

Chemistry Chat

My Familiar Compound Family

–1,3-Dicarbonyl Compounds –

Nagatoshi Nishiwaki

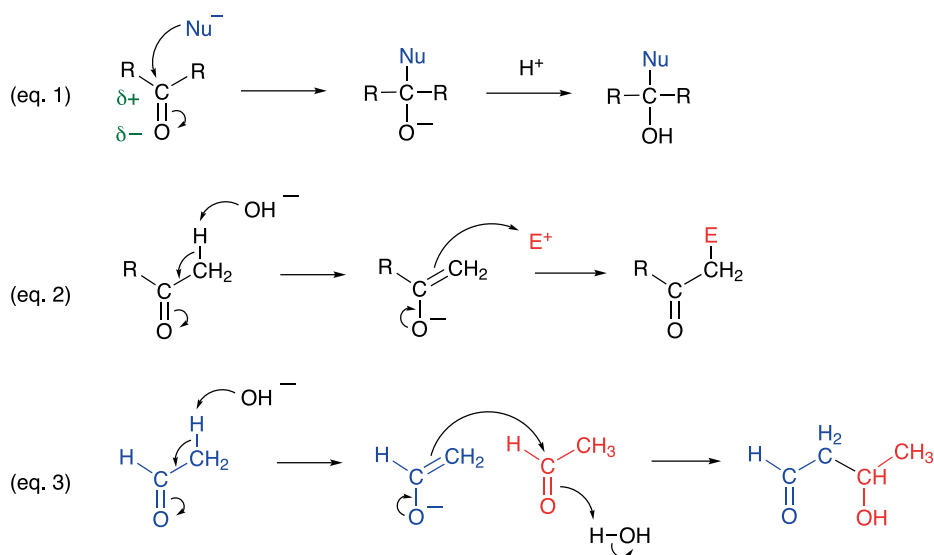
School of Environmental Science and Engineering, Kochi University of Technology

During the course of your research, you are bound to come across one or two compound families that interest you or that you deal with frequently. During my many years in synthetic organic chemistry, I have become quite familiar with a particular compound family. I would like to introduce this family and my new encounters with it in this three-part series. I hope some readers will find useful information contained herein.

Dual Nature

Carbonyl compounds are ubiquitous in research, and their appeal is largely due to their dual nature. The polarized carbon-oxygen double bond makes them excellent electrophiles (**Scheme 1**, eq. 1), while the

tautomeric enols and their deprotonated forms, enolates, serve as nucleophiles (eq. 2). Both roles are utilized in the aldol reaction (eq. 3). This duality is what makes this group of compounds so attractive.



Scheme 1. Reactions of carbonyl compounds with nucleophiles and electrophiles

In the case of 1,3-dicarbonyl compounds (active methylene compounds), the collaboration of the two carbonyl groups results in a variety of new reactivities, such as the formation of highly acidic methylene groups and relatively stable enols. When I was a student, the phrase “active methylene compounds in times of trouble”

