Chemistry Chat

My Familiar Compound Family

– Nitro Compounds –

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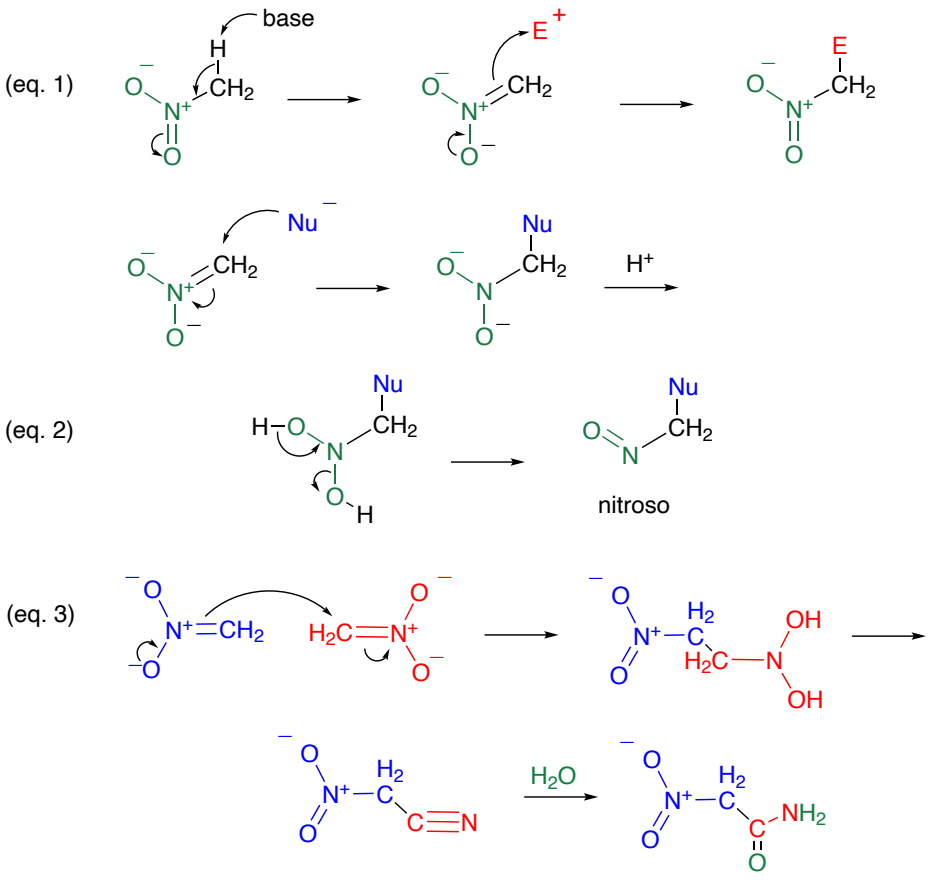
I encountered nitro compounds at the first university I was employed at after completing graduate school. Nitro compounds (like cyano compounds) are only regarded as compounds related to amines without being devoted to a single chapter in textbooks. They were completely unknown to me, as I myself had hardly ever used them, even when I was a student. It is strange that now, after 30 years, nitro compounds have been the central focus of my research. Furthermore, I have written a review article on nitro compounds.[1]

Diverse Reactivity

Nitro groups exhibit diverse reactivity similar to carbonyl groups.[2] The first thing that comes to mind is that they can make substrates electron-deficient by inductive electron-withdrawing and resonance effects. Nitro groups are also often used as nucleophiles because of their high acidity at the α-position and the stable anions they produce (**Scheme 1**, eq. 1). Furthermore, they have a similar reactivity to carbonyl compounds, such as acting as



Scheme 1. Reactions of nitro compounds with electrophiles or nucleophiles

electrophiles when the other reactants are nucleophiles (eq. 2) and reacting with other nitro groups (eq. 3). However, the major difference between a nitro group and a carbonyl group is that a nitro group can act as a leaving group. The nitro group itself may be substituted directly, or it may leave together with the hydrogen at the adjacent position as a nitrite, forming a double bond. Furthermore, a nitro group is a useful functional group in synthetic chemistry because it can be derivatized into various frameworks by chemical transformation, including reduction.

