three to test, based on the resources available in your research facility.

So, how can you enhance your decision-making process? The solution lies in developing a deep understanding of the reaction mechanism. This includes a solid understanding of the structural features, as well as the physical and chemical properties of the starting materials, reagents, catalysts, and products involved. With this knowledge, you can anticipate potential challenges, such as reaction selectivity, the need for functional group protection, compatibility between functional groups and reaction conditions, side reactions, and the intricacies of workup and purification. By addressing these factors proactively, you can refine every detail of your synthetic approach. This meticulous preparation will naturally lead to a higher success rate and improved yields in your synthetic reactions.

1.9 Know the Mechanism of the Reactions You Perform

At the start of a medicinal chemistry career, particularly for research assistants or associates, it's common to follow synthetic designs and references provided by a supervisor rather than creating your own. In such cases, you may not need to design the synthesis yourself. However, if you lack an understanding of the reaction mechanisms involved, mistakes are likely to occur during your work. While thoroughly reviewing the synthetic design and deciphering the reaction mechanisms requires extra time and effort, it is a crucial step for professional growth. Human nature often leans toward taking the path of least resistance—if one can perform tasks without deep thinking, they may avoid it. But if you are genuinely committed to enhancing your professional skills and problem-solving abilities, investing energy in understanding reaction mechanisms will significantly improve your work efficiency and accelerate your development.

If you simply follow the synthetic design and references provided by your supervisor without engaging deeply, you may blame the design or reference method when a reaction fails, claiming it “doesn’t work.” This passive attitude will not help you improve your problem-solving skills. Ultimately, you are responsible for your reactions. Frustration can set in after a week of unsuccessful attempts, making work feel like a burden and a source of stress.

On the other hand, if you actively engage in the synthetic design and develop a clear understanding of each reaction's mechanism, you gain control over the process. The molecules in your flask will transform into new compounds as you direct. When your reactions and syntheses proceed smoothly, yielding the desired products as planned, you'll experience a profound sense of accomplishment and success. This approach not only enhances your skills but also brings joy and satisfaction to your work, making it a rewarding and fulfilling experience.

1.10 Always Learn Something from the Reaction You Performed

Every reaction we conduct, whether it succeeds or fails, offers valuable lessons.

Understanding why a reaction worked is essential for successful reactions. Conversely, for unsuccessful ones, we need to analyze why they failed. Was there no reaction at all, or was an unexpected product formed? What caused the outcome? Identifying the root cause of a problem makes it easier to find a solution. Failure itself isn't the issue; the real problem lies in not understanding why it happened or failing to uncover the true reason behind the failure.

1.11 Knowing Reaction Mechanisms Alone Doesn't Make an Excellent Chemist—But It's Essential

Understanding the mechanisms of organic reactions is essential for becoming an outstanding synthetic medicinal chemist, but it is not enough on its own. To excel in any profession, you must first have a genuine passion for it. As a synthetic chemist, you also need to possess exceptional practical skills, a strong work ethic, and unwavering perseverance. Success belongs to those who remain steadfast in their beliefs. These qualities are the cornerstone of the scientific spirit. Understanding reaction mechanisms is like having a clear path before you, making it easier to reach your goals. Conversely, not understanding these mechanisms is like running in the dark—you are more likely to stumble or fall into obstacles along the way.

1.12 Patents Do Not Tell You the Full Story of Chemistry

As a medicinal chemist regularly engaged in synthetic work, you will frequently consult reactions documented in patents. However, it's important to recognize the significant differences between patents and journal articles. Patents typically do not include detailed reaction mechanisms. If new methods are disclosed, they often only present the results without explaining the rationale or development process behind the innovation. Additionally, patents rarely cite references for the synthetic methods they employ. The yields reported in patents are usually not optimized and may even be inaccurate, meaning they should only be used as a rough guideline rather than a reliable benchmark for calculating the yield of your own synthetic routes. In some cases, yields may not be provided at all. Furthermore, the characterization data for intermediates and final products in patents is often incomplete or insufficiently detailed.

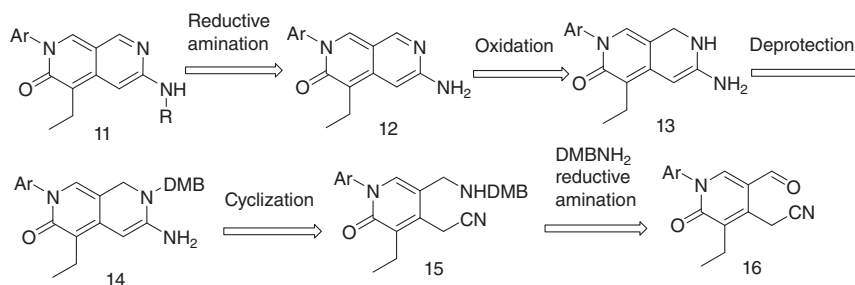
1.13 Summarize Your Work After Completing a Synthesis

Once a synthesis is completed, it is important to promptly create a summary. Throughout the synthesis process, you may have faced challenges, encountered difficulties, or taken unnecessary detours. Now that you have gained insights into resolving these issues and avoiding similar pitfalls in the future, it is an opportune time to reflect on whether there are more efficient synthesis methods or improved approaches. Writing a summary not only enhances your writing skills but also significantly strengthens your ability to summarize, as well as your logical and analytical thinking.

