博士論文 (要約)

Synthesis of Heterocyclic Compounds Based on Neighboring Group Participation of Iminyl Nitrogen

（窒素カチオンへの隣接基関与に基づくヘテロ環生成反応）

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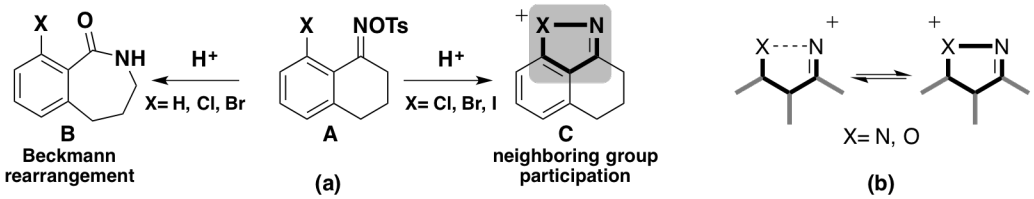
Introduction

Oximes are easily prepared from the corresponding carbonyl compounds and hydroxylamine. The electrophilicity of the imino carbon is low, and addition of nucleophiles to the N atom of *O*-substituted oximes occurred smoothly. One of the well-known examples is the Beckmann rearrangement, in which amide products are generally obtained by reacting activated oximes in acidic condition (**Scheme 1**, **A** to **B**).

I have reported the neighboring group participation on the oxime N atom within a five membered ring (**C**), which occurred competitively with the Beckmann rearrangement reaction on *peri*-substituted tetralones (**A**). The formation of X-N bonds (X= Br and I) was confirmed in solid and solution states. In my study, the generality of electron donors in the related neighboring group participation was explored. (**Scheme 1**, (**b**)) It was found that both tertiary nitrogen amine (NR_3) and sp^2-hybridized oxygen (O=C) could stabilize the iminyl nitrogen, leading to the formation of strong X-N bonding.



Scheme 1. Beckmann rearrangement and neighboring group participation for *peri*-substituted tertralone

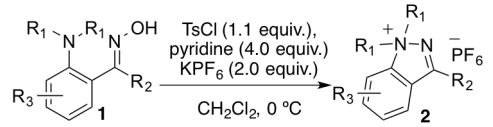
Results

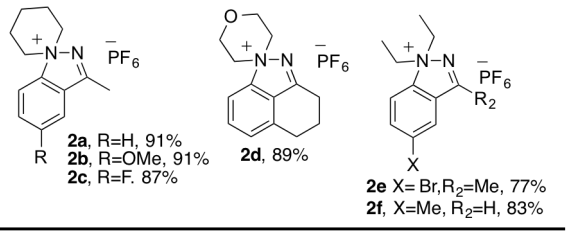
1. Synthesis and structure of 1, 1-disubstituted indazolium hexafluorophosphates

It was found that the presence of *peri*-N substituents on the tetralone skeleton can stabilize the iminyl nitrogen cation, and 1*H*-indazoles were obtained after N-N bond formation (**Scheme 1**, X= NH).

Indazole rings are found in many natural products with a variety of biological activities, and are generally present in the form of the 1,2-disubstituted indazolium ions. Various approaches have been reported for the construction of the pyrazole rings of 1*H*-indazoles and 1,2-disubstituted indazolium ions. On the other hand, although 1,1-disubstituted indazolium ions are structurally similar, synthetic approaches are still

Table 1. Scope of reaction for the synthesis of **2**.





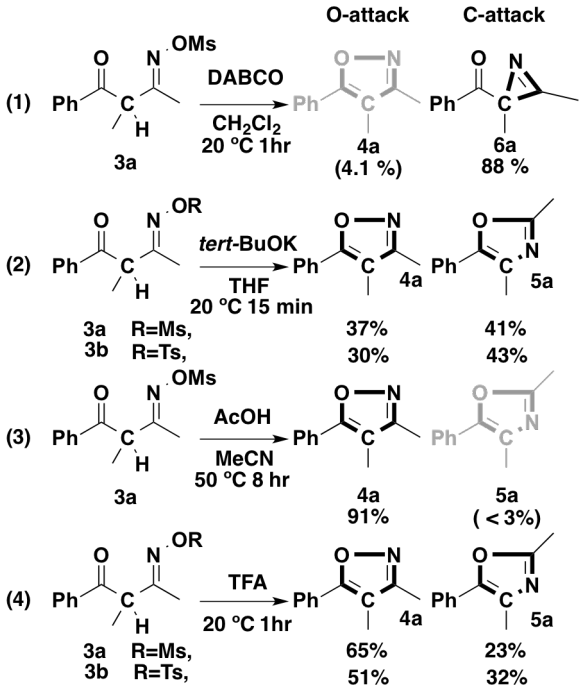
extremely limited, despite the pharmacological potential of these compounds. Considering the high stability of imino-halonium cations otained from neighboring group participation (**Scheme 1**, **C**, X= Br and I), I deemed that similar strategy can be employed for the construction of 1, 1-disubstituted indazoliums.

