A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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Editorial

Organic Syntheses: The "Gold Standard" in Experimental Synthetic Organic Chemistry

Experimental Synthetic Chemistry: Art or Science?

It has often been suggested that the practice of synthetic organic chemistry is as much an art as a science. Commenting on the controversy over the reproducibility of the Rabe synthesis of quinine, the late William von Eggers Doering wrote

> *"It is almost never possible to reproduce published details. They assume an indefinable amount of experience and cannot be written for the first time cook who has never mastered the elementary techniques! The premise that the best, detailed descriptions suffice to guarantee reproducibility is contrary to universal experience. Try writing two sets of descriptions for playing a piano composition - the one to reproduce the performance according to Ogdon, the second Horowitz!"*[1]

Is this truly the case? Is it impossible to prepare a written experimental procedure that enables any chemist "skilled in the art" to reproduce the yields and selectivity reported for a synthetic reaction? This is the question that will be addressed in this editorial and its sequel.

Reproducibility: A Perennial Concern in Synthetic Chemistry

There is no denying that the reproducibility of reactions found in the chemical literature cannot be taken for granted. Who among experienced synthetic chemists has not at one time or another found themselves unable to obtain the reported yield for a reaction, even after repeated trials? Some in the community would even argue that the situation has grown worse in recent years. This may indeed be the case, and one can suggest several reasons why reproducibility may be more problematic now than in the past.

- **Increasing sensitivity of reactions to precise conditions**. Reactions today often call for reagents that are exceptionally sensitive to even traces of air and/or moisture. Many reactions are carried out at low temperature and are sensitive to exotherms, local heating effects, etc. The penalty for deviating from optimal conditions can be quite severe.

- **Catalytic reactions**. More and more often, reactions employ reagents in catalytic amounts. Catalytic processes can be especially sensitive to trace impurities and minor departures from the optimal protocol.
- **Reactions carried out on a very small scale**. It is not unusual in a paper reporting a new synthetic method to find that no case was run on a scale producing more than 10-25 mgs of product. This certainly increases the likelihood that problems will be encountered when the reaction is attempted on a ”preparative” scale.
- **Carelessly prepared experimental procedures**. Unfortunately, it is all too common these days to find that experimental procedures lack adequate detail, are carelessly written, and contain unclear or ambiguous instructions that are easily misinterpreted. This may be a consequence of the fact that today experimental procedures are usually relegated to ”supporting information” (SI) rather than appearing incorporated in the main text of an article. The frequency with which errors, ambiguous language, grammatical mistakes, etc. appear in SI procedures suggests that these procedures are not receiving the same scrutiny from the principal authors and from reviewers that would be afforded to procedures included in the main text.[2]

Organic Syntheses as the “Gold Standard” for Synthetic Chemistry

Since 1921, the mission of *Organic Syntheses* has been to provide the community with detailed and reliable procedures for the synthesis of organic compounds. Unique among chemistry publications, every reaction published in *Organic Syntheses* is “checked” for reproducibility in the laboratory of a member of the Board of Editors (BoE). The eleven academic and industrial scientists on the BoE serve 8-year terms (5 years in the case of editors from outside North America) and are elected by the current members of the Board. The chemists elected to the BoE are drawn from the most distinguished members of the synthetic organic chemistry community to ensure that checking is carried out by highly competent and experienced researchers under the supervision of the leading figures in the field.

The following system has been developed over the years in order to maximize the reproducibility of the initial versions of procedures submitted to checking, as well as the final versions published in *Organic Syntheses*.

1. Comprehensive and very explicit ”Instructions to Authors” have been prepared that require submitters to provide much more detail in experimental procedures than is typical in other publications.
2. Every article submitted to *Organic Syntheses* is first reviewed by each member of the BoE who provides detailed comments to the Editor in Chief. If the consensus favors checking, the Editor in Chief assigns the procedure to the laboratory of one of the editors for checking.
3. In the initial review, BoE members carefully scrutinize each submitted experimental procedure to identify any aspects of the procedure that are unclear or ambiguous. Authors are contacted and asked to provide additional details clarifying such points before checking begins.
4. In order for an article to be accepted for publication, each experimental procedure must be reproduced at least twice in the checking editor’s laboratory with yields and selectivity close to that reported by the submitters. If problems are encountered, the original authors are consulted for advice and assistance.
5. When results slightly differ, the checking editor’s data are reported in the final article, with the submitting author’s results generally mentioned in an accompanying note.

In spite of all of these measures, currently 3-5% of the articles submitted for publication eventually must be rejected due to the inability of the checkers to satisfactorily reproduce the results of the submitters. This figure actually represents an improvement in recent years, since during the period 1982-2005 the rejection rate was ca. 12%! Why do so many procedures prove not to be reproducible? Part 2 of this editorial will discuss the most common causes of problems based on the experiences of the Board of Editors.

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Organic Syntheses

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[1] W. E. Doering email to J. I. Seeman, Cambridge, MA, May 18, 2005 as reported in Seeman, J. I. *Angew. Chem. Int. Ed.* **2007,** *46*, 1378-1413.

[2] Beginning in 2011, the *Journal of Organic Chemistry* has published experimental procedures in the main text of articles (rather than in SI). It is hoped that other journals will follow suit!