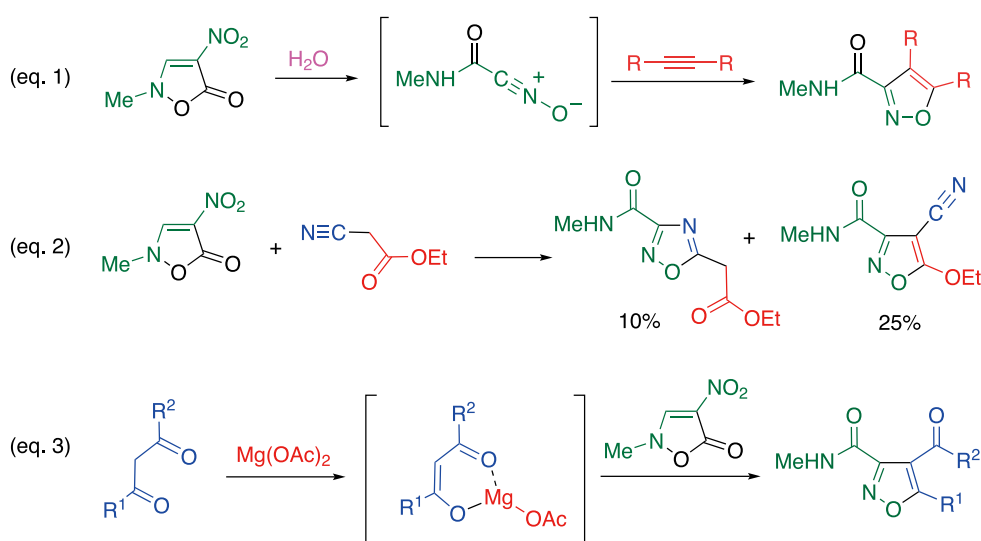
was often used in the laboratory. This was because when we got stuck while developing reactions, 1,3-dicarbonyl compounds could be used as substrates to get some kind of reaction going, and in some cases, they could bring out new reactivity. On two occasions, 1,3-dicarbonyl compounds have played a leading role in my research.

Dipolarophile

We found that a nitrile oxide with a carbamoyl group is generated simply by treating nitroisoxazolone with water (**Scheme 2**, eq. 1).¹ The cycloaddition reaction proceeds in the presence of alkynes and nitriles to readily construct functionalized isoxazole and oxadiazole frameworks. In this process, we found that when ethyl cyanoacetate was used as a substrate, not only the cycloadduct of the cyano group but also an isoxazole having a cyano group was produced (eq. 2).² In an attempt to make this reaction more versatile and practical, I employed various active methylene compounds as

dipolarophiles, but no progress was observed. Then, I had the idea that if a chelate complex is formed with a metal ion, it would fix the 1,3-dicarbonyl compound in the enol form. When copper acetate was added, the reaction proceeded as expected, and I was delighted. After trying various metal salts, the best results were obtained when magnesium acetate was used (eq. 3).³

Lesson learned: “Even though it is a side reaction, it can grow into a great discovery if you're chasing it.”



Scheme 2. Generation of a nitrile oxide from nitroisoxazolone and its cycloaddition