I found that the cyclization reaction of **1a** occurred smoothly with TsCl/pyridine, furnishing **2a** in 91% yield in the presence of KPF_6 (**Table 1**). It can be inferred from the high-resolution mass spectrum (ESI-TOF) that oxime N-O bond cleavage occurred during the formation of **2a**, and determination of the crystal structure of **2a** confirmed the formation of the N-N bond. The N-N bond length of **2a** is 1.486 Å (in the crystal state), which is slightly longer than the sum of the covalent radii (1.42 Å) and much shorter than the sum of the van der Waals radii (3.10 Å), suggesting a strong interaction between the two N atoms of **2a**. This N-N bonding is maintained in the solution state, as an nOe signal between the methyl group and aromatic proton was observed in CD_2Cl_2.

Further study suggested that the reaction conditions established for the synthesis of **2** are compatible with a range of substrates (**Table 1**). Notably, unsubstituted **2f** (R_3=H) was also obtained from the aldoxime precursor **1f**, in which the acidic imidoyl proton survived the reaction conditions. The crystal structures of **2d** and **2e** were also determined. **2e** has a N-N bond length (1.485 Å) similar to that of **2a**; but **2d** featured an elongated N-N bond (1.511 Å), probably due to the back-clamping effect of the tetralone skeleton. Computational studies suggested a covalent bonding character of the N-N bond, with diminished aromaticity of the newly formed pyrazolium ring due to the quaternary ammonium atom, in contrast to the aromatic character of the parent indazole.

2. Ambident-like reactivity of 3-hydroxyimino-2-methyl-1-phenyl-1-butanones.

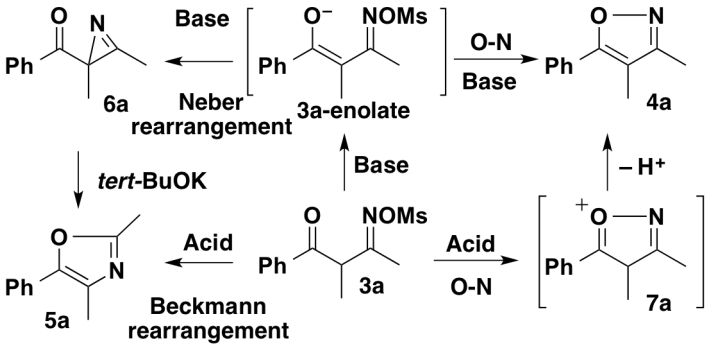
It was expected that a neighboring O atom (**Scheme 1**, X= O) can stabilize the iminyl nitrogen atom, in both sp^3 (enolate) and sp^2 (ketone) hybridization states. Also such neighboring group participation can probably occur in an open-chain system. Therefore 3-hydroxyimino-2-methyl-1-phenyl-1-butanones **3a** and **3b** were designed as model compounds. **3a** and **3b** were found to afford different products depending on the reaction conditions (**Scheme 2**). Compounds **3a** and **3b** possess both a carbonyl group (C=O) and hydroxyimino group (C=N–OR) in a single molecule. I performed the reactions of **3a** and **3b** under Brønsted basic conditions (**Scheme 2**, reaction (1) and (2)) and acidic conditions (reaction (3) and (4)). High selectivity for C-attack (C-N bond formation) was observed in the reaction of **3a** with a relatively mild base, 1,4-diazabicyclo[2.2.2]octane (DABCO), yielding the 2*H*-azirine **6a** (reaction (1)). When **3a** was treated with *tert*-BuOK, isoxazole **4a** and oxazole **5a** were obtained in comparable yields (reaction (2)). Product **4a** contains a new O–N bond, which indicates O-



Scheme 2. Reactions of **3a** and **3b** under Brønsted acidic (reactions 1 and 2) and basic conditions (reactions 3 and 4).

atom reactivity. On the other hand, a preference for O-attack, leading to the formation of an O-N bond, was observed under acidic conditions using AcOH (reaction (3)). When stronger trifluoroacetic acid (TFA) was used, the reaction again gave a mixture of **4a** and **5a** (reaction (4)).

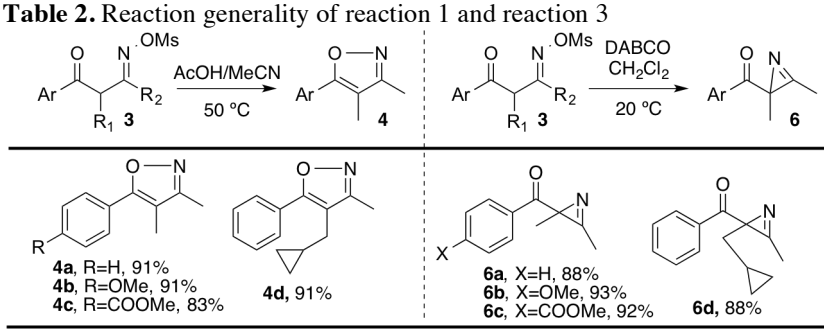
Both experimental and computational results on the reaction mechanism suggest that the enolization occured before the extrusion of products when **3a** was treated with basic conditions (**Scheme 2**, **3a** to **3a-enolate**). The resulting enolates (enols) can react at either O or C atom, leading to **4a** and **6a** (**5a**) respectively. **6a** arised from Neber-type rearrangement, and **4a** was formed by O-amination, in a similar manner to the previously reported neighboring group participation reactions (**Scheme 1**, X= O). For reaction (1), deprotonation is the rate-determining step; the formation of C-attack (**5a**) and O-attack (**4a**) products from enolate in the reaction of **3a** with *tert*-BuOK can be explained by the reactivity-selectivity principle, and the selectivity is likely diffusion-controlled.



