

Transformation of Carbonyl Compounds to Different Azaheterocycles via Direct Catalytic C-C Bond Cleavage

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Transformation of Carbonyl Compounds to Different Azaheterocycles
via Direct Catalytic C–C Bond Cleavage
(触媒的直接炭素-炭素結合切断による、カルボニル化合物から異なる
窒素含有複素環化合物への変換反応の開発)

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【序論】

Activation and cleavage of carbon–carbon (C–C) bonds in organic molecules represent a fundamental challenge in organic synthesis due to the intrinsic strength and inertness of these bonds. Although recent advances have focused on transition metal-catalyzed transformations and the use of pre-activated substrates, such approaches are often limited by high cost, low functional group tolerance, and the requirement for toxic reagents. As a result, the development of new C–C bond cleavage reactions remains a topic of significant research interest.

In previous studies, it was reported that the C–C bond in 2-acylimidazoles can be cleaved in the presence of nucleophiles alone, without the need for any catalysts or additives.¹ Building on this concept, I developed a method in which 2-acylimidazoles and other 2-acylazaarenes undergo C–C bond cleavage with bifunctional nucleophiles such as o-phenylenediamine. This reaction proceeds via a benzimidazoline intermediate under acidic conditions.²

However, in these cases, the presence of heteroatoms on the aromatic ring was essential for the reaction to occur. Simple aromatic or aliphatic ketones lacking such heteroatoms generally do not undergo C–C bond cleavage under similar conditions. Aliphatic ketones with α -quaternary carbon centers have previously been reported to undergo photochemical Norrish-type reactions,³ typically requiring photocatalysts. Notably, I discovered that such ketones can also be cleaved under acid-catalyzed conditions in an argon atmosphere, without the need for oxidants or light, and with higher reactivity than previously reported systems.

This observation led me to investigate the underlying mechanism of this transformation, with the goal of developing a novel and general C–C bond cleavage strategy for ketone compounds bearing α -quaternary carbon centers.

【方法】

- a. To investigate the C–C bond cleavage reaction of 2-acylazaarenes, I first optimized the reaction conditions using 1-(1-methyl-1H-imidazol-2-yl)-3-phenylpropan-1-one as a model substrate. This involved a systematic screening of acid catalysts, solvents, and reaction concentrations. Under the optimized conditions, I evaluated the influence of various N-substituents by employing a series of N-substituted acylimidazole derivatives. The substrate scope was further examined by introducing different functional groups onto the acylimidazole framework. In parallel, various bifunctional nucleophilic reagents were tested to assess their influence on product diversity and reaction efficiency. To explore the generality of this transformation, other acylated heteroaromatic compounds were also examined as potential substrates. Mechanistic insights were obtained through control experiments and density functional theory (DFT) calculations.
- b. In a separate study focusing on aliphatic ketones, I employed 2,2-dimethyl-1-phenylpropan-1-one as a model compound. Similar to the previous system, the reaction conditions were optimized through catalyst, solvent, and concentration screening. A preliminary substrate scope was evaluated, and mechanistic investigations—including control experiments and basic DFT calculations—were conducted to compare this transformation with known C–C bond cleavage reactions under photochemical or oxidative conditions.

【結果】

- a. In the study of 2-acylazaarene derivatives, Sc(OTf)₃ was identified as the optimal catalyst and chlorobenzene as the most suitable solvent following systematic optimization. Under these conditions, a wide range of N-substituted acylimidazole substrates were successfully converted to the corresponding products in moderate to excellent yields. The reaction exhibited broad functional group tolerance, accommodating ester, hydroxyl, triisopropylsilyl (TIPS), and alkene functionalities without significant loss of efficiency. Moreover, when various bifunctional nucleophilic reagents were employed, over a dozen heterocyclic products were synthesized with consistently high reactivity. Notably, substrates bearing benzopyridine moieties—which are typically resistant to direct C–C bond cleavage—also afforded the desired products in high yields. Mechanistic studies indicated that the cleavage proceeds via formation of an imine intermediate, followed by proton transfer. These findings were further supported by DFT calculations, which were in good agreement with the experimental observations.
- b. In the study involving aliphatic ketones with α -quaternary carbon centers, NH₄OTf was found to be more effective than Sc(OTf)₃ in promoting the reaction. Unlike the conventional Norrish-type photochemical reactions, the C–C bond cleavage in this system proceeded efficiently under thermal conditions, without the need for light or photocatalysts. Radical trapping experiments provided evidence for the involvement of radical species, indicating a mechanistic pathway distinct from established photochemical processes. A plausible reaction mechanism was proposed based on these findings.

【考察】

In summary, I developed a novel C–C bond cleavage reaction for the construction of benzimidazole derivatives. This transformation proceeds under Lewis acid catalysis and is applicable to a broad range of functionalized 2-acylimidazoles as well as other nitrogen-containing acylated heterocycles. By employing structurally diverse nucleophiles, various heterocyclic products could be obtained, demonstrating the versatility of the method. Mechanistic investigations suggested that the imidazolium moiety plays a key role in facilitating the C–C bond cleavage. These findings may offer a new strategy for the activation of otherwise inert C–C bonds under mild conditions and expand the utility of 2-acylimidazoles as versatile intermediates for further derivatization.

In addition, I discovered an alternative C–C bond cleavage pathway for tert-butyl ketones that deviates from the conventional Norrish reaction. Despite the likely involvement of radical intermediates, this reaction proceeds efficiently under thermal conditions without the need for light or photocatalysts. This feature renders the method more practical and potentially more scalable than traditional photochemical approaches. Further mechanistic elucidation, reaction condition optimization, and extension of the substrate scope are warranted to fully realize the synthetic potential of this transformation.

【引用文献】及び【発表論文】

1. C–C Bond Cleavage of Unactivated 2-Acylimidazoles
Hai-Long Xin, Bo Pang, Jeessoo Choi, Walaa Akkad, Hiroyuki Morimoto, Takashi Ohshima, *J. Org. Chem.* **2020**, 85, 11592.
2. Sc(OTf)₃-Catalyzed C–C Bond Cleavage of Unactivated Acylazaarenes with 1,2-Diamines to Afford Azaarenes and Imidazoles
Bo Pang, Hai-Long Xin, Jeessoo Choi, Hiroyuki Morimoto, Takashi Ohshima, *Org. Lett.* **2025**, 27, 2075.
3. Photochemical Norrish type I reaction as a tool for metal nanoparticle synthesis: importance of proton coupled electron transfer.
Scaiano, J. C., Stamplecoskie, K. G. & Hallett-Tapley, G. L. *Chemical Communications*. **2012**, 48, 4798.