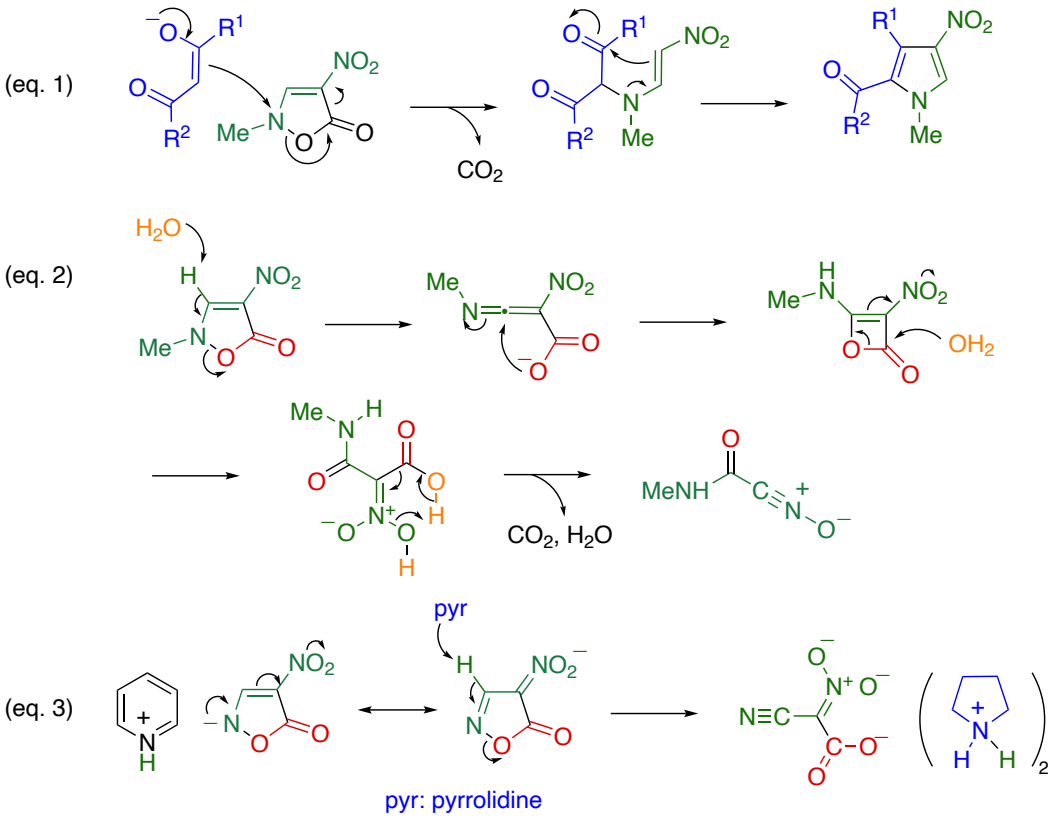
Electron-withdrawing Effect

As mentioned above, a nitro group acts as a strong electron-withdrawing group. Even when only looking at the inductive effect, the pKa of nitroacetic acid is 1.68, which is comparable to that of dichloroacetic acid (1.29), indicating an affinity equivalent to that of two chloro groups. Furthermore, if the resonance effect is added, the substrate becomes highly electron-deficient.

2-Methyl-4-nitro-3-isoxazolin-2(5*H*)-one (nitroisoxazolone) is the compound that made me realize the electron-withdrawing effect of the nitro group in particular: the ring nitrogen at the 2-position is electron-withdrawn by the nitro group and carbonyl group through a double bond. In addition, a highly electronegative oxygen is bonded to the adjacent position, and a carbonyl group is bonded further ahead. Indeed, the ring nitrogen is highly electrophilic, and in the reaction of 1,3-dicarbonyl compounds with enolate ions, ring transformation proceeds accompanied by decarboxylation to give polysubstituted pyrroles (**Scheme 2**, eq. 1).[3]

The acidity of the hydrogen at the 3-position of nitroisoxazolone is also quite high, and water acts as a base to deprotonate it. Subsequent ring-opening, ring-reclosing, dehydration, and decarboxylation would produce the nitrile oxide (eq. 2).[4] The 3-position proton of pyridinium salt,[5] the precursor of this isoxazolone, is also highly acidic even though it is anionic. Indeed, it can be deprotonated by organic bases such as pyrrolidine, which undergoes ring-opening to give dianionic cyanoacinitroacetates (eq. 3).[6,7] This compound can be used as a cyano(nitro)methylating agent that can be safely handled instead of nitroacetonitrile, which is explosive.[6]

Lesson learned: "We are the ones not taking full advantage of the compound's specs."