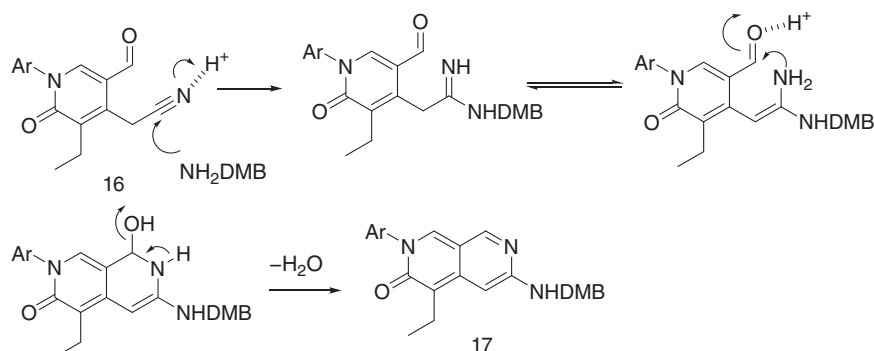
1.14 Two Examples

Here I would like to present two examples to illustrate the importance of understanding reaction mechanisms in solving chemistry problems.

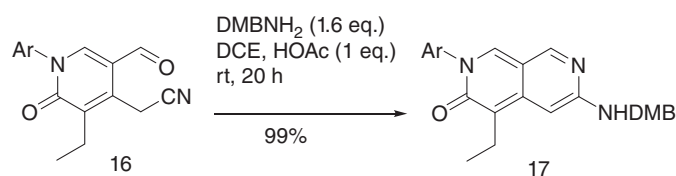
One example is selected from our research experience and the results were presented in a patent application [1]. In a medicinal chemistry project, we wanted to synthesize a series of platelet-derived growth factor receptor inhibitors, which structure is shown in the scheme below as compounds **11**. Those compounds consist of the core structure, named as a 2,7-naphthyridin-3(2*H*)-one. Our synthetic plan included the reductive amination of the key intermediate **16**, then cyclization, de-protection of 2,4-dimethoxybenzyl (DMB) and oxidation to form the amino pyridine **12**.



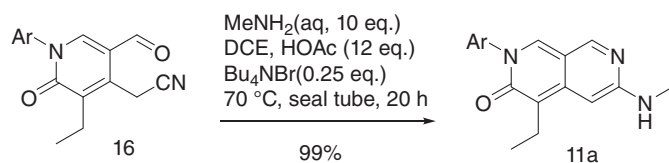
It seems in the above design, each step is reasonable. However, when the reductive amination of **16** with DMBNH₂ with NaBH(OAc)₃ in 1,2-dichloroethane was performed, the expected product **15** was not obtained. Instead, a cyclized product **17** was obtained in 37% yield. That was the key intermediate for the synthesis of our target compounds. Understanding the mechanism for the formation of **17** from **16** was crucial for us for developing a practical synthesis of **11**. The formation of **17** could be explained by the following mechanism. Since the commercially available NaBH(OAc)₃ always contains residual HOAc, which can be easily smelled when you open the chemical container, trace amount of HOAc catalyzed the formation of **17**.



Based on this mechanism, $\text{NaBH}(\text{OAc})_3$ should not play any role for the formation of 2,7-naphthyridin-3(2*H*)-one (**17**) and the reaction should be catalyzed by acid. Thus, a preparation of **17** from **16** and DMBNH_2 catalyzed by HOAc was designed and performed. To our delight, the reaction gave the desired product in quantitative yield.



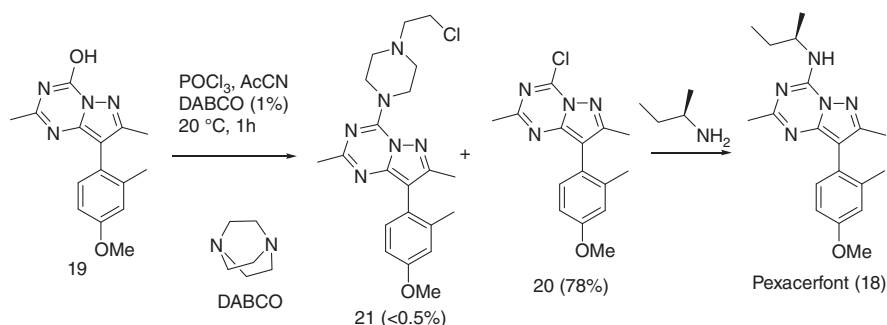
Encouraged by the above discovery, when methylamine was employed as a substrate, the desired product **11a** was produced in a single step in quantitative yield. As methylamine was used as an aqueous solution, a phase transfer catalyst, Bu_4NBr (0.25 eq), was also added.