Scheme 3. Mechanistic studies of **1a** reacting in basic and acidic conditions.

The reactions of **3a** under acidic conditions provide unprecedented examples of ambident-like reactivity of ketones. The reactions in AcOH and TFA are activation-controlled, and the selectivity can be rationalized in terms of the Marcus theory. Participation of O atom with iminyl nitrogen of ketone-form **3a** affords the cationic intermediate **7a**, which is preferentially aromatized into **4a**. The C atom of ketone can react as a nucleophilic site without tautomerization to the corresponding enol, even though the enolization is a possible alternative in TFA.

Table 2. Reaction generality of reaction 1 and reaction 3

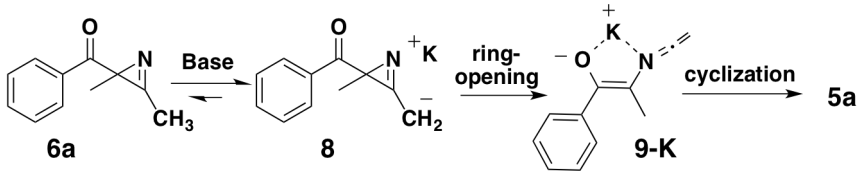


By controlling the selectivity for O and C atom reactivity, chemoselective synthesis of isoxazoles and 2*H*-azirines, which are important synthons in organic chemistry, can be achieved from the same substrate under different conditions. (**Table 2**).

3. Base-induced transformation of 2-acyl-3-alkyl-2*H*-azirines **6** to oxazoles **5**.

I am also interested in the reactivity of 2-acyl-3-alkyl-2*H*-azirines **6** under basic conditions. Oxazole **5a** was obtained in the reaction of **3a** with *tert*-BuOK, but **6a** was the only product when **3a** was reacted with mild base (DABCO, **Scheme 2**).

In view of the similarity of the (pseudo)-π-isolobal properties of 2*H*-azirine and nitrile functionalities, the deprotonation of 2*H*-azirines to afford ketenimines (ethenimines, **9**) is feasible. Our mechanistic study supports this assumption. After deprotonation to afford anion **8**, cleavage of the C-C bond of the azirine ring could occur through a Grob-type fragmentation (**8** → **9-K**), in a similar manner to heterolytic cleavage of donor-acceptor

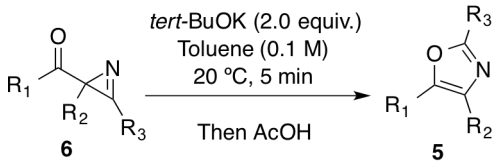


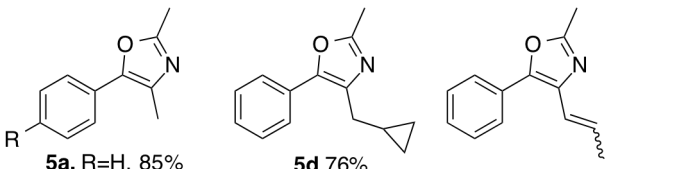
Scheme 4. Deprotonation initiated mechanism for the transformation of **4a** to **3a**

cyclopropanes. The cleavage can be explained by the high strain in the azirine ring and the electron-withdrawing nature of the neighboring carbonyl group. Cyclization of the resulting ketenimine intermediate (**9**) would occur to give **5a** after protonation (**Scheme 4**).

I have also studied the generality of the deprotonation-initiated rearrangement reaction from related azirines to oxazoles (**Table 3**). With the optimal conditions, the azirines with electron donating substituents (**6b**) and electron withdrawing substituents (**6c**) react smoothly. The reaction of **6d** bearing a cyclopropyl group (R_2) also gave oxazole **5d** in a good yield (76%), which excludes the possibility of radical generation. Substrate **6e**, possessing an allyl group, is prone to generate thermodynamically more stable oxazoles (***E*)-5e** and (***Z*)-5e**.

Table 3. Generality of isomerization from **6** to **5.**





[a] Obtained from **6e**.

In summary, the generality of electron donors in neighboring group participation with iminyl nitrogen was studied. It was also demonstrated that such participation from oxygen atom could occur in open-chain systems efficiently. The reactions lead to the formation of X-N bonds, which can be a versatile strategy for the synthesis of nitrogen contained heterocyclic compounds.