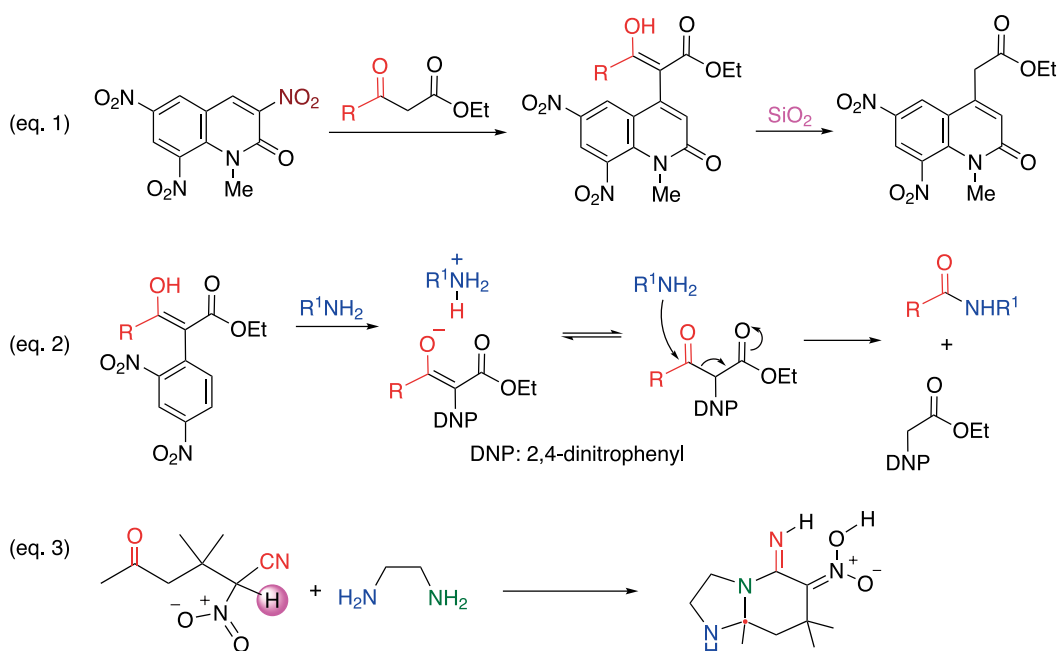
Transacylation

Numerous papers on active methylene compounds have been reported and summarized in review articles, giving the impression that the subject has been exhausted. I myself thought that I would never discover new reactivity of active methylene compounds.

To my surprise, then, when a 1,3-dicarbonyl compound was applied to a trinitroquinolone, I found a *cine*-substitution reaction in which substitution proceeded at the 4-position, accompanied by the elimination of the nitro group at the 3-position. When the products were purified by column treatment, deacylation proceeded in the case of a keto ester-substituted product (**Scheme 3**, eq. 1).⁴ I considered that the activated acyl group could be utilized in organic synthesis. Indeed, when an α -phenylated keto ester was reacted with an amine, the acyl group was transferred to the amine without any detectable by-

products (eq. 2).⁵ At the time, when I presented my work at a conference, I could not successfully refute the claim that it was simply a retro-Claisen reaction. However, subsequent studies showed that the bulkiness of the benzene ring is important. The keto form is destabilizing, so it exists in the enol form. As a result, the acidity increases considerably and the reaction proceeds efficiently because the amine is in close proximity to the enol. Subsequently, I named the reaction a “pseudo-intramolecular reaction” and have employed it in the synthesis of diverse skeletons (eq. 3),⁶ which continues to this day.

Lesson learned: “Even when you think you have taken all you can get, there are blessings left.”



Scheme 3. Transacylation and construction of bicyclic framework using “pseudo-intramolecular reaction”

References

1. N. Nishiwaki, K. Kobiro, H. Kiyoto, S. Hirao, J. Sawayama, K. Saigo, Y. Okajima, T. Uehara, A. Maki, M. Ariga, *Org. Biomol. Chem.* **2011**, *9*, 2832.
2. N. Nishiwaki, K. Kobiro, S. Hirao, J. Sawayama, K. Saigo, Y. Ise, Y. Okajima, M. Ariga, *Org. Biomol. Chem.* **2011**, *9*, 6750.
3. N. Nishiwaki, K. Kobiro, S. Hirao, J. Sawayama, K. Saigo, Y. Ise, M. Nishizawa, M. Ariga, *Org. Biomol. Chem.* **2012**, *10*, 1987.
4. N. Nishiwaki, A. Tanaka, M. Uchida, Y. Tohda, M. Ariga, *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1377.
5. N. Nishiwaki, D. Nishida, T. Ohnishi, F. Hidaka, S. Shimizu, M. Tamura, K. Hori, Y. Tohda, M. Ariga, *J. Org. Chem.* **2003**, *68*, 8650.
6. N. Nishiwaki, S. Hirao, J. Sawayama, K. Saigo, K. Kobiro, *Chem. Commun.* **2011**, *47*, 4938.

Author Information



Professor Nagatoshi Nishiwaki received a Ph.D. in 1991 from Osaka University. He worked in Professor Ariga's group in the Department of Chemistry, Osaka Kyoiku University, as an assistant professor (1991-2000) and associate professor (2001-2008). From 2000 to 2001, he was with Karl Anker Jørgensen's group at Århus (Aarhus) University in Denmark. He worked at the Center for Collaborative Research, Anan National College of Technology as an associate professor from 2008 to 2009. Then, he moved to the School of Environmental Science and Engineering, Kochi University of Technology in 2009, where he has been a professor since 2011. His research interests comprise synthetic organic chemistry using nitro compounds, heterocycles (synthesis, ring transformation, 1,3-dipolar cycloaddition, application as tools in organic synthesis), pseudo-intramolecular reactions.