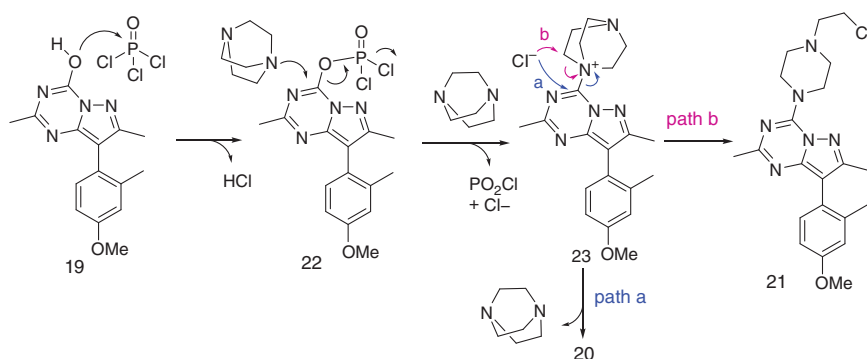
Thus, an excellent procedure for synthesis of 2,7-naphthyridin-3(2*H*)-ones was developed by understanding the mechanism of the formation of an unexpected product [1].

The second example is selected from the work of Bristol-Myers Squibb Company. Pexacerfont (**18**) is a pyrazolotriazine corticotropin-releasing factor receptor 1 (CRF1) antagonist. During a process study, chemists investigated the chlorination of **19** by POCl_3 catalyzed by tertiary amines [2]. In the presence of DABCO (1 mol %), the desired chloropyrazolotriazine **20** was obtained in 78% yield within 1 h at 20 °C.

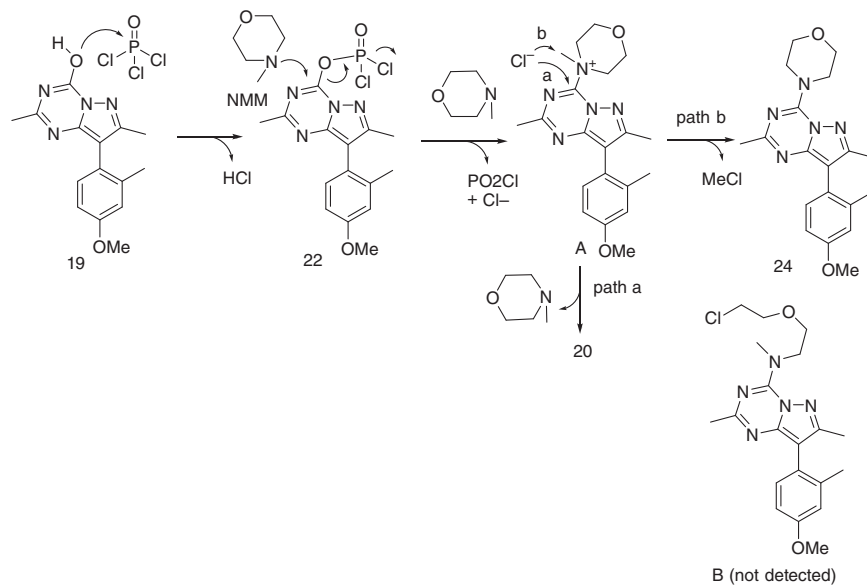
While an impurity **21** (<0.5%) was also generated. Since this impurity is a potential alkylating agent and would interfere with the next reaction, its level required close monitoring in the final product. How this impurity was produced and how to avoid its formation?



The formation of **21** was the result of nucleophilic attack of DABCO on the proposed *O*-phosphorylated intermediate **22**. Presumably, chloride ion displacement of DABCO (**path a**) provides the desired product **20**. Conversely, attack at either of the three α -carbons of the activated DABCO intermediate **23** (**path b**) would produce impurity **21**.



Realizing that side-reaction, the chemists from BMS used 0.5 mol % of *N*-methylmorpholine (NMM), leading to >98% conversion to **20** within 1 h at 25 °C, although a trace amount of the amination impurity **24** still formed in analogy to the DABCO catalyzed reaction. Importantly, the chlorinated impurity **B**, analogous to **21**, was not observed. Since the chloride ion would presumably attack the primary methyl group of NMM, only trace amounts of chloromethane—a volatile impurity—would form and likely evaporate during the reaction and workup. Thus, no alkylating impurity existed in the products.



References

- 1 Zhang, W.; Wang, X.; Liu, H.; Zhou, Z.; Wang, Y.; Yang, L.; Li, T.; Zhao, X.; Zou, Z.; Gao, Y.; Lin, S.; Wang, W. WO 2020/063860 A1.
- 2 Broxer, S.; Fitzgerald, M. A.; Sfougataakis, C.; Defreese, J. L.; Barlow, E.; Powers, G. L.; Peddicord, M.; Su, B.-N.; Tai-Yuen, Y.; Pathirana, C.; Sherbine, J. P. *Org. Process Res. Dev.*, **2011**, *15*, 343.