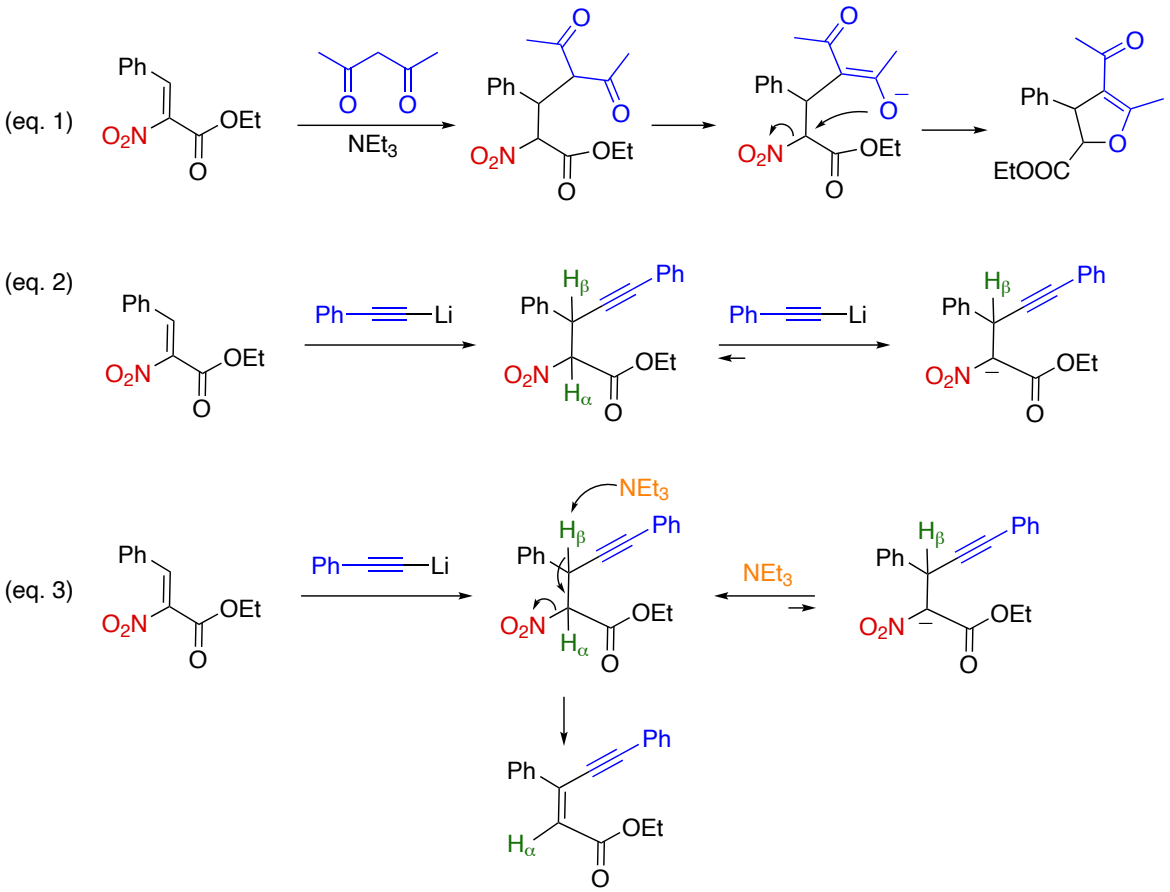


Scheme 2. Chemical transformations of nitroisoxazolone

Leaving Ability

The nitro group works as a leaving group: in the reaction of ethyl α-nitrocinnamate with acetylacetone, the enolate ion intramolecularly displaces the nitro group to give dihydrofuran (**Scheme 3**, eq. 1).[8] We hypothesized that when ethyl α-nitrocinnamate is in the presence of acetylide, a conjugate addition proceeds. We thought that the functionalized enyne could be obtained by elimination of nitrous acid, since the conjugate addition proceeds when the acetylide reacts with ethyl α-nitro cinnamate. However, we had to struggle with the quirky behavior of the elimination reaction not occurring not eliminating when we wanted it to. Thinking that the lack of elimination was due to an insufficient amount of base, we used an excess amount of acetylide, but no change at all was observed (eq. 2). After various trials, we almost gave up, but then we tried using triethylamine, a weak base, at last. As a result, the deprotonation proceeded efficiently and we succeeded in obtaining enyne in high yield (eq. 3).[9] In the case of acetylide, the equilibrium was biased toward the anion from which the α-hydrogen of the nitro group was withdrawn because it is a strong base. So, the reaction did not proceed. To the contrary, triethylamine is a weak base and there is an equilibrium between deprotonation and protonation. When the base then withdraws the β-hydrogen, the deprotonation proceeds to afford enynes. We learned that when the reaction does not proceed, we often use more reagents with higher reactivity or harsher reaction conditions, but sometimes the reaction proceeds by decreasing the reactivity.

Lesson learned, "If you push and it does not work, try pulling."



Scheme 3. Reactions using a nitro group as a leaving